Textbook of Vitreoretinal Diseases and Surgery
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Science and technology related to medicine is a fast growing field.

Latest advances related to various diseases such as cell biology, molecular engineering, physical sciences, application of mathematics and information technology are being added up to the knowledge pool almost every year. So is true for vitreoretinal diseases, and the literature has started touching the related aspects such as genetics, stem cell research and nanotechnology.

While the thickness of the neurosensory retina is just around 200 microns, the body of knowledge on vitreoretinal diseases is gigantic. This book that summarizes the deliberations of the *Textbook of Vitreoretinal Diseases and Surgery* takes us to a further level of understanding the current concepts in the diagnosis and management of diseases affecting retina.

Starting with the first chapter on genetics of age-related macular degeneration with such intricately woven information on the latest developments and trends in twin analysis, gene mapping and screening, role of oxidative stress and inflammation, this book takes us through a journey via the various vitreoretinal diseases, which have been a topic of debate and discussion in the recent past. Delicately touching the medical and surgical aspects of adult and paediatric retinal diseases, lasers, and diagnostic modalities, the information contained in the text is vast and enormous, with the material organised as an integrated text.

Written by the experts in the field, each of the twenty-three chapters begins with an introductory note, progressing gradually into the detailed but concise and up-to-date knowledge with well illustrated figures, legends and references, to impart a visual impact on the reader. As a result, the text presents factual and concise package and expert perspective with the latest in the field.

We wish to congratulate Chief Editors, Dr S Natarajan and Dr Nazimul Hussain and the Co-Editor Dr Supriya Dabir, who undoubtedly have presented the information in the book with a focused approach guided by their immense experience in academics.

The book will be a useful guide to the clinicians, scientists and students. It appears as a complete quantum of basic, medical and surgical information, garnished with molecular genetics and stem cell flavors.
Preface

After the great triumph of the 8th International Advanced Vitreoretinal Surgery Conference held in picturesque Kuala Lumpur early in 2008 with world renowned faculty, it became imperative for me to share the thoughts, speeches and ideas which made the conference a resounding success.

As the Chairman of the Scientific Committee for this conference, I feel extremely privileged to bring you this book which marks the first such successful compilation of the collection of scientific sessions with bridging plenary lectures focusing on the updates in vitreoretinal diseases.

This anthology addresses the latest treatment modalities in both medical as well as surgical retina. It also highlights the painstaking research in genetics, stem cell therapy, lasers etc. Apart from this, focus has been on the utility of various advanced diagnostic modalities in day-to-day practice.

This book is meant to cater to not only to nascent retinal surgeons but also practicing surgeons as an update to their knowledge. Since the conference limits the audience to a few, this book is meant to rejuvenate the information on the updates in the field of vitreoretinal surgery to all those unable to attend the meet.

I would like to thank all the guests and invited speakers from across the world from the bottom of my heart. Their time and contributions are greatly cherished and undoubtedly provide the icing on the academic cake. A book of this stature would be incomplete without its scientific programme and I am duty bound to felicitate all those who have provided scientific contributions. I would also like to thank and appreciate Dr Nazimul Hussain and Dr Supriya Dabir who have worked tirelessly with me and contributed immensely in completing the book.

Ultimately, they have justified the efforts of the Organising and Scientific Committees.

“A man’s learning is imperishable and a precious wealth
All other possessions are less golden”

—Thirukkural-Verse 400

Thank you for granting me the privilege of serving as the Chairman of the Committee.

S Natarajan
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Chapter 1

Genetics of Age-related Macular Degeneration
**Abstract**

Age-related macular degeneration (AMD) is a late-onset complex disorder with multifactorial etiologies. Both genetic and environmental factors play a role in the disease pathogenesis. AMD is the third leading cause of blindness in the elderly. Familial aggregation, segregation studies and linkage analysis have provided both qualitative and quantitative evidence on the genetic basis in AMD. Several candidate loci have been earlier mapped in AMD but variants in genes viz. \(\text{APOE}, \ ABCA4, \ FBLN6 \) and \(\text{EFEMP1} \) harboring these loci have accounted for only a small proportion of cases. Recent screening of two major loci has led to the identification of the Complement Factor H (\(\text{CFH}\)) on 1q32 and \(\text{LOC387715} \) and \(\text{HTRA1} \) on the 10q26 gene cluster. Single nucleotide polymorphisms (SNPs) in \(\text{CFH} \) (Y402H), \(\text{LOC387715} \) (A69S) and a promoter variant in \(\text{HTRA1} \) have been associated with AMD in large case-control cohorts. These SNPs exhibited large effect sizes and high disease odds for the risk genotypes across different populations. Interestingly, these associations have been widely replicated across multiple ethnic groups worldwide indicating their potential role in the disease pathogenesis. In this article, we would outline the genetics of AMD with special emphasis on \(\text{CFH} \) followed by other genetic variants based on studies done by our group and colleagues worldwide. We would also provide a brief overview on the possible molecular mechanisms leading to AMD.

**Introduction**

Visual impairment leading to blindness is a major impediment towards growth and development in populations worldwide. The burden of blindness is a global challenge that needs to be tackled on a war footing. Recent estimates of the World Health Organization (WHO) indicate that around 45 million people are blind and 135 million are visually impaired worldwide and 90% of these people live in the developing countries. Among the blinding conditions, cataract accounts for 60% of global blindness, followed by glaucoma (12.3%). Age-related macular degeneration (AMD) is the third leading cause of blindness and accounts for 8.7% of the world population (WHO Fact sheet no. 282). Although AMD is more common among the elderly in developed countries, it is also becoming a cause of concern in the developing countries, with fast demographic changes in lifestyle and senescence.

**The Problem**

AMD causes progressive impairment of central vision and is a leading cause of irreversible vision loss worldwide. The overall prevalence of late stage AMD varies from 1.4 to 1.7% across different epidemiological cohorts (Klein et al, 1992; Mitchell et al, 1995) and increases significantly with age. The prevalence of AMD in India ranges from 1.84-2.7% (Nirmalan et al, 2004), similar to the global prevalence. It is estimated that by the year 2020, around 8 million people will have vision loss due to retinal complications including AMD (Bressler, 2002). As it leads to irreversible blindness, managing AMD is a global public health challenge.

**Risk Factors in AMD**

Epidemiological surveys conducted on large case-controls cohorts have identified several demographic and environmental risk factors in AMD. The Age-related Eye Disease Study (AREDS) conducted on large Caucasian cohorts indicated gender, age and smoking as important risk factors in the development of AMD (AREDS 2000, 2004). This was later replicated in many studies done on other ethnic groups (Krishnaiah et al, 2005; INDEYE study 2007). These risk factors are briefly described as follows:
**GENDER**

The incidences of early and late AMD are 2 and 7 times more in females above > 75 years of age, compared to males below 75 years of age (Klaver et al, 1998). The high risk in females may be due to the loss of a protective effect of estrogens in postmenopausal women.

**RACE**

The prevalence of AMD was shown to vary greatly among different races. All forms of AMD are more prevalent in the white population than darkly pigmented races (Bressler et al, 2008; Friedman et al, 1999). Although the exact mechanism is not known, it was suggested that may melanin protect against the formation of lipofuscin, which is a marker of cellular senescence and promoter of oxidative damage (Kawasaki et al, 2008). A recent study found no differences in macular or melanin pigment densities between eyes with and without early AMD (Kayatz et al, 2001).

**CIGARETTE SMOKING**

Smoking has been postulated to cause AMD by depression of serum antioxidant levels and alteration of choroidal blood flow and detoxification of the retinal pigment epithelium (RPE). It has been hypothesized that decrease in luteal pigments in human retina due to cigarette smoking may cause oxidative damage to the macula, thereby leading to an increased risk of developing AMD. Many population-based studies have shown the association of smoking with increased risk of AMD (Berendschot et al, 2002; AREDS 2000; Delcourt et al, 1998). It was also shown that prior and current smokers are prone to develop AMD atleast 5 to 10 years before non-smokers. A risk ratio of 2 or higher was observed for neovascular AMD (Klein et al). Stryker et al, reported that men who smoked one pack of cigarettes per day had only 72% of the plasma \(\alpha\)-carotene levels of nonsmokers, even after adjusting for dietary differences between smokers and nonsmokers. The APEDS study reported an odds ratio of 3.29 \([95\%\text{CI}, 1.42–7.57]\) for AMD in individuals with the history of cigar smoking (Nirmalan et al, 2004).

**ALCOHOL CONSUMPTION**

Alcohol intake causes tissue damage by increasing the oxidative stress or affecting mechanisms that protect against oxidative damage to retina. The inconsistent findings among various studies, however, suggest that consumption of alcoholic beverages is not likely to be an important risk factor for the incidence of AMD at this point of time (Eye Disease Case–Control Study Group; 1992).

**DIET**

Diet has been related to several chronic conditions including cancer, coronary heart disease, and cataract. It may also have an important role in preventing and slowing the development of AMD (Seddon et al, 1994).

**LIGHT EXPOSURE**

There have been conflicting reports on association of ultraviolet or visible light with AMD. Blumenkranz and associates found a statistically significant difference in the incidence of AMD between sun-exposed and sun-protected skin, whereas the Eye Disease Case-Control Study Group did not find sunlight exposure a risk factor in AMD. Majority of studies however, found no associations between estimated ambient UV-B exposure/sunlight exposure and age-related maculopathy (Stryker et al, 1988).
HYPERTENSION
Systemic hypertension was found to be associated with neovascular AMD. Hyman et al, conducted a case-control study of risk factors for neovascular and non-neovascular age-related macular degeneration (AMD). It was observed that neovascular AMD was positively associated with diastolic blood pressure greater than 95 mm Hg (odds ratio [OR] = 4.4), as opposed to non-neovascular AMD (Khan et al, 2006). The association of hypertension with advanced AMD was also reported by AREDS study [OR = 1.45] (AREDS, 2005).

GREATER BODY MASS INDEX
The association of greater body mass index with AMD has been reported by some studies (Klein et al, 2003; van Leeuwen et al, 2003; Johnson et al, 2005). Johnson et al, reported that the risk of obesity with AMD could be related to the physiologic changes such as increased oxidative stress, changes in the lipoprotein profile, and increased inflammation. These changes would also result in increased destruction and decreased delivery of lutein and zeaxanthin to the macula of the eye. Therefore, association to AMD risk could be through indirect effects on changes in lutein and zeaxanthin status and metabolism (Johnson et al, 2005).

CATARACT SURGERY
There are few studies, which reported cataract surgery as a risk factor for AMD. Wang et al, studied the association of cataract surgery and 5-year incidence of late-stage age-related maculopathy in the patients from the Beaver Dam and Blue Mountains eye studies. It was found that over a period of five years either neovascular AMD or geographic atrophy developed in 6.0 to 7.5% of aphakic eyes (10 of 168 right and 11 of 147 left eyes), compared with 0.7% of phakic eyes (40 of 5504 right and 37 of 5572 left eyes) (Abecasis et al, 2004). According to APEDS, prior cataract surgery was significantly associated with increased incidence of AMD (adjusted OR 3.79; 95% CI, 2.1– 6.78) (Nirmalan et al, 2004).

Genetics of AMD
The genetic basis of AMD was relatively ignored for many years as other causes for the disease were explored. Genetic epidemiological studies have revealed that genetic differences between populations might play an important role in explaining the prevalence among diverse ethnic groups. Higher concordance among the monozygotic twins, familial aggregation and segregation analyses have suggested a strong genetic basis for the disease (Seddon et al, 1997, 2005; Klaver et al, 1998).

TWIN ANALYSIS
Twin studies allows the exact comparison of the relative contribution by genetic as well as non-genetic factors on a trait. Such studies provide an exact quantification of the contribution of genetic factors or heritability which is the proportion of variance of a trait that is attributable to genetic factors. Such studies have provided more direct evidence of AMD heritability by comparing disease concordance rates in monozygotic (MZ) vs. dizygotic (DZ) twins. In a large USA population based survey of 840 elderly male twins, including 210 MZ twin pairs, 181 DZ twin pairs, and 58 singletons 268 twins were having signs of maculopathy, of which 106 had advanced disease. Analyses of this twin data yielded heritability estimates of 0.67 for intermediate and advanced disease (grades 3, 4,
and 5), and 0.71 for advanced disease only, including geographic atrophy and exudative AMD (grades 4 and 5). Hammond and colleagues evaluated concordance rates for early ARM in a cohort of 506 female volunteer twin pairs (226 MZ twin pairs and 280 DZ twin pairs). ARM was defined as the presence of soft drusen 0.63 mm in diameter in the macular area or the presence of pigmentary changes along with any type of drusen. The concordance for ARM in MZ twins was 0.37 compared with 0.19 in DZ twins, and the heritability of ARM was estimated to be 45% (95% CI 0.35 to 0.53).

**FAMILY BASED GENE MAPPING STUDIES**

These studies aimed at identifying regions on the chromosome shared by the closely related affected members in families using microsatellite markers or single nucleotide polymorphisms (SNPs) spread across the whole human genome. This procedure is very straightforward and has been successfully used for Mendelian traits. However, AMD being a late onset complex disorder suffered major hurdles from the unavailability of the closely affected relatives (parent and siblings) and no clear cut inheritance pattern.

Several such genome-wide linkage studies have identified a number of putative loci for AMD but only a few of these regions have been replicated independently. The first locus for AMD at 1q25-31 was mapped by Klein et al.,(1998) in a large family, however, the mutation Q5345R in the *Fibulin* gene harboring this locus could not sufficiently prove its contributions to AMD pathogenesis. Subsequently the susceptible loci have been mapped to chromosomes 3p, 3q, 4p, 5p, 5q, 6q, 8q, 9p, 9q, 10q, 12q, 15q, 16p, 16q, 17q, 18p, 20q and 22q, but no causative mutation has been reported in the genes located in these regions (Weeks et al, 2000; Seddon et al, 2003; Weeks et al, 2004; Majewski et al, 2003; Schmidt et al, 2004, Haddad et al, 2006). The chromosomal regions at 1q31–32 and 10q26 were identified in several independent studies and confirmed by meta-analysis of six datasets and these regions harbor the largest effect susceptibility variants for AMD (Swaroop et al, 2007).

**CANDIDATE GENE SCREENING**

Candidate genes for AMD were identified based on both genome-wide scan results and knowledge about gene function/expression data. Initially, genes involved in the pathogenesis of retinal degenerations similar to AMD were screened. Several Candidate genes responsible for macular and retinal dystrophies (*ELOV4* and *ABCA4*: Stargardt disease; *TIMP3*: Sorsby fundus dystrophy; and *Peripherin*: Retinal degeneration) that share common features with AMD were extensively screened for their involvement in AMD (Ayyagiri et al, 2001; Allikemets et al, 2001, 1999; Akimoto et al, 2001; De La Paz et al, 1997; Shastry et al, 1999). But the variation in these genes could account for only a small subset of AMD cases.

Currently, AMD candidate genes have been examined mainly by the way of case-control association studies using SNPs in the known loci which point to the identification of the possible disease-causing genetic variants or to the variations that might be lying in the close vicinity of the actual disease causing allele. Such studies evaluate whether specific alleles occur at a significantly higher frequency among the affected individuals vs. controls and can led to the identification of specific DNA signature or haplotype that can help in predicting the risk of AMD. The advent of high throughput SNP arrays has facilitated greatly the gene discovery especially for multigenic or complex diseases. Recently, some major candidate genes have been identified using these arrays in large case-control cohorts that explain a substantial proportion of AMD.
**Complement Factor H (CFH) Gene**

The polymorphism Y402H in the Complement Factor H (CFH/ARMS1) gene has been shown to be significantly associated with AMD susceptibility. *CFH* on 1q32 is an important regulator of complement system of innate immunity. A T→C substitution at 1277 nucleotide in exon 9 of *CFH* resulting in a change of tyrosine to histidine (Y402H) increases an individual’s risk of having AMD by several folds. The odds ratio for AMD reported by these studies ranged between 2.4- 4.6 for the risk allele “C” and between 3.3-11.5 for those with the risk genotype “CC”. The association of the Y402H SNP in AMD has been shown across different studies worldwide. Magnusson et al, (2006) further investigated the association of *CFH* and AMD based on genotype-phenotype correlations and observed that the Y402H allele confers a significant risk to both late stages (neovascular AMD, Geographic Atrophy) and early stages of AMD (soft drusens) in US and European AMD patients. It was also observed that the Y402H variant contributes to increased risk of advanced AMD through its involvement on the development of soft drusen which are precursors of advanced AMD phenotypes. This SNP has been implicated in most AMD populations worldwide, except in the Japanese (Gotoh et al, 2006, Okamoto et al, 2006).

Hageman et al, (2005) analyzed haplotypes using eight intragenic SNPs in *CFH* and also the immuno-histochemical status of drusen and sections of cadaveric eye in AMD patients. Their analysis revealed a risk haplotype, which had almost two-folds higher frequency among the cases (50%) than controls (29%). Two protective haplotypes for AMD were also identified among the controls. *CFH* is an important regulator of complement system of innate immunity against microbial infection. This regulation of complement activity is achieved by the binding of *CFH* to C3b (generated by the cleavage of a chains of C3), thereby stopping the production of C5b-9 (the component of membrane attacking complex). The Y402H residue located within the binding sites for heparin and C-reactive protein. Altered binding of *CFH* to these proteins results in changes in *CFH*’s ability to suppress the complement-related damage to the host cells (Clark et al, 2005, Johnson et al, 2006).

Discovery of complement factor H gene as a major candidate for AMD led to the investigation of other complement pathway genes for their involvement in AMD pathogenesis. *CFH* is a member of the RCA (Regulators of complement activation) gene cluster located on chromosome 1q32 spanning 21.45 cM and including more than 60 genes of which 15 are complement related. All these complement genes are arranged in tandem through duplications and gene conversions. *CFH* lies in the close vicinity of CFHR1 and CFHR5 genes that encode for five *CFH* related plasma proteins. A *CFH* haplotype harboring the deletion of the ‘*CFH*-related’ genes CFHR1 and CFHR3 was found to be protective against AMD but in small proportion of AMD cases.

**Factor B and Complement Component**

Gold et al, (2006), reported a strong association of variation in the Factor B (BF) and complement component 2 (C2) genes with AMD. *BF* and *C2* genes are located in the major histocompatibility complex class III region (6p21). The L9H and R32Q variants in *BF* and E318D and an intron 10 variant in *C2* were found to confer significantly reduced risk of AMD. When these haplotypes were analyzed together with *CFH* variants it was shown that variation in these two loci can predict clinical outcome in 74% of the affected individuals and 56% of the controls.

*BF* and *C2* are expressed in the neural retina, RPE and choroids. Additionally the *BF* protein was observed in ocular drusen and Bruch’s membrane. Glutamine at position 32 of this protein has been shown to have reduced hemolytic activity as compared to wild type Arg32 (Lokki and Koskimies, 2006).
Genetics of Age-related Macular Degeneration

1991). BF is an important activator of the alternative complement pathway and thus may result in AMD by abnormal BF activity.

Recently two studies reported significant associations between AMD and variants in the complement component 3 (C3) gene on chromosome 19p13. C3 plays an important role in activation of both the classical and the alternative complement pathways and the plasma complement C3a levels are significantly elevated in AMD cases compared to controls. A fourth recent study also found ARM associated variants in the C7 and MBL2 (Gene ID 4153) complement pathway genes by complement pathway focused analysis of an earlier genome-wide association scan.

Genes in the 10q26 Cluster

The second AMD locus mapped on 10q26 harbored three important candidate genes PLEKHA1 (OMIM 607772), hypothetical LOC387715 and HTRA Serine Peptidase 1 (HTRA1; OMIM 602194) (Jakobsdottir et al, 2005). Resequencing of this cluster revealed a significant association of the A69S (rs10490924) SNP in LOC387715 gene in two large AMD cohorts of German origin (Rivera et al, 2005). These results were further replicated in Caucasian (Conley et al, 2006; Ross et al, 2007; Seddon et al, 2007), Japanese (Tanimoto et al, 2006) and Russian (Fisher et al, 2006) AMD patients. It has also been shown that the presence of the rs10490924 SNP, along with an associated history of smoking, strongly modifies the risk of AMD (Schmidt et al, 2006). The combined effect of the rs10490924 SNP and smoking significantly enhanced the risk of AMD in some populations (Seddon et al, 2007; Wang et al, 2007; Schaumberg et al, 2007) but this finding could not be replicated in a large dataset comprising the AREDS (Age-Related Eye Disease Study) and CHS (Cardiovascular Health Study) cohorts (Conley et al, 2006). The combined additive effect of the rs1061170 (CFH) and rs10490924 SNPs exhibited a high population attributable risk percentage (PAR %) in AMD (Seddon et al, 2007; Schmidt et al, 2006).

Very recently, another SNP (rs11200638) located 512bp upstream of the transcription site of HTRA1 gene in the same 10q26 cluster, was implicated in three independent reports on Caucasian (Yang et al, 2006; Cameron et al, 2007), Chinese (Dewan et al, 2006) and Japanese (Yoshida et al, 2007) AMD subjects. It was also demonstrated that this SNP in the promoter region was in LD with rs10490924 that was a further 6.6 kb upstream of HTRA1 (Dewan et al, 2006) Earlier studies done on Chinese (Dewan et al, 2006), Japanese (Kondo et al, 2007; Yoshida et al, 2007) and Caucasian populations in the US22 (Yang et al, 2006; Cameron et al, 2007) have demonstrated the association of rs11200638 (HTRA1) in AMD. It was also shown that the rs11200638 confers similar risk in dry and wet AMD cases in the Caucasian populations.

While, the function of both these variants are yet uncharacterized, two locus odds ratios have indicated significant risk conferred by the HTRA1 variant in conjunction with the CFH variant Y402H (Cameron et al, 2007). Recent studies, however, have provided convincing evidence of the significant involvement of the LOC387715 SNP but not HTRA1, in the development of AMD (Kanda et al, 2007). Although the underlying functions of LOC387715 are yet to be unveiled, it was suggested that rs11200638 is a strongly associated marker in the vicinity of rs10490924 because of the strong LD between these SNPs (Kanda et al, 2007; Dewan et al, 2006).

Functionally, the presence of LOC387715/ARMS2 mRNA has been demonstrated in the retina and other cell lines; it localizes to the mitochondrial outer membrane in transfected mammalian cells (Kanda et al, 2007). Although the functional implications of the rs11200638 SNP in AMD pathology has been suggested based on the detection of HTRA1 in drusen of both wet (Dewan et al, 2006) and
dry AMD (Cameron et al, 2007) eyes and in promoter-based assays, this finding was not replicated in another study (Kanda et al, 2007). Thus, the precise role of the LOC387715 and HTRA1 SNPs in AMD is as yet unknown, and their interactions with different factors in the complement pathway remain speculative. However, such speculations cannot be addressed unless extensive data on gene–gene interactions in the background of other nongenetic factors leading to the pathophysiology of AMD are elucidated (Swaroop et al, 2007).

**APOE**

In the past few years, association of variants in genes involved in lipid metabolism such as Apolipoprotein E (APOE) have increased our understanding of the underlying mechanism of AMD development. Based on common pathogenic features including lipid deposition (drusen and plaque formation), thickening of connective tissue (Bruch’s membrane and arterial inner lining) and elevated levels of CRP in serum, a common mechanism for the development of AMD and atherosclerotic cardiovascular diseases was proposed (Freidman 2000). However, it was noted that the effect of APOE alleles on AMD risk was contrastingly different than that of atherosclerosis and cardiovascular diseases (Baird et al, 2004; Zareparsi et al, 2004). Association of APOE in AMD has been reported by several groups (Klaver et al, 1998; Schmidt et al, 2002; Baird et al, 2004; Zareparsi et al, 2004) showing a reduced risk of AMD with APOE-e2 allele and higher risk with allele APOE-e4. However, APOE polymorphisms have exhibited varied geographical and ethnic variations across AMD patients worldwide (Kaur et al, 2006).

**Toll like Receptor 4 (TLR4)**

A recent study by Zareparsi et al, (2005) implicated the TLR4 gene (9q32-33) in AMD pathogenesis. Toll like receptors are involved in innate immunity and pathogen recognition (Cook et al, 2004), linked to regulation of cholesterol efflux and participates in phagocytosis of photoreceptor outer segments by the RPE (Kiechl et al, 2002; Castrillo et al, 2003; Kindzelskii et al, 2004; Blander et al, 2004). The D299G polymorphism in TLR4 was associated with a 2.65 folds increased risk of AMD, thereby suggesting that altered TLR4 signaling by this variant may influence phagocytic function of RPE which in turn may contribute to RPE damage. It was also shown that TLR4-D299G had an additive effect on AMD risk (OR = 4.13, p = 0.002) with allelic variants of APOE and ATP binding cassette transporter-1 (ABCA1), which are involved in cholesterol efflux. However, the effect of TLR4, APOE and ABCA1 variants on AMD susceptibility was in contrast to that seen in atherosclerosis. But TLR4 polymorphisms have not been explored extensively across different world AMD populations compared to other candidate genes.

**Mechanisms of AMD Development**

Several pathogenic mechanisms have been proposed to understand the complex etiologies of AMD development including RPE cell death, oxidative damage of cellular components, mitochondrial dysfunction and accumulation of toxic components such as lipofuscin and advanced end glycation products (Haddad et al, 2006). It was thus proposed that variations in genes involved in inflammation, oxidative stress and cholesterol metabolism play significant role in the pathogenesis of AMD.
ROLE OF COMPLEMENT ACTIVATION AND INFLAMMATION IN THE PATHOGENESIS OF AMD

Inflammation has been implicated in several diseases of aging like Alzheimer’s disease, stroke and cardiovascular disease. Interestingly all these diseases share lots of similarities with AMD with respect to pathological features and common biomarkers for the disease such as increased levels of CRP, CFH and Homocysteine in plasma of patients, presence of serum amyloid P component in drusens (the levels of which are elevated in plasma of Alzheimer patients) and association with CFH (Y402H) and APO E variation, etc.

Protein profiling studies of the drusen also revealed the presence of immunoglobulins, components of the complement pathway (C3, C5b-9 complex) (Johnson et al, 2000), molecules involved in acute phase response to inflammation (e.g. Amyloid P component and 1-antitrypsin), proteins that modulate immune response (vitronectin, clusterin, apolipoprotein E, membrane cofactor protein, complement receptor 1), major histocompatibility complex class II antigens and HLA-DR and cluster differentiation antigens (Mullins et al, 2000). Accumulation of all these proteins and cellular debris suggest that cells are subjected to a chronic sublethal complement attack mediated by choroidal dendritic cells and macrophages resulting in the further degradation of Bruch’s membrane (Johnson et al, 2001, Hageman et al, 2001). These studies gave a strong evidence for the role of inflammation and dysfunction of complement pathways in the pathogenesis of AMD.

ACCUMULATION OF LIPOFUSCIN IN THE RPE

Lipofuscin are autoflourescent lysosomal storage bodies that accumulate in the postmitotic metabolically active cells throughout the body due to normal aging process. These bodies originate primarily from the degradation of different intracellular organelle and the incomplete degradation of extracellular material taken into the cells by phagocytosis. RPE lipofuscin are formed due to ingestion of photoreceptor outer segments as evident from the presence of retinoids, high concentration of DHL-Lipids, etc. Accumulation of lipofuscin in RPE has been associated with the development of AMD though evidence for the same has not been provided.

ROLE OF OXIDATIVE STRESS MEDIATORS AND MODIFICATIONS IN AMD PATHOGENESIS

The evidence for oxidative stress playing a major role in AMD pathogenesis includes increased risk of AMD in smokers, presence of oxidative modified proteins in the drusen/Bruch’s membrane/RPE / choroidal tissues and slower progression of AMD in patients fed on regular supplementation of antioxidant vitamins and Zinc. Several studies have pointed out that oxidative protein modifications serve as a primary catalyst for macular degeneration, the reactive oxygen species/oxidative products being provided by photo-oxidative rich milieu in the retina particularly the lipids and retinoid rich photoreceptor segments. Proteome study of drusens also demonstrated the elevated levels of oxidatively modified proteins like μ-carboxyethyl pyrrole (CEP) adducts in the drusen, Bruch’s membrane and plasma of AMD patients. It was found that the mean level of CEP adducts was 1.5 fold higher (p = 0.004) and that of antibody titers in plasma was 2.3-fold higher (p = 0.02) in patients with AMD compared with normal age-matched controls (Gu et al, 2003). Of individuals (n = 13) exhibiting both antigen and autoantibody levels above the mean for non-AMD controls, 92% had AMD. Based on the results, CEP immunoreactivity and autoantibody titer may have diagnostic utility in predicting AMD susceptibility.

These CEP adducts are generated from oxidation of polyunsaturated fatty acids (PUFAs) particularly docasohexanoic acid (DHA) present in photoreceptor outer segments and have been
shown to induce choroidal neovascularization (CNV) in retinal tissues. In-vitro treatment of human RPE cells with CEP dipeptide or CEP-HSA did not induce increased VEGF secretion and suggesting that anti-CEP therapeutic modalities might be of value in limiting CNV in AMD (Ebrahem et al, 2006). CNV in retinal tissues can also be stimulated by the complement components (C3a and C5a) present in the drusen. It was shown that genetic ablation of receptors for C3a or C5a reduces VEGF expression, leukocyte recruitment and CNV formation after laser injury. These experiments suggested that antibody-mediated neutralization of C3a or C5a or pharmacological blockade of their receptor could be therapeutic modalities for AMD (Nozaki et al, 2005).

Conclusions

Genetic association studies have led to the implication of several candidate genes in AMD in the last few years. These association studies have been meaningful as they have been widely replicated across multiple populations with varied ethnic backgrounds in clinically well characterized cohorts (Todd 2006). Moreover, the effect sizes of these variants, particularly the CFH (Y402H), LOC387715 (A69S) and HTRA1 have been substantially large that permitted a proper association amidst varied sample sizes in different studies. In future, more such studies are required across wider geographical regions to identify candidates that contribute to the AMD pathogenesis. Genetic typing of AMD patients would also permit clinicians to develop correlations with genotypes for estimating disease risk and progression. Identification of susceptible gene variant(s) would allow early intervention in subjects ‘at-risk’ of developing AMD for a better prognosis. While the underlying biological functions of these candidate genes and their interactions are yet to be characterized, large multicentre studies with these variants should be undertaken with respect to the treatment modalities in order to understand the therapeutic mechanisms in subjects carrying the risk genotype(s).

Bibliography


Genetics of Age-related Macular Degeneration

Cell Therapy in Retinal Diseases
Introduction

Cell therapy is an exciting area of research that is aimed at regeneration of tissues or organs in patients with irreparable damage to these tissues or organs. Cell therapy is no longer restricted to transfer of cells from a healthy subject to a patient, as in bone marrow transplant or corneal transplant. We can now envisage cell therapy that involves generation of patient-specific cells for transplantation, manipulate them \textit{in vitro} into the desired cell type and transplant these cells into a patient for functional restoration of the damaged tissue. Although many cell therapies are currently being tested in animal models and their clinical application might take much longer, results from these studies are encouraging and suggest that regeneration of custom-made organs might indeed be possible in real life.

Cell therapy in the form of simple blood transfusion and bone marrow transplant has been in use for a long time. This was limited to collecting healthy cells from matched donors and introducing these cells into the patient. The cells were not propagated or manipulated in any way \textit{in vitro} prior to transplantation. The first culture and transplantation of dermal epithelial cells was performed to replace damaged skin in burns patients\textsuperscript{1,2} and taking cues from these experiments, similar approach was used to regenerate corneal epithelium in patients with limbal stem cell deficiency.\textsuperscript{3} Simultaneously embryonic stem cells were first established in 1981\textsuperscript{4,5} and further understanding of mechanisms underlying self-renewal and differentiation of stem cells into various types of cells led to designing of new therapeutic strategies.

Degenerative diseases of retina like retinitis pigmentosa (RP), age-related macular degeneration (AMD) and diabetic retinopathy lead to irreparable damage to the retina and are a major cause of blindness in developed countries (Figure 2-1). Several genetic disorders such as retinitis pigmentosa or Leber congenital amaurosis also lead to retinal degeneration and blindness. A therapeutic approach that can regenerate retinal cells or the entire retina would help improve visual acuity and quality of life of these patients. Use of cell therapy for retina however is not easy as the retina consists of several cell types and retinal disorders can occur due to damage to any of these cell types. The neural retina consists of rod and cone photoreceptors, bipolar cells, ganglion cells, horizontal cells, Müller cells and amacrine cells that are arranged in a definite three-dimensional structure. The neural retina rests on the retinal pigment epithelium (RPE), which is in close contact with photoreceptors and is vital for maintenance of photoreceptor homeostasis. Degeneration of any type of cells in the neural retina or RPE can lead to retinal degeneration and loss of vision. Retinal disorders could also occur due to uncontrolled growth of endothelial cells leading to neovascularization in the retina that can eventually lead to retinal detachment in diseases like diabetic retinopathy and AMD. The current attempts at retinal cell therapy are therefore aimed at regeneration of cells in neural retina, regeneration of RPE and re-establishment of correct retinal vasculature. For treatment of inherited retinal disorders, the cell therapy also might involve manipulations to correct the genetic defect by gene therapy.

Cell therapy is an interdisciplinary field that requires inputs from the field of stem cell biology, regenerative biology, material science, developmental biology, genetic engineering and clinicians. The success and feasibility of any cell therapy depends on a number of factors, such as availability of suitable source of stem cells, expansion and manipulation of cells to generate the desired type of cell, introduction of cells \textit{in vivo}, survival and integration of cells to reconstruct degenerated tissue and restoration of its physiological function (Figure 2-2).

An appropriate source of stem cells that can generate and sustain cells/tissue of interest is an important starting point for cell therapy. Stem cells are the cells that have the ability to renew
themselves and also differentiate into any other cell of the body. They could be embryonic stem cells, which are derived from the inner cell mass of blastula or adult stem cells, which are present in the adult tissues such as bone marrow, liver, muscles, skin and cornea. Embryonic stem cells are totipotent, i.e. they have the ability to differentiate into any other cell type. Adult stem cells on the other hand have limited capacity to divide and can differentiate only into specific types of cells. They can be either multipotent stem cells that can differentiate into many types of cells, such as the bone marrow stem cells, or unipotent stem cells that can differentiate into only one type of cell, e.g. limbal stem cells. For retina, several sources of stem cells such as embryonic, fetal and adult stem cells from eye and bone marrow have been investigated as discussed below. An autologous source of cells would be preferred in order to avoid complications of rejection associated with graft rejection, but it may not be possible to use an autologous source if retinal degeneration is due to an inherited disorder.

The next important issue is the ability to culture these stem cells \textit{in vitro} to expand them. The number of cells available for transplantation, especially if they are from adult tissues, is often limited and the cells need to be cultured \textit{in vitro} to obtain sufficient number of cells. Expansion of cells while maintaining their characteristics such as their stemness or their differentiation status is a challenge and requires standardization of culture conditions. This involves identification of correct culture
medium, growth factors, feeder cells and it may also involve standardization of correct matrix that will help cellular growth and differentiation or harvesting of cell at the time of transplantation.

After expansion, stem cells might be directly introduced in the animal to allow it to differentiate in the niche provided by the recipient or the cells might be coaxed to undergo differentiation \textit{in vitro} to generate the cell or cells of interest. Directed differentiation of a stem cell into a cell of interest is extremely challenging and requires understanding of mechanisms underlying the development of that particular tissue during embryogenesis. The differentiation of a stem cell into the desired cell type is regulated by both intrinsic information present within the cell and the cues provided by the niche it is residing in. Therefore for directed differentiation, stem cells need to be cultured under specific conditions that would allow their differentiation into cells of interest. Extensive experimentation to understand the developmental biology and cell differentiation of the tissue of interest needs to be carried out using various animal models to understand the conditions required for such \textit{in vitro} manipulations. This is particularly complicated for tissues like retina, which is made up of several cell types. For treatment of genetic disorders, the defective copy of the gene needs to be replaced with the wild type or the correct copy of the gene at this stage.

The correct route of introduction of these differentiated cells \textit{in vivo} also needs to be investigated. In retinal cell therapy, the mode of introduction, whether subretinal or intravitreal, is important. Once introduced in the body, the transplanted cells are monitored for their survival. The cells are also monitored to check if they maintain their state of differentiation. If undifferentiated cells have been introduced, whether they can differentiate \textit{in vivo} into the desired cell type needs to be monitored. The cells should also integrate well in the tissue. In the retina, it is important that transfected cells establish synaptic connections for restoration of retinal function. Similarly in the

\textbf{FIGURE 2-2:} Different steps in cell therapy
case of RPE cells, the cells should integrate and establish contact with photoreceptors in order to maintain their homeostasis. All these steps are important in ensuring that the transplanted cells function well in vivo and are a true substitute for the degenerated or damaged tissue.

Last but not the least transplanted cells should not cause any undesirable changes in the recipient. Cell therapy involves removal of stem cells from their normal niche and introduction into a new environment. Changes in the stem cell niche could lead to unsafe situations like uncontrolled cell division leading to tumor formation. The application of cell therapy to humans should be performed only after ensuring that the cell therapy is free of such safety issues and it restores normal functioning.

Sources of Stem Cells for Retinal Therapy

Both ocular and extraocular sources of stem cells have been explored for their potential to restore retinal function. The ocular tissues investigated so far are retinal cells, RPE cells, ciliary cells, iris pigment epithelial (IPE) cells and limbal cells. The advantage of using ocular cells is they arise from the same progenitor cells, with the exception of limbal cell, and share common pathways of differentiation during early development. These cells therefore would require less manipulation in vitro. The extraocular cells investigated so far are embryonic stem (ES) cells, bone marrow stem cells, cells from central nervous system (CNS) and cord blood cells. ES cells, bone marrow cells and cord blood cells have better capacity to self-renew, can differentiate into several cell types, are easier to culture and therefore might be preferred over ocular stem cells.

STEM CELLS FROM OCULAR SOURCE

Retinal Stem Cells

Retinal progenitor cells give rise to all cells of the retina. They generate ganglion cells, horizontal cells, cone photoreceptors and amacrine cells during early embryogenesis and rod photoreceptors, bipolar cells and Muller glia during late embryogenesis and the early postnatal days. While many studies have shown that a particular stem cell can be differentiated into a retinal progenitor cell or retinal neurons, only transplantations of fetal or neonatal retinal cells in degenerating retina have shown integration and at least partial restoration visual function, suggesting that committed retinal progenitors from fetal or neonatal cells are most suitable for therapeutic purpose. This can perhaps be attributed to the fact that immature neurons from fetal tissues have better ability to reconnect with neurons and cells from fetal tissue are already committed to a particular fate and require less manipulation in vitro to direct their differentiation.

Fetal retinal sheets consisting of retina and RPE have been transplanted in subretinal space of Royal College of Surgeons (RCS) rats, which is a model for retinal degeneration. These fetal sheets integrated well and restored normal morphology of rat retina. Functional studies were not performed in this report. Xenotransplantation of neonatal mouse retinal cells into opossum also resulted in integration of retinal cells into all layers of the retina and the transplanted cells expressed neuronal and retinal markers. This study indicated that the host age is important for integration, as cells injected in 5-10 days postnatal retina integrated well while those injected in older animals survived in vitreous but did not integrate. In another study, sheets of rat embryonic retinal cells were used for transplantation in rat model of retinal degeneration and it led to some restoration of visual function, as detected by electrophysiological experiments. The restoration was restricted only to
the superior colliculus region. A more systematic study in mouse to check cells at what stage are able to integrate in adult retina showed that postnatal P1-P7 retinal cells which express retina-specific transcription factor Nrl, but not embryonic cells, could integrate well in the retina. The integrated cells formed functional synaptic junctions and also improved visual function as seen by pupillometry and extracellular field potential recordings from ganglion cell layer. This study identified the specific ontogenic stage of transplanted cells that is important for integration of retinal cells and can restore retinal function.

Human studies have also been carried out which show quite encouraging results. Transplantation of fetal retina in patients with retinitis pigmentosa showed that fetal retina integrates well into the degenerating retina and can improve visual acuity. A recent report of clinical trial from the same group shows that transplantation of fetal retinal sheets led to improvement in visual acuity of 7 out of 10 patients suffering from RP and AMD. No adverse events were reported in these studies and the grafts survived well. This is encouraging although its application to large population could have ethical and practical problems. However with the information available now it might be possible to differentiate stem cells in vitro to a similar ontogenic stage before transplanting these cells into the retina.

Studies show that retinal stem cells (RSCs) present in neonatal retinas can certainly be isolated, propagated and differentiated in vitro to generate retinal cells. This is important, as it would be helpful if cells from one fetal retina could be used for several transplantations. Neonatal/fetal tissues would likely have less number of stem cells/progenitor cells and ability to increase their number before transplantation would increase success rate of this treatment. Using epidermal growth factor (EGF), retinal progenitors from neonatal rats could be differentiated into both early and late neuronal cells. Similar studies were also performed in pigs, where progenitor cells from neural retina of pig could be cultured in vitro and when injected subretinally in laser-injured retina, could integrate and express photoreceptor cells markers. Mouse retinal progenitors from postnatal day 1, when transplanted into hosts lacking rhodopsin, were able to develop into mature neurons, express recoverin, rhodopsin or cone opsin and integrate into the retina. Interestingly these cells could also rescue cells in the outer nuclear layer, with improvement in light-mediated behavior as compared to uninjected animals. On the other hand, subretinal injection of radial glial cells from retina of newborn mice into rd1 or VPP mice led differentiation of injected cells into either ganglion cells or glial cells. Another study has shown that incubation of mouse radial glia cells with FGF-2 and B27 also can lead to differentiation of these cells into photoreceptors with high yield. More extensive studies need to be carried out to investigate whether these cells are functionally as competent as normal retinal cells.

**RPE Cells**

RPE cells also have been investigated for their potential to generate retinal cells, as both neural retina and RPE develop from neuroepithelium and follow similar developmental signal during initial development. Indeed rat RPE cells from early embryonic stages have the potential to develop into retinal neurons. In the presence of bFGF, RPE cells from stages E12-E14 could differentiate into cells expressing markers of rod cells, amacrine cells and RGC cells. Although RPE cells appear to have the potential for differentiation into retinal cells, they are difficult to harvest, this might hinder their use for cell therapy.

On the other hand, homologous transplantation of RPE cells has shown promising results. Replacing degenerating RPE cells by transplanting healthy, autologous RPE cells from peripheral retina has
been used a therapeutic approach for treating AMD. Dissociated RPE cells as well as RPE explants from the mid-periphery have been transplanted in patients with neovascular AMD and this led to some improvement in visual acuity. The procedure however can lead to complications such as retinal detachment and improvement in visual acuity can be transient.

**Ciliary Stem Cells**

The ciliary margin zone in lower animals such as Xenopus, the adult ciliary margin zone harbors retinal progenitors, which are capable of regenerating all types of retinal cells throughout their life. A similar structure that ensures continuous regeneration of retinal cells is unfortunately not present in mammals but this observation prompted researchers to investigate the potential of ciliary body as a source of retinal progenitors. Studies indeed showed that ciliary epithelium of mouse, specifically the pigmented ciliary margin, harbors stem cells that could differentiate into photoreceptors, bipolar neurons and Muller glia. Such cells have also been reported in ciliary margin of rat and pig. These cells are also present in human ciliary body and could differentiate into early and late retinal neurons. Stem cells have been isolated from cadaveric human pars plana and pars plicata, from eyes from subjects as old as 70 years indicating that progenitor cells are present in the human retina throughout life. In vitro these cells could differentiate into all cell types of neural retina as well as RPE, although the frequency of each cell type varied. Moreover these cells could integrate into postnatal mouse retina and embryonic chick retina where they differentiated into photoreceptors. In mouse the percentage of photoreceptor precursors from pars plana increased significantly during retinal injury induced by N-methyl-N-nitrosourea, suggesting that in vivo the ciliary stem cells could indeed play a role in retinal repair. A similar phenomenon was observed in response to ganglion cell death after optic nerve axotomy. Ciliary epithelial cells can also be directed towards photoreceptor differentiation by transfection of transcription factor Crx. Further studies need to be carried to investigate whether these cells are functionally competent to replace retinal cells.

**Iris Stem Cells**

Adult iris tissue is easy to harvest by routine iridectomy and can express neuronal antigens when cultured in vitro, which makes it a viable option for generating photoreceptors. When cultured iris pigmented epithelial (IPE) cells were transfected with transcription factor Crx, expression of photoreceptor-specific genes was observed in IPE cells. Postnatal IPE cells, when co-cultured with embryonic retinal cells, were able to express photoreceptor and Muller glia-specific proteins, suggesting a potential of these cells for retinal cell therapy. IPE cells engineered to express pigment epithelium-derived factor (PEDF) were also able to protect degenerating photoreceptor in RCS rats, suggesting they can also exert a trophic effect for rescue of degenerating retina.

The potential of IPE as a substitute for RPE has also been investigated with promising results. Autologous transplantation of IPE in subretinal space in rabbit showed that IPE cells survive well in the subretinal space and also show fragments of rod outer segments in their phagosomes, suggesting that they could functionally replace RPE in degenerative diseases like AMD. Transplantation of autologous IPE cells harvested by iridectomy have also been transplanted subretinally in patients with RPE degeneration or after traumatic loss of RPE cells and this led to either improved or stable visual acuity. In addition IPE cells transduced with viral vector expressing BDNF can rescue photoreceptors against phototoxicity both in vitro and in vivo in rats.
**Limbal Stem Cells**

Limbal tissue surrounding the cornea harbors stem cells that normally regenerate the corneal epithelium. Limbal cells are easy to harvest, harbor stem cells and can be cultured *in vitro*, which makes them a good source of cells for cell therapy. Interestingly rat limbal cells have been directed to differentiate into a neural progenitors when incubated with noggin, an inhibitor of BMP-mediated signaling. Further studies showed that co-culture of limbal cells with postnatal day 1 retinal cells led to expression of photoreceptor-specific proteins such as opsin, rhodopsin kinase, arrestin and IRBP.40 These neural progenitors, when injected intravitreally in mice with retinal damage, were able to incorporate into the retina. Similar properties have also been observed in human limbal cells. Whether these incorporated cells are functional *in vivo* needs to be further investigated.

**STEM CELLS FROM EXTRAOCULAR SOURCE**

*Embryonic Stem Cells*

Embryonic stem (ES) cells have several advantages over adult stem cells. Embryonic cells are totipotent and can be differentiated into any other type of cell. They can also be cultured and expanded more easily than adult stem cells. It is however also associated with ethical issues. Due to debates on ethical issues on use of embryonic stem cells, research on ES cells is restricted or banned in some countries. Also, being allogogenous, once transplanted into a patient, embryonic stem cells could express MHC proteins and cause rejection of graft. Despite these problems, laboratory studies on mouse and human embryonic stem cells have proved valuable for providing information about differentiation of retinal cells, which can be extrapolated to differentiation of adult stem cells into retinal progenitor cells. These studies have helped in understanding the nature of molecular signals required for retinal development and show that the niche provided by the developing embryo is important for differentiation of retinal cells.

A structure resembling the eye has been generated *in vitro* from human embryonic stem cells by co-incubation with PA6 stromal cells and FGF-2, dexamethasone and cholera toxin. This structure had lens-like refractile structure surrounded by cells expressing markers of retinal cells, which in turn was surrounded by RPE-like cells. Thus the structure showed organized morphology resembling the structure of eye. Cells expressing markers of a particular type were clustered together although these clusters were not exactly arranged the way different cells are arranged in the eye. Further studies by the same group showed that further treatment of these cells with Wnt2b led to proliferation of retinal progenitor cells and when transplanted into the enucleated optic cup of chick embryos, they were able to form a single mature layer of RPE-like cells. The cells also differentiated into cells expressing markers of ganglion cells in some cases. Cells expressing retinal markers have also been generated by co-incubation of mouse ES cells with developing retina. Recent studies have used more defined factors and shown that mouse ES cells can be differentiated into retinal precursors in a step-wise manner. In this study mouse ES were incubated with cells with Wnt antagonist Dkk1 and nodal antagonist LeftyA to generate rostral brain progenitors, followed by treatment with activin and serum that led to differentiation of rostral cells into retinal precursors. These precursors generated cells with photoreceptor phenotype when co-cultured with embryonic retinal cells. These experiments suggest that ES cells are a feasible alternative for retinal cell transplantation.

Human ES cells have also been differentiated into retinal progenitors in a similar step-wise manner, using a different strategy. In this study, human ES cells on feeder cells were first treated with
noggin, followed by incubation with fibroblast growth factor (FGF) and epidermal growth factor (EGF) in serum-free medium. This treatment promoted differentiation of ES cells into neural progenitors and these neural progenitors also expressed several markers of retinal cells. In another study human ES cells were treated with noggin, Dkk1 and insulin-like growth factor (IGF) to generate embryoid bodies, followed by incubation with bFGF for three weeks to generate retinal progenitors. This treatment was more efficient and generated retinal progenitors with high efficiency, up to 80%. The cells were also able to integrate into degenerating mouse retina. In addition both human and mouse ES cells have been shown to differentiate into RPE and other types of neurons when cultured on denuded, gelatin-coated human amniotic membrane. This method suggests an alternative to use of xenogenic feeder cells as has been reported previously.

The studies mentioned above use fetal calf serum or fetal tissues as feeder layers to direct differentiation of ES cells into photoreceptors. The differentiation medium used here is not defined and would involve use of xenogenic agents and hence may not be suitable for transplantation in human patients. Recent study by Osakada and coworkers reported the use of a completely defined medium to generate photoreceptors and RPE cells from mouse, monkey and human ES cells. The authors used a combination of purified signaling molecules in a step-wise manner and combined this with selection of cells based on progenitor-specific markers at each step to finally generate photoreceptors from ES cells. They first generated neural retinal precursors from mouse ES cells using serum-free suspension culture in the presence of Wnt and nodal antagonists as described earlier. From these cells, retinal progenitors were selected based on expression of retinal progenitor marker Rx. These cells were further cultured on laminin-fibronectin coated dishes along with DAPT, an inhibitor of notch signaling. Around 22% of the treated cells expressed Crx, photoreceptor-specific marker and were post-mitotic. 10% of these cells expressed cone-specific markers. A further incubation of these cells with combination of aFGF, bFGF, taurine, sonic hedgehog and retinoic acid, led to generation of 17% cells that expressed rod-specific markers. A similar approach was also used for generation of human and monkey photoreceptors. RPE cells were also generated from monkey ES cells using defined medium, only this time selection was done for expression of Mitf, marker for RPE progenitor, instead of Rx. It remains to be seen whether these cells can establish connections with neurons and whether they are functionally active.

ES cells can also provide a niche for degenerating retinal cells that can prevent further damage under certain conditions. Mouse ES cells differentiated to neuronal lineages have been shown to delay retinal degeneration in mouse models. The ES cells differentiated into neuronal cells after removal LIF and addition of retinoic acid, these neuralised cells were introduced in mnd mice, which suffer from lysosomal storage disorder that causes retinal degeneration. These cells could integrate into the retina, reduce lysosomal storage bodies and delay photoreceptor degeneration. This suggests that neuralised ES cells could prevent or delay disease progression if not completely rescue the disease.

While use of ES cells for therapeutic purpose in humans is questionable at this stage, development of two important techniques that can reprogram differentiated adult cells into stem cells have caused excitement among scientists and such cells could be further differentiated into retinal progenitors using the information that is already available from research on embryonic stem cells. The first technique is that of somatic nuclear transfer, which involves transfer of nucleus from an adult cell into an enucleated oocyte (Figure 2-3A). The combination of factors present in the oocyte can reprogram the adult nucleus and the resulting cell acquires characteristics of a totipotent stem cell which, when transferred into a surrogate mother, can develop into a complete animal.
FIGURES 2-3A and B: Reprogramming of adult nucleus. A: Reprogramming by somatic cell nuclear transfer. B: Reprogramming by introduction of four transcription factors to generate induced pluripotent cells

sheep was the first animal developed by this technique. The technique although promising, again requires use of oocytes, which may not be ethically acceptable and the success rate of this technique is low.

The second and more recent breakthrough in stem cell biology is the generation of induced pluripotent cells (Figure 2-3B). For the first time scientists were able to completely dedifferentiate a differentiated dermal fibroblast to generate a pluripotent stem cell by transfection of four transcription factors; Oct3/4, Klf4, c-myc and Sox2. When introduced into a blastula, these cells could give rise to all tissues of the fetus, including germ cells, indicating that reprogrammed adult cells behaved like embryonic stem cells. This technique will allow generation of stem cells from patient’s own cells, which can be further manipulated to generate cells of our interest. It also does not require use of oocytes or embryonic tissue and the use of induced pluripotent cells should therefore be free of ethical issues. Use of these cells will also avoid graft rejection. Such cells can be induced into photoreceptors as described and then introduced into patients with retinal degeneration to prevent further damage.

Bone Marrow Stem Cells

Due to their plasticity, feasibility of using autologous cells and their ability for self-renewal, potential of bone marrow cells for regenerative medicine has been explored extensively for several disorders.
**Cell Therapy in Retinal Diseases**

*In vivo* bone marrow hematopoietic stem cells can differentiate into cells of lymphoid and myeloid origin while bone marrow mesenchymal cells form endothelial cells, chondrocytes, skeletal muscles and osteocytes. In addition *in vitro* they can also be differentiated into cardiocytes, renal cells, pancreatic cells and hepatocytes. Bone marrow cells can also differentiate into neurons *in vitro* and as retina is also of neural lineage, the potential of bone marrow cells has been explored for retinal cell therapy. In addition potential of bone marrow cells for revascularization of retina and for trophic support for survival retinal cells has also been explored.

Bone marrow cells can differentiate into retinal cells both *in vitro* and *in vivo*. When chimeric mice with hematopoietic cells expressing GFP, were subjected to laser-induced Bruch’s membrane rupture, GFP-positive astrocytes, vascular endothelial cells and RPE cells were found in the retina. Systemically injected bone marrow stromal cells also migrated to the subretinal space in rats with NaIO$_3^-$ induced RPE degeneration and expressed RPE65. These studies indicate a role for bone marrow cells in retinal wound repair *in vivo* and their ability to home the site of retinal injury. CD90$^+$ marrow stromal cells have also been used to generate retinal progenitor cells using a combination of activin A, taurine and EGF *in vitro*. After incubation with this cocktail, these cells expressed markers of photoreceptors such as rhodopsin, opsin and recoverin. When injected into the subretinal space of RCS rats, these cells integrated into the retina and formed structures similar to photoreceptor layer. However restoration of cone and rod function by these cells need to be further examined. Bone marrow stromal cells also acquired RPE-like characteristics when transduced with adenovirus and co-cultured with RPE cells. When injected subretinally into RCS rats, these cells integrated into host RPE and prevented further photoreceptor degeneration of RCS rats for up to two months after injection. This effect was enhanced when the stromal cells were transduced with PEDF prior to injection, suggesting a role for PEDF in this trophic support by stromal cells.

Interestingly bone marrow cells can also rescue retinal degeneration by contributing to angiogenesis in the retina. Lineage negative (Lin$^-$) hematopoietic cells contain a population of endothelial cells. Intravitreally injected Lin$^-$ cells incorporated into the retinal vasculature of neonatal mice and also in the vasculature of injury-induced angiogenesis in adults. Importantly these cells could also rescue retinal vascular degeneration in rd1 and rd10 mice, which are models of retinitis pigmentosa, and which in turn could rescue photoreceptors. The vasculature preferentially rescued cones from degeneration and this was accompanied by increased expression of anti-apoptotic genes. A detectable, although abnormal, electroretinogram recording was also observed in injected mice. Retinal vasculature thus appears to be an important regulator of retinal integrity and restoration of retinal vasculature could be a feasible approach for treating retinal degeneration.

**CNS Stem Cells**

In the adult central nervous system, stem cells and neural progenitors exist in the areas like ventricular zone, subventricular zone and hippocampus. As retina originates from CNS and retinal precursors develop from neural progenitors, it is logical to use neuronal stem cells (NSCs) for retinal repair. NSCs from hippocampus were able to incorporate into mechanically injured rat retina, although these cells differentiated into neuronal cells but not into photoreceptors. However in xenotransplantation of neonatal murine brain progenitor into opossum the murine cells were able to incorporate in opossum retina and expressed neuronal and retinal markers. Adult hippocampal neural progenitors cells have also been transplanted in opossum at different stages, from postnatal to adult, and these studies show that survival and integration of NPCs was influenced by age of the recipient and maximum integration was observed in the developing retina. These studies indicate
that the retina itself can provide the correct cues for differentiation of neuronal cells into retinal cells till a certain stage of development. The studies carried out using NSCs so far do not provide any evidence for functional rescue of retinal cells during retinal degeneration.

**Cord Blood Stem Cells**

Cord blood stem cells are another attractive source of stem cells that can be explored for regeneration of retinal cells. Cord blood cells are easily available and can be cultured *in vitro* for long periods. Like bone marrow cells, they are multipotent and can differentiate into a variety of cell types. Most importantly they can differentiate into neurons. Recently lineage-negative cord blood cells were also reported to undergo differentiation *in vivo* to generate cells expressing retinal markers, when they were injected into subretinal space in mice. Further studies need to be carried out to investigate whether these cells can integrate and generate functional equivalents of retinal cells.

**Future Perspectives**

Cell therapy holds great promise as potential therapeutic approach for treatment of retinal disorders. Studies carried out so far provide evidence that stem cells from a number of sources have the potential to differentiate into cells with retinal phenotype. These cells when transplanted in animal models can also survive and integrate into the retina in some cases but the evidence for restoration of retinal function is available only for a few of these studies. This suggests that more stringent tests investigating function of retinal cells should be performed in addition to investigating the expression of various retinal markers. Exactly which characteristics of transplanted cells and recipient’s retina are important for functional integration is not clear yet. But fetal and neonatal retinas probably hold the answers to these questions. Fetal/neonatal retinas provide both progenitor cells that can restore some visual function when transplanted into a degenerating retina and a niche that can differentiate stem cells into retinal cells. The challenge ahead of us is to generate retinal cells, which are at the appropriate stage of differentiation so that they are capable of restoring retinal function. At the same time caution should be exercised to ensure the safety of these cell therapies and to avoid undesirable outcomes of cell therapy. With the advances in stem cell biology, it is also now possible to generate patient-specific pluripotent stem cells that are capable of generating all types of cells, if the correct milieu is provided. It remains to be seen whether these cells can be coaxed *in vitro* to differentiate into retinal cells that can integrate and restore retinal function.

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Introduction

As the diabetic population burgeons globally, so will the unusual presentations of the disease become increasingly manifest. The retinopathy of diabetes will be no exception to this rule. This essay attempts to chronicle the various atypical manifestations of diabetic retinopathy (DR) hitherto reported. The protean manifestations can be due to the inherent variability of DR, systemic and ocular diseases that may modify its course or as a result of exceptional novel features.

The Inherent Variability of Diabetic Retinopathy

FLORID DIABETIC RETINOPATHY

A rare complication, occurring in less than 1% of cases of proliferative diabetic retinopathy (PDR), florid DR is a rapidly progressing, bilateral, severely ischemic retinopathy with poor vision that usually occurs in young, type 1 poorly controlled diabetic patients. Extensive panretinal photocoagulation with early vitrectomy when mandated will help improve their visual outcome.

FEATURELESS RETINA

Featureless retina is a unique, rare type of PDR wherein retinal neovascularization may present without the characteristic preproliferative background retinal lesions such as microaneurysms, hemorrhages, cotton-wool spots and intraretinal microvascular abnormalities. The absence of these features may be explained by the presence of extensive areas of capillary non-perfusion seen in these cases which leads to the disappearance of these lesions in these severely ischemic zones. Although it may appear atrophic at first glance, fluorescein angiography may reveal undetected areas of neovascularization with extensive capillary non-perfusion (Figures 3-1A and B).

PERIPHERAL ABNORMALITIES IN DIABETIC RETINOPATHY

Occasionally, cases of diabetic retinopathy (2-3%) show predominant involvement of the periphery with relative sparing of the posterior pole. Such patients are at risk of developing peripheral
Atypical Manifestations of Diabetic Retinopathy

FIGURE 3-2: Fundus photograph of an eye with massive deposition of hard exudates at the posterior pole

neovascularization that may be difficult to discern clinically (Figure 3-2). Neovascularization of the disc may occur despite adequate perfusion of the area centralis. A fibrovascular ridge at the ora was reported intraoperatively, in a series from Japan, in about half the eyes with PDR and peripheral avascularity. The ridge was noted to be strongly associated with the presence of neovascularization of the anterior segment. Peripheral new vessels were found emanating from the choroid by Ishibashi et al in an eye with PDR enucleated for neovascular glaucoma.

DIABETIC DISC EDEMA

Diabetic papillopathy (DP) is an edema of the optic nerve head that is typically transient, usually unilateral and associated with good vision in chronically diabetic patients. It has been described as the microangiopathy of DR manifesting on the optic nerve head. No association with age was reported in two studies.

It is important to be able to differentiate this entity from the more noxious pathologies like papilledema, malignant hypertension and non-arteritic anterior ischemic optic neuropathy (NA-AION) (Figures 3-3A to F). While the former two are essentially bilateral, the latter is usually unilateral. Papilledema may be confirmed by neuroimaging and a lumbar puncture, while malignant hypertension by a measurement of the blood pressure. NA-AION is distinguished from DP by the more severe visual loss, field defects, moderate to marked afferent pupillary defects and poorer visual outcome. Neovascularization of the disc can be made out by the radial arrangement of the new vessels and their intense leak on angiography (Figures 3-3G and H).

DIABETIC TRACTIONAL PAPILLOPATHY

Vitreous traction confined to the optic nerve head resulting in elevation of the disc tissue was demonstrated first by Kroll et al. Vitreous traction in these cases was explained on the basis of
FIGURES 3-3A TO H: (A) Fundus photograph of an eye with diabetic papillopathy with significant edema of the disc. (B) Fluorescein angiogram of the same eye showing mild leakage of the disc. (C) Fundus photograph showing an eye with malignant hypertension induced disc edema, shallow peripapillary and macular detachment with hard exudates in the form of a macular fan. (D) Fundus photograph of an eye with the pallid disc edema of anterior ischemic optic neuropathy. (E, F) Fundus photograph of the right and left eye respectively of a patient with the characteristic bilateral disc edema of papilledema. (G) Fundus photograph of an eye with massive neovascularisation of the disc secondary to proliferative diabetic retinopathy. (H) Fluorescein angiogram of the same eye demonstrating the intense leak of the neovascular complex.
the mechanical stretch of the axons and compromised blood flow. Vitrectomy was noted to improve both vision and visually evoked potentials.

**ATYPICAL COTTON-WOOL SPOTS**

Giant cotton-wool spots ranging in size from 2-4 disc diameters have been described. These were reported to occur after a stenosis or total obstruction of a first order arteriole at the site of its branching from the parent artery. There appeared to be an attempt to maintain circulation by the surrounding arterioles and venules with the venules displaying a reversal of blood flow. The cotton wool spots were observed to be flanked by arteriovenous communications.

**FOVEAL NEOVASCULARIZATION IN DIABETIC RETINOPATHY**

Neovascularization within the foveal ring is a rare occurrence that was reported initially by Finkelstein et al and later by Joondeph et al. These new vessels were noted to be nonprogressive, had good vision and associated with long standing diabetes (Figure 3-4). Midperipheral areas of neovascularization were noted additionally in most cases. This phenomenon was explained on the basis of there invariably always being some amount of capillary nonperfusion in the posterior pole.

![Fluorescein angiogram revealing foveal neovascularization along with neovascularization in the mid-periphery in a case of proliferative diabetic retinopathy](image)

**SPONTANEOUS REGRESSION OF PROLIFERATIVE DIABETIC RETINOPATHY**

Spontaneous regression of retinal neovascularization was first reported in three pregnant women with type 1 diabetes, none of whom had a significant reduction in glycemic levels. Reperfusion of the ischemic areas was noted on angiography. Similar spontaneous regression of new vessels has been documented with amelioration of blood sugar levels and at the end of a pregnancy. Given the extreme rarity of this scenario, panretinal photocoagulation remains the standard of care for high-risk PDR.
Systemic Diseases Affecting Diabetic Retinopathy

**CAROTID OCCLUSIVE DISEASE**

Diabetic retinopathy has for long been known to be affected by carotid occlusive disease. Gay et al\textsuperscript{19} and later Moss et al\textsuperscript{20}, in the Wisconsin Epidemiological Study of Diabetic Retinopathy, proposed that it may exert a protective influence on the course of DR.

**LIPEMIC RETINOPATHY**

A milder form of lipemia retinalis, “lipemic diabetic retinopathy” occurs when serum lipids, especially triglycerides, increase in a diabetic patient. The posterior pole is characterized by excessive deposition of hard exudates. Reduction of such extensive deposition of exudates may be achieved with statins, which may however not translate into visual improvement.\textsuperscript{21,22}

Ocular Diseases Affecting Diabetic Retinopathy

Moss et al\textsuperscript{20} and Dogru et al\textsuperscript{23} showed that myopia was protective against the progression of DR to PDR. Even in non-myopes with diabetes, eyes with retinopathy had shorter axial lengths than those without retinopathy.\textsuperscript{24} The mechanisms suggested have been reduced ocular blood flow, thinning of retina in the myopic eye improving oxygen diffusion, and better pressure dissemination by the arteriolar network.\textsuperscript{25,26}

The severity and progression of DR is also mitigated by glaucoma, which may be related to the retarded metabolic activity secondary to the ganglion cell loss and reduced blood perfusion in glaucoma.\textsuperscript{27} Optic atrophy has also been shown to similarly retard DR progression.\textsuperscript{28} Total posterior vitreous detachment is also known to slow the progression of retinopathy.\textsuperscript{23} Patients with retinitis pigmentosa, owing to the reduction in photoreceptors, demonstrate a low rate of DR progression.\textsuperscript{29}

Miscellaneous

Assymmetric DR, reported in about 5 to 10\%, has been defined as PDR in one eye and nonproliferative DR or no retinopathy in the fellow eye for a period of at least 2 years.\textsuperscript{30,23} The pathologies mentioned in the section above retard DR progression while cataract surgery and vein occlusions tend to faster progression.

Conclusion

The identification of the rarer and unusual presentations of diabetic retinopathy are important, given the rising incidence and prevalence of this disease world over. Uncommon and atypical presentations of the disease may, in addition, pave the way for newer treatment modalities for this malady.

References

Anti-VEGF Therapy in Proliferative Diabetic Retinopathy
Introduction

Neovascularization is one of the key morbid manifestations of ocular pathologies, especially diabetic retinopathy (DR). The current gold standard for effective therapy in proliferative diabetic retinopathy (PDR) is panretinal photocoagulation (PRP), but associated with inherent tissue destruction. Hence, the need to investigate novel therapies that may yield similar, if not greater efficacy associated with less tissue damage.

Neovascularization and VEGF—The Nexus

The stimuli for ocular neovascularization are multiple, though ischemia has been implicated primarily.1 The microvascular occlusion, one of the pathophysiological hallmarks of diabetic retinopathy, results in ischemia-driven release of Vascular Endothelial Growth Factor (VEGF).1,2 VEGF causes various events at the microvascular level, namely increased vascular permeability leading to diabetic macular edema, and formation of new blood vessels or the proliferative stage of DR. Intraocular VEGF levels correlate well with the severity of neovascularisation in PDR.3 Essentially a peptide growth factor, alternative messenger RNA splicing and post-translational modification produces at least 6 different VEGF isoforms, of which VEGF-165 is the major pathogenic form. VEGF acts by binding to the 2 membrane-bound tyrosine kinase VEGF receptors (VEGFR-1 and VEGFR-2). Neovascularization is largely due to VEGFR-2 blockage. The ligand binding results in dimerization and phosphorylation of the receptor with activation of intracellular signaling mechanisms leading to vascular endothelial cell proliferation and migration.4

A number of anti-VEGF therapies are currently being investigated and are under trial.

The Anti-VEGF Triumvirate

The three anti-VEGF agents in use are:

i. Bevacizumab (Avastin)—A 149-kDa humanized, monoclonal, recombinant full-length antibody. It has approval for use as an intravenous chemotherapeutic agent in the treatment of colorectal cancers.5 It binds all the VEGF isoforms. Although not approved for intraocular use, its low-cost high efficacy profile has made it the most popular anti-VEGF agent today.6 The commonly used dose for injection is 1.25 mg/0.05 ml.

ii. Ranibizumab (Lucentis)—A 48-kDa humanized, monoclonal, recombinant antibody fragment (Fab). It has gained approval for use as intravitreal medication for neovascular age related macular degeneration (ARMD). 0.5 mg/0.05 ml was determined to be the most efficacious dose.7

iii. Pegaptanib sodium (Macugen)—A pegylated RNA aptamer, it specifically binds the VEGF-165 isoform.8 The first anti-VEGF agent to obtain FDA approval for intraocular use (in exudative ARMD). It is administered in a dose of 0.3 mg/0.09 ml.

The Role of Anti-VEGF Agents in PDR

As stated before, owing to its low-cost, ease of access and high efficacy, most of the evidence in literature for the use of anti-VEGF agents in PDR stems from reports on bevacizumab.9,11-15
FLORID PDR/PDR WITH MASSIVE NEW VESSELS

Often cases with florid PDR or massive neovascular complexes are unsuccessfully treated with a regular full-scatter panretinal photocoagulation (PRP), necessitating repeated treatment. Anti-VEGF therapy, in the form of bevacizumab, as demonstrated by Avery et al, can regress new vessels. In a subgroup analysis of cases of diabetic macular edema treated with pegaptanib sodium (Macugen), regression of coexistent neovascularisation was noted too. Regression of these new vessels has been noted to occur within days. These agents can thus be used as primary therapy or in combination with PRP to treat neovascular complexes, especially large and widespread ones. It is prudent to follow-up anti-VEGF injections, with a regular PRP for long-term stability, the advantage accrued being in the rapid control over the neovascularisation as well as the reduced area and episodes of retinal photocoagulation (Figures 4-1A and B).

POST-PRP REFRACTORY PDR

As a corollary to the clinical scenario portrayed above, PRP may fail to regress new vessels or they may continue to recur despite maximal laser photocoagulation. As Avery et al, Jorge and workers have shown, bevacizumab may be employed to regress recurrent neovascularisation in cases refractory to PRP (Figures 4.2A and B).

VITREOUS HEMORRHAGE (MOBILE)

Fresh, mobile, dispersed vitreous hemorrhage may be contained with intravitreal bevacizumab. It is believed that the recurrent bleeds that contribute to the chronicity of such hemorrhages may be mitigated by the regressive effect of the anti-VEGF agents on the neovascular sprouts. Preventing continued hemorrhage can allow the eye to recuperate from a single hemorrhagic episode. Careful upright positioning, close follow-up with opportunistic application of laser photocoagulation to retina uncovered by a receding vitreous hemorrhage may help in the early rehabilitation of these patients. Anti-VEGF therapy, it needs to be emphasized, is unlikely to be of much use in cases of organized or chronic vitreous hemorrhages, for which vitrectomy is the only practical option.
FIGURES 4-2A AND B: (A) A persistent large neovascular vessels with preretinal hemorrhage despite adequate panretinal photocoagulation. (B) Significant regression of the new vessels post-injection bevacizumab.

FIGURES 4-3A AND B: (A) A case with new vessels overlying a diabetic tractional detachment. (B) Regression of the neovascularization with minimal conversion to fibrous tissue one week after intravitreal bevacizumab injection administered as a preoperative adjuvant.

**AS A PREOPERATIVE ADJUVANT PRIOR TO VITRECTOMY FOR DIABETIC MACULAR TRACTIONAL RETINAL DETACHMENT (TRD) WITH NEOVASCULARIZATION**

Vitrectomy for diabetic TRD’s is often complicated by the presence of active neovascular fronds astride the detachments that lead to hemorrhages and make membrane peeling a hazardous task. A preoperative injection of an anti-VEGF agent such as bevacizumab, can regress the neovascular tissue facilitating vitrectomy and membrane peeling significantly (Figures 4-3A and B). However, one needs to ensure that the time span between the injection and vitrectomy is kept short, preferably 3–7 days. Delaying the vitrectomy beyond 2 weeks entails the risk of excessive fibrosis (Figures 4-4A and B). The epiretinal membranes may become tougher and more adherent to the retina, while the detachments themselves may increase in size.

**PDR WITH NEOVASCULARIZATION OF IRIS (NVI) / NEOVASCULAR GLAUCOMA (NVG)**

Rubeosis in cases of PDR may also be tackled with injections of anti-VEGF such as bevacizumab either by intravitreal or intracameral administration (Figures 4-5A and B). More often than not,
Anti-VEGF Therapy in Proliferative Diabetic Retinopathy

FIGURES 4-4A AND B: (A) A diabetic macular tractional detachment with marked neovascularization. (B) Excessive fibrosis with complete regression of the neovascular tissue noted 1 month after intravitreal bevacizumab injection.

FIGURES 4-5A AND B: (A) Neovascularization of the iris in a case of proliferative diabetic retinopathy. (B) Significant regression of the iris new vessels following an intravitreal injection of bevacizumab.

however, if the ischemia is enormous, these injections have only a transient effect-regressing the rubeosis rapidly albeit for a short while. They thus need to be supplemented with the long-term effect of PRP. They are useful, as a preoperative adjunct to surgery, in cases with new iris vessels, such as prior to vitrectomy (as stated in the previous section), silicon oil removal, trabeculectomy for neovascular glaucoma and cataract surgery. Pegaptanib has also been shown to transient regression of rubeosis.16

PDR WITH CSME

Anti-VEGF therapy has the advantage of being efficacious against neovascularisation as well as macular edema.24 All the three anti-VEGF agents (Bevacizumab, Ranibizumab, Pegaptanib Sodium) have been shown to have a beneficial effect on diabetic macular edema.17,18,19 There can be a concomitant regressive effect on the neovascularization too, in cases of PDR with DME.10 While these reports profess multiple injections to treat DME, a single injection may be followed up with a reduced
macular grid photocoagulation. This method appears to avoid the negatives of multiple injections as well as extensive macular photocoagulation for DME.

**Conclusion**

The promise of these anti-VEGF injections needs to be balanced against the problems of repeated injections such as endophthalmitis, cataracts, retinal detachments, vitreous hemorrhage. Although intravenous bevacizumab chemotherapy was associated with systemic problems like hypertension, thromboembolic events, myocardial infarction, gastrointestinal perforation and death, the vastly reduced intraocular dose sequestered into the vitreous cavity helps mitigate this risk. However, trace plasma levels of these anti-VEGF drugs have been noted post-intravitreal injections suggesting that systemic absorption and its attendant perils, need to be watched for, especially in high-risk patients. Hence one needs to temper enthusiasm towards such invasive therapy in favour of a more conservative practice pattern.

**References**

Chapter 5

Vascular Endothelial Growth Factor: Inhibitors in Age-related Macular Degeneration
Introduction

Age-related macular degeneration (AMD) is associated with gradual progressive visual decline as a consequence of dysfunction of the central retina, retinal pigment epithelium and choroid in older adults. The disease has been traditionally classified as early and late stages.

The early stages consist of alterations in the color of the macular pigment epithelium, hypo or hyperpigmentation, and the presence of drusen, greater than 125 microns in diameter. They have modest visual symptoms including micro-scotomata, reduced contrast sensitivity, metamorphopsia and nyctalopia.

The exudative phase is typically late in onset, occurring in eyes with high-risk characteristics including the presence of extensive soft drusen, Bruch’s membrane thickening and focal hyperpigmentation. There is rapid loss of vision over 6-12 months and formation of a central disciform scar. Without intervention, the visual acuity generally decreases to the range 20/200 or worse, 12 months following the onset of this phase.

Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) plays a principal role in the neovascular forms of age-related degeneration. It causes endothelial proliferation, migration and new capillary formation inducing angiogenesis. It also enhances vascular permeability.

There are 6 different isoforms of VEGF having 121,145,165,183,189 and 206 amino acids. VEGF 165 is thought to be predominantly responsible for pathological neovascularization and exists in both soluble and bound forms.

Its function at the retinal pigment epithelial level is poorly understood. It probably plays a role as a vascular survival factor for the choriocapillaries as well as maintainence of fenestrations in the choriocapillaries through directed secretion from the basal portion of the pigment epithelium.

VEGF Receptors

VEGF has two receptor tyrosine kinases: VEGFR-1 and VEGFR-2 through which it exerts its action. VEGFR-1 is upregulated by a hypoxia–inducing factor dependent mechanism (HIF). The receptor undergoes weak tyrosine autophosphorylation in response to VEGF. It is thought to be a decoy receptor rather than a mitogenic stimulus. It causes down-regulation of the activity of VEGF by sequestering and rendering the factor less available to VEGFR-2.

VEGFR-2 binds VEGF with lower affinity relative to VEGFR-2 and is felt to be a major mediator of mitogenic, angiogenic and permeability enhancing effects of VEGF.

In addition, there appear to be several other receptors on tumors and endothelial cells that bind VEGF principally neuropilin (NRP1 and NRP2). They may induce neuronal guidance and are thought to be specific for VEGF 165.

The permeability changes resulting from VEGFR-2 are mediated by endothelial nitric oxide synthetase-based generation of increased nitric oxide levels and associated calcium flux.

These effects are reversed by the indirect inhibition of VEGF effects through modulation of ICAM, or indirect effects on nitric oxide phosphorylase, nitric oxide synthetase, or protein kinase C, another modulator of permeability.
There are a class of compounds called Aptamers, which are chemically synthesized single strand nucleic acids either DNA or RNA, that bind to target molecules with high selectivity and affinity leaving non-targeted protein functions intact. Other methods include inhibition of tyrokinase receptors VEGFR-1 and VEGFR-2 either by systemic administration or gene transfer.

We will now be discussing the various anti-vascular endothelial growth factors in current use.

**Pegaptanib Sodium (Macugen™)**

Pegaptanib (Macugen) is a selective anti-VEGF165 pegylated (two 20-kD polyethylene glycol molecules attached in each end) and fluorinated sugar backbone 28-mer RNA aptamer. It inhibits pathologic angiogenesis with associated leakage and spares physiologic vasculature.\(^5,6\)

Aptamers are synthesized by SELEX (systematic evolution of ligands of exponential enrichment). SELEX is a combinatorial chemistry methodology. This method uses *in vitro* selection to evolve the best inhibitor to a target.\(^5\) It is given by intravitreal injections and its plasma concentration reflects its vitreous concentration by a factor of 1 per 1000 to 1 per 350. Its vitreous half-life is about 4 days and with the doses tested therapeutic level concentrations are attained for about 6 weeks after a single injection.

**Clinical Trials**

Phase III studies were performed through two simultaneously conducted, identically designed, large, multicentric, prospective, randomized, double-masked, dose-ranging trials in patients with broad spectrum of vision and sub-foveal types of choroidal neovascular membrane (CNV) subtypes of AMD called VEGF inhibition.

**VISION Trial (Studies in Ocular Neovascularization)**\(^7\)

The first trial consisted of 586 patients at 58 sites across North America. The second trial included 622 patients at sites located around the world. The 1208 patients from both studies were randomized 1:1:1:1 to receive 0.3 mg of pegaptanib, 1.0 mg of pegaptanib, 3.0 mg of pegaptanib, or sham injection. Patients received an injection of pegaptanib or sham injection every 6 weeks for 48 weeks. Four patients were not included in the final analysis because of insufficient baseline assessments. The primary efficacy endpoint was measured by the percentage of patients losing less than 15 letters at week 54. Efficacy was demonstrated in all of the pegaptanib groups (\(P < 0.001\) for 0.3 mg and 1.0 mg of pegaptanib, and \(P = 0.03\) for 3.0 mg of pegaptanib compared with sham injections). Seventy percent of the patients in the lowest efficacious dose (0.3 mg) group lost less than 15 letters at week 54 versus 55% in the sham group. The risk for severe visual loss of greater than 30 letters dropped from 22% to 10% in patients receiving 0.3 mg of pegaptanib compared with sham. Thirty-three percent of patients maintained or gained visual acuity from baseline over the course of the study, compared with only 22% with sham injection (\(P = 0.03\)).

In another study Quiram PA et al found that Pegaptanib as primary therapy for naïve CNV lesions offers a 90% rate of improvement or stabilization of vision-outcomes that exceed those reported in the VISION trial.\(^8\)
Safety Profile

The most frequent potential VEGF-inhibition-related adverse events, such as ischemic coronary artery disorders, vascular hypertensive disorders, thromboembolic events, heart failure, and serious hemorrhagic events, were comparable between the treatment and control groups and all less than 10%. Most common effects were eye pain, floaters, punctate keratitis, non-traumatic cataracts, anterior segment inflammation, vitreous opacities, etc. The serious adverse effects were endophthalmitis, traumatic cataracts and retinal detachments.7

Retinal pigment epithelium (RPE) tear is a rare complication and optical coherence tomography (OCT) imaging of eyes following Pegaptanib therapy may be helpful in identifying this complication. Patients with AMD, especially those with occult CNV and fibrovascular pigment epithelial detachment (PED) receiving pegaptanib therapy should be monitored for RPE tears, which may warrant deferral of further injections.9

Pegaptanib Use in the Presence of Photodynamic Therapy and Ranibizumab

Though ranibizumab has generated considerable excitement because this is the first time mean visual acuity improvement has been noted in wet AMD treatment.10 A recent exploratory analysis of the Pegaptanib VISION trials showed that there is an enhanced efficacy associated with early treatment of neovascular AMD and that about 20% of patients in the treatment group may experience significant vision gain.11 These numbers are close to the 25% of vision gain that was experienced in the MARINA trial of ranibizumab.

The overall magnitude of the efficacy results is very similar to the PDT trials and question why there is so much enthusiasm about a treatment that entails intravitreal injections every 6 weeks instead of PDT every 12 weeks. Truly, PDT is not equally efficacious across the lesion subtypes and sizes, whereas Pegaptanib has effect with all lesion subtypes.

Ranibizumab

INTRODUCTION

Choroidal neovascular (wet) age-related macular degeneration is becoming more prevalent worldwide as life expectancy continues to increase. Ranibizumab (Lucentis(TM) Genentech, South San Francisco, CA) is a monoclonal antibody fragment (Fab) directed towards all isoforms of VEGF-A that was specifically designed to target wet AMD. The human antibody fragment is produced by an E. coli expression system and has a molecular weight of 48kD allowing for excellent retinal penetration. The actions of ranibizumab result in reduced cell proliferation; reduced formation of new blood vessels, and minimization of vascular leakage.12 It was approved by the US Food and Drug Administration (FDA) for the treatment of AMD in June 2006.13

CLINICAL TRIALS

In December 2005, Genentech submitted a Biologics License Application to the FDA for the use of ranibizumab in the treatment of neovascular wet AMD based on 1-year clinical efficacy and safety
data from the two pivotal phase III trials, ANCHOR and MARINA, and the phase I-II FOCUS trial. The efficacy of ranibizumab has been studied in these clinical trials having the same primary efficacy end point, the proportion of patients losing <15 letters from baseline at 12 months (Early Treatment of Diabetic Retinopathy Study chart). The multicenter, Phase III, randomized, double-blind, sham-controlled, 24-month clinical trial evaluated ranibizumab 0.3 and 0.5 mg with minimally classic or occult choroidal neovascularization (CNV) associated with ARMD. Ranibizumab showed loss of less than 15 letters in visual acuity in 90% of the patients as compared to 53% in sham.

A 2-year, Phase I/II, single-masked (masked patient and visual acuity examiner, unmasked investigator), multi-center trial evaluated the tolerability and efficacy of the combination of ranibizumab 0.5 mg and verteporfin photodynamic therapy (PDT) compared with verteporfin PDT alone with predominantly classic CNV. Finally, an international Phase III, double blind, active-controlled study compared ranibizumab 0.3 and 0.5 mg with verteporfin PDT with predominantly classic lesions associated with CNV secondary to ARMD. The results showed loss of less than 15 letters in visual acuity in 64% of patients undergoing PDT compared to 96% of those with Lucentis. The findings of these 3 large clinical trials suggest that ranibizumab was effective and well tolerated in patients. The benefits apply to all angiographic subtypes of neovascular AMD and across all lesion sizes. Although the pivotal phase III trials (MARINA and ANCHOR) used monthly injections of ranibizumab for 2 years, the ongoing PIER PrONTO, and SAILOR trials are investigating less frequent dosing regimens, and preliminary results from the PrONTO study suggest that fewer injections will most likely result in visual acuity improvements similar to the results from the phase III trials. When comparing the ANCHOR results with the FOCUS results, it also becomes apparent that the combination of ranibizumab with PDT does not necessarily result in better visual acuity outcomes, and the use of PDT may even reduce the visual acuity benefits achieved with ranibizumab alone. It seems unlikely that combination therapy provides any significant advantage over ranibizumab alone unless the combination of PDT and ranibizumab can decrease the need for frequent retreatment. The results from the PrONTO Study already suggest that less frequent treatment with ranibizumab is possible by using a variable dosing regimen with OCT.

SAFETY PROFILE

Ranibizumab also seems to be safe, with the 2-year MARINA data showing no increase in the incidence of systemic adverse events that could be associated with anti-VEGF therapy, such as myocardial infarction and stroke. There was a hint of a safety concern, however, in the pooled 1-year safety results from the MARINA and ANCHOR trials. Although the combined rate of myocardial infarction and stroke during the first year of the ANCHOR and MARINA trials was similar in the control and the 0.3 mg ranibizumab arms (1.3% and 1.6% respectively), these adverse events were slightly higher in the 0.5 mg ranibizumab arm (2.9%). These differences are not statistically significant, however, and probably do not represent a dose-dependent increase in risk because the 2-year results from the MARINA trial with the same monthly injection regimen showed no increased risk of thromboembolic events. The most common ocular complaints of patients receiving ranibizumab injections in randomized clinical trials were transient conjunctival hemorrhage, vitreous floaters, intraocular inflammation, increased intraocular pressure and eye pain. The rates of serious adverse events such as retinal detachment, cataract and endophthalmitis were similar to those that have been reported with other intravitreal injections and patients should always be treated under strict aseptic conditions to reduce this risk.
Bevacizumab (Avastin)

Bevacizumab is a full-length recombinant, humanized antibody of a molecular weight of 149-kDa binding to all VEGF isoforms. Since the binding affinity of bevacizumab is about 100 times lower than that of ranibizumab (N. Ferrara, unpublished data), a comparison of clinical efficacy is difficult without clinical trials. The drug was originally developed to target pathologic angiogenesis in tumors and was approved by the FDA for the treatment of metastatic colorectal cancer.

The intravitreal use of bevacizumab is off label. There is no long-term information on safety and efficacy, although the preliminary data are very encouraging. When used on patients with wet age-related macular degeneration (AMD) who continued to deteriorate anatomically or visually after photodynamic therapy (PDT) with or without pegaptanib (Macugen), a non-randomised trial showed highly significant improvement in vision at 4 and 8 weeks after treatment with intravitreal bevacizumab.19

There are several other case series, and a pilot RCT with short follow-up supporting the role of bevacizumab in the treatment of wet AMD. However, it remains unlicensed, and there are no large randomised trials to date. There are no true dose escalating/ranging studies for intravitreal bevacizumab. As such the optimum dose and dose-frequency for intravitreal bevacizumab remain unknown.

Due to its substantially larger molecular weight, local and systemic clearance of bevacizumab may be delayed, resulting in an extended durability of the treatment, but associated with higher systemic toxicity.21

Avery et al. described complete resolution of retinal edema in 37% of eyes 4 weeks after initial injection of bevacizumab and in 49% of eyes 8 weeks after initial injection when treated monthly on an as-needed basis. Rich et al also treated 53 eyes on an as-needed basis, reporting decrease in mean central retinal thickness by 99.6 µm. Spaide et al. also reported statistically significant improvement in central retinal thickness measurements for 3 months after monthly bevacizumab injections.

A recent international survey of over 7000 injections in more than 5000 patients indicated hypertension at a rate of approximately 2 in 1000 and other systemic complications less than 1 in 1000 for each (cerebrovascular accidents, myocardial infarctions, and thrombo-embolic event); these complications might or might not be related to the intravitreal use of bevacizumab. However, such surveys of self-reported complications are likely to under-report their occurrence.

Anecortave Acetate

Anecortave acetate (AA) is a new molecular entity currently being evaluated in clinical trials for its ability to protect at-risk eyes of patients with unilateral CNV from progressing to bilateral CNV and preserving visual function. AA was created by modifying the chemical structure of cortisol acetate. Three modifications were made to cortisol to generate AA. The 11β-hydroxyl group, which is essential for glucocorticoid activity, was removed from cortisol. A double bond between C9 and C11 was added to prevent enzymatic rehydroxylation at C11, and acetate group was added at C21 to enhance ocular penetration and provide ideal physical chemical properties for the administration of a slow release depot.
MECHANISM OF ACTION
AA inhibits the angiogenic proteolytic cascade by inhibiting the expression of urokinase plasminogen activator and matrix metalloproteinases and up-regulating the expression of the urokinase plasminogen activator inhibitor-1. In addition, AA inhibits vascular endothelial cell proliferation and migration. IGF, insulin-like growth factor; VEGF, vascular endothelial growth factor.24

MODE OF ADMINISTRATION
Although several routes of drug administration have been studied for best delivery of AA to the retina and choroid to target CNV associated with AMD, a unique procedure was developed to ensure localized delivery.25 Therapeutic level of the drug is achieved only when AA is placed into direct contact with the posterior scleral surface. The drug is delivered as a periocular posterior juxtascleral depot using a specially designed blunt-tipped cannula25 to deliver the drug onto the outer surface of the sclera over the macula. Re-treatment is necessary after 6 months.

CLINICAL TRIALS
The monotherapy study evaluated the safety and efficacy of AA, 30, 15, and 3 mg, compared with placebo, in 128 patients exhibiting CNV secondary to AMD. In this study the 15 mg dose was demonstrated to be an effective primary therapy for the treatment of CNV, as determined by visual function and lesion growth. The percentage of patients that maintained vision with administration of the drug every 6 months for 1 year was significantly greater for AA, 15 mg, compared with placebo (P = 0.0323). This was supported by a statistically significant difference in the percentage of patients who maintained vision at the 2-year time point (73% versus 47%). Furthermore, AA was superior to placebo in patients with predominantly classic lesions at baseline, with 80% versus 42% maintaining vision.26,27

A study of the safety and efficacy of AA when used in conjunction with verteporfin PDT demonstrated that it is safe to use both treatments concurrently for treatment of CNV. In the third study, AA (15 mg) was compared with verteporfin PDT in this study of patients with predominantly classic subfoveal CNV. Five hundred thirty patients were enrolled and randomized to treatment with AA, 15 mg, or PDT. In the AA group, the drug was administered by posterior juxtascleral depot initially and at Month 6, along with an initial sham PDT, which was repeated every 3 months if there was evidence of leakage based on fluorescein angiography. The PDT treatment group received up to four PDT treatments at 3-month intervals based on leakage by fluorescein angiography, along with a sham posterior juxtascleral depot at the beginning of the study and at month 6. The percentages of patients exhibiting less than three logMAR lines of visual acuity loss from baseline were 44.9% and 48.6%, respectively, in the AA and PDT treatment groups (P = 0.4305) 1 year after initial treatment. AA was statistically equivalent to PDT in terms of preventing vision losses in this study,28 although the primary non-inferiority statistical outcome was not met. In addition, patients in the AA group who had no reflux of the drug on administration and had retreatment within 6 months from the initial treatment showed 57% responders compared with 49% in the PDT treatment group.

AA suspension (15 and 30 mg) is currently under evaluation to reduce the risk of disease progression in patients with dry AMD (the AART study). The study’s objective is to determine the safety and efficacy of AA suspension when used to treat patients with non-exudative AMD who are at risk of progressing to exudative AMD.
Squalamine Lactate

Squalamine lactate (Evizon, Genaera, Plymouth Meeting, Pennsylvania) is a systemically administered antiangiogenic compound that is among the group of drugs being investigated for neovascular age-related macular degeneration. The first drug candidate from the aminosterol class, it has a unique and multifaceted mechanism of action.

ORIGIN

Squalamine lactate (3b,5a,7a,24R)-3-[3-[(4-aminobutyl) amino]propyl]amino]-7-hydroxy-cholestan-24-yl hydrogensulfate di[(S)-2-hydroxypropanoate] (salt) was isolated by extraction and purification of the natural substance from the dogfish shark liver.

The natural and synthetic forms of the aminosterol free-base have been proved to be structurally identical. The investigational drug is produced by chemical synthesis.29-32

MECHANISM OF ACTION

Squalamine inhibits angiogenesis by inhibiting the development of new vessels and inducing the regression of newly developed vasculature. This effect seems to be mediated by a multifaceted blockade of vascular endothelial cell activation and vessel development by multiple mitogens (including VEGF, basic fibroblast growth factor, and platelet-derived growth factor).33

A. Cellular uptake: The basis for selectivity. Caveolae are small invaginations that occur on the cellular membrane of endothelial cells. Activated endothelial cells (following exposure to VEGF) are inhibited by squalamine in a dose dependent fashion. Endothelial cells that have not been activated do not respond to the drug and this may protect normal vascular structures. The contrast between the relatively brief intravenous half-life of squalamine compared with the long intracellular half-life of the drug may help explain the favorable adverse event profile of the drug seen in human trials.

B. Effect on intracellular signal transduction: The squalamine-induced binding and redistribution of intracellular calmodulin correlates with changes in calcium-calmodulin intracellular signal transduction that is involved in down-regulating endothelial cell activation. These changes include dephosphorylation and loss of function for myosin light chain kinase; inhibition of VEGF stimulation of MAP kinases p42 (ERK-2)–p44 (ERK-1); inhibition of actin filament formation; focal adhesion kinase and stress-activated protein kinases (SAPK1/JNK and SAPK2/p38); and inhibition of expression of integrins.33

METHOD OF DELIVERY

In clinical trials for wet age-related macular degeneration, squalamine is administered as an intravenous infusion. A peripheral vein is chosen for the infusion site and a 0.25 mg/mL solution of squalamine is administered over 10 to 40 minutes (approximately 1–2 mg/min).

CLINICAL TRIALS33

Study 106

Study MSI-1256F-106 was the first study of squalamine in exudative age-related macular degeneration that involved humans subjects were provided with weekly doses of 25 mg/m² (approximately
equivalent to a 42.5 mg fixed dose) and 50 mg/m² (approximately equivalent to an 85 mg fixed dose). If no unacceptable or dose limiting toxicities were observed in the first three subjects in each of the treatment groups, then additional subjects were to be enrolled. Subjects received weekly infusions of squalamine for 4 weeks and then followed for an additional 3 months. During the trial, there was a modification in infusion rate and concentration. During the trial, there was a modification in infusion rate and concentration. Preliminary results of the change from baseline VA in subjects grouped by CNV subtype in the study eye showed six (22%) subjects with classic CNV and four (33%) subjects with occult CNV demonstrating positive VA gains. Twenty-one (78%) subjects with classic CNV and eight (67%) subjects with occult CNV demonstrated stable VA results at study month 4. When VA was evaluated by dose group in the study eye, four (21%) subjects in the 25 mg/m² dose group and six (30%) subjects in the 50 mg/m² dose group demonstrated a positive result at the study month 4 follow-up visit. VA was stable in 15 (79%) subjects in the 25 mg/m² dose group and in 14 (70%) subjects in the 50 mg/m² dose group. Evaluations of color photographs and fluorescein angiography revealed no signs of retinal or choroidal toxicity.

Study 207

Study MSI-1256F-207 was conducted to assess the pharmacokinetics of weekly infusions of squalamine lactate in subjects with wet age-related macular degeneration. Subjects were assigned to three treatment groups and received doses of 40 mg (N = 6), 20 mg (N = 6), or 10 mg (N = 6) of squalamine weekly for 4 weeks. Plasma drug concentration curves were generated from samples collected during visits for the first and fourth weekly infusions.

Study 208

Study MSI-1256F-208 was designed as a 45-subject masked, randomized, controlled clinical trial of three doses of squalamine lactate used in conjunction with photodynamic therapy (PDT) with verteporfin. Subjects were randomly assigned to receive 10, 20, or 40 mg of squalamine on weeks 1, 2, 4, and 5 of the trial, followed by monthly infusions to total study duration of 6 months. PDT was performed on all subjects during week 3 of the trial, and could then be repeated if needed as often as every 12 weeks if the subject met certain VA or fluorescein angiography criteria. An active control group was comprised of subjects receiving sham infusions of each of the three squalamine doses, but receiving PDT as defined previously. As the trial neared its conclusion, the decision was made to extend the study, allowing an additional 1 year of squalamine use on an open-label basis.

In addition to the trials reported here, there are three additional ongoing studies of squalamine use in exudative age-related macular degeneration. Study MSI-1256F-209 is a 1-year trial of the drug in 112 subjects using the 20 and 40 mg doses of squalamine. This trial is designed to evaluate the safety and efficacy of therapy in a slightly larger and more general age-related macular degeneration population, without the study-mandated use of PDT as a concomitant medication.

As in study 208, a 1-year, open-label extension of the trial has been initiated. Studies MSI-1256F-301 and MSI-1256F-302 are large, multinational phase III programs that will enroll over 700 subjects worldwide. The phase III program was initiated in mid 2005, and is designed to lead to submission of squalamine lactate to global health authorities for the indication of exudative age-related macular degeneration.
Si-RNA

Each human cell consists of a nucleus and a cytoplasm, and the machinery to produce a protein is localized in the cytoplasm of each cell. The nucleus houses the blueprint for the protein and harbors the machinery to translate this blueprint into a template that can produce the specific proteins. DNA makes up chromosomes that contain the code for gene sequences. The gene sequences are transcribed into messenger RNA. The messenger RNA acts as the templates for mass-producing gene products called proteins. Ribosomes are responsible for translating the code of mRNA into peptide sequences that eventually become proteins. Genes are transcribed into messenger RNA. Many proteins can be made from one mRNA. Inhibiting mRNA is an ideal means of preventing production of proteins.34

Antisense molecules bind mRNA and prevent the ribosome from translating the mRNA transcript into proteins. One antisense molecule binds one mRNA, which diminishes the potency of antisense as seen in Figure 5-1. Ribozymes are like antisense molecules, except when they bind an mRNA they splice the mRNA transcript.34

Double-stranded RNA (dsRNA), if greater than 22 nucleotide in length, are processed by an enzyme called dicer. Dicer cuts the dsRNA into 21-22 nucleotide sequences called small interfering RNA (siRNA). The siRNA activates a protein complex called RNA-induced silencing complex (RISC). The activated complex acts as a machine that binds and splices mRNA that carry the sequence homologous to the siRNA. The activated complex is stable and destroys many mRNA with the targeted sequence in a multiple turnover kinetic fashion. One siRNA molecule with the activation of the RNAi machinery can destroy many targeted mRNAs and consequently prevent the production of more proteins.34 This catalytic mechanism makes siRNA a potent means of suppressing gene expression.

In AMD, VEGF is up-regulated in the retinal pigment epithelial cells and macrophages near the choroidal neovascular membrane.35 Furthermore, a large component of VEGF up-regulation is mediated by mRNA stability.36 Because both RPE and macrophages are phagocytic cell types, these cells can ingest siRNA readily facilitating intracellular delivery. By destroying mRNA, siRNA can provide long-lasting suppression of VEGF because a large component of VEGF up-regulation is caused by the persistence of VEGF mRNA transcript. Because there are few enzymes that degrade siRNA once in the cell and especially after an siRNA has bound the RISC complex, it was clear that

FIGURE 5-1: Schematic of the role of vascular endothelial growth factor A (VEGF-A) in age-related macular degeneration (AMD)
the high thermostability of a nonmodified double-stranded RNA is more than adequate for the siRNA to be delivered in the eye and enter postmitotic cells that can continuously mediate RNAi.37 This stepwise development of siRNA to become therapeutic for the eye led to the first demonstrations of therapeutic potential of siRNA delivered in a clinically relevant fashion. SiRNA directed against either VEGF or green fluorescent proteins was able to suppress expression of these respective gene products greatly in a mouse eye.38

The two siRNAs undergoing clinical trial are Cand5 and siRNA-027. Cand5 is an siRNA against all isoforms of VEGF. siRNA-027 is an siRNA against a VEGF receptor 1. The results are awaited.

**VEGF Trap**

VEGF Trap is a fully human soluble decoy receptor protein that consists of a fusion of the second Ig domain of human VEGF receptor (VEGFR) 1 and the third Ig domain of human VEGFR2 with the constant region (Fc) of human Ig IgG1.39 This is used as a means of blocking the normal VEGF signaling pathway by inhibiting the binding of VEGF to its normal VEGF receptors rather than to the decoy soluble receptors.

The VEGF Trap was engineered to have optimized pharmacokinetic properties and a very high affinity for all isoforms of VEGF-A (<1 pM), as well as placental growth factor, a closely related angiogenic factor.39 VEGF Trap has shown robust anti-tumor effects in numerous mouse models of cancer and is now in clinical trials.40 These molecules are now being tested in preliminary clinical trials.

**References**

16. Eter N. Focus study 2-year results: Combination therapy with ranibizumab and photodynamic therapy with verteporfin 2006.
Role of Combination Therapy in Diabetic Macular Edema
Introduction

Diabetic macular edema (DME) is the most common cause of moderate visual loss in patients with diabetes. Untreated, there is a 25-30% risk of developing clinically significant macular edema (CSME) with moderate visual loss (doubling of the visual angle within 3 years).

- DME is defined as retinal thickening within 2 disc diameters of the center of the macula.
  - Focal edema is associated with hard exudate rings resulting from leakage from microaneurysms.
  - Diffuse edema results from breakdown of blood-retinal barrier with leakage from microaneurysms, retinal capillaries, and arterioles.

- CSME, as defined by the Early Treatment Diabetic Retinal Study (ETDRS), exists with any of the following findings (Figure 6-1):
  - Retinal thickening within 500 mm of the center of the fovea.
  - Hard, yellow exudates within 500 mm of the center of the fovea with adjacent retinal thickening.
  - At least 1 disc area of retinal thickening, any part of which is within 1 disc diameter of the center of the fovea.
  - Visual acuity is an important parameter in following the progression of CSME, although it does not aid in the diagnosis of CSME because patients may have a visual acuity of 20/20.

**FIGURE 6-1:** Showing clinically significant macular edema (Courtesy: Nazimul Hussain, Al Zahra Hospital, UAE)
Role of Combination Therapy in Diabetic Macular Edema

• Diffuse DME is one which measures greater than 300 microns on the Optical Coherence Tomography (OCT) is at least two disc diameters in size and a significant reduction in the reflectivity of the outer layer; subfoveal fluid collection on optical coherence tomography or both should be present (Figure 6-2).

International Clinical Classification of Diabetic Retinopathy Severity of Diabetic Macular Edema³

<table>
<thead>
<tr>
<th>Proposed Classification</th>
<th>Findings Observed Upon Dilated Ophthalmoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic Macular Edema Absent</td>
<td>No retinal thickening or hard exudates in posterior pole</td>
</tr>
<tr>
<td>Diabetic Macular Edema Present</td>
<td>Some retinal thickening or hard exudates in posterior pole</td>
</tr>
</tbody>
</table>

If diabetic macular edema is present, it can be categorized as follows:

<table>
<thead>
<tr>
<th>Proposed Classification</th>
<th>Findings Observed Upon Dilated Ophthalmoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic Macular Edema Present</td>
<td><strong>Mild Diabetic Macular Edema</strong> Some retinal thickening or hard exudates in posterior pole but distant from the macula</td>
</tr>
<tr>
<td></td>
<td><strong>Moderate Diabetic Macular Edema</strong> Retinal thickening or hard exudates approaching the center of the macula but not involving the center</td>
</tr>
<tr>
<td></td>
<td><strong>Severe Diabetic Macular Edema</strong> Retinal thickening or hard exudates involving the center of the macula</td>
</tr>
</tbody>
</table>

FIGURE 6-2: Showing OCT image of diffuse diabetic macular edema with central macular thickness of 660 microns and subfoveal fluid (serous macular detachment). *(Courtesy: Dr. Nazimul Hussain, Al Zahra Pvt. Hospital, UAE)*
CSME is purely a clinical diagnosis and hence suffers from subjective variations, depending upon an individual’s experience and expertise in picking up macular thickening.

**Role of Fluorescein Angiography in DME**

Fluorescein angiography is useful in the treatment of diabetic macular edema. It distinguishes and localizes areas of focal versus diffuse leakage, thereby guiding the placement of laser photocoagulation. The proximity of the leakage to the foveal avascular zone (FAZ) should be noted. Also areas of macular ischaemia in the form of widening of FAZ > 1000 microns, irregularity in the margin of FAZ, capillary budding in the region of FAZ, and intercapillary distance decide whether photocoagulation will help in preventing visual loss (Figure 6-3).

![FIGURE 6-3: Fundus Fluorescein Angiography showing macular ischemia (Courtesy: Dr. Nazimul Hussain, Al Zahra Pvt Hospital, UAE)](image)

**Use of Optical Coherence Tomography in DME**

Fundus fluorescein angiography may give us information about excess leakiness of the macular blood vessels, focal, diffuse or cystoid, but gives no information about macular thickening. Also, a patient after receiving therapy for DME may not improve quantitatively in vision, but there may be a significant decrease in macular edema/thickening. Clinical examination may not pick up this very change, especially if it is within 50 microns.

In contrast to all the above, Optical Coherence Tomography (OCT) is the perfect tool that gives an objective assessment of macular thickening, even prognosticating a change in the same, provided it is greater than 20 microns. However, it is less frequent that changes in thickness on OCT may actually correlate with a corresponding change in visual acuity. Also, OCT suffers from the minor disadvantage of not being able to document macular ischemia.
Role of Combination Therapy in Diabetic Macular Edema

Having said the above, it is actually the qualitative rather than the quantitative aspects of OCT that deserve highlighting. The various patterns of DME seen on OCT include:

1. **Diffuse retinal thickening (DRT)** as increased retinal thickness (defined as greater than 200 microns) with reduced intraretinal reflectivity and expanded areas of lower reflectivity, especially in the outer retinal layers greater than 200 microns in width (Figure 6-4).

2. **Cystoid Macular Edema** was identified by the localization of intraretinal cystoid-like spaces that appeared as round or oval areas of low reflectivity with highly reflective septae separating the cystoid-like cavities (Figure 6-5).

3. **Posterior Hyaloid Traction (PHT)** was defined as a highly reflective signal arising from the inner retinal surface and extending towards the optic nerve or peripherally.

4. **Tractional retinal detachment (TRD)**, defined as a peak-shaped detachment of the retina.

5. **Subretinal fluid without PHT/TRD** was defined as an accumulation of subretinal fluid (which appeared dark) beneath a highly reflective elevation, resembling a dome of the detached retina (see Figure 6-2). The identification of the highly reflective posterior border of detached retina distinguished subretinal from intraretinal fluid.

Histopathologic studies by Yanoff and associates, suggest that the development of macular edema is initiated by fluid accumulation within Mueller cells. In this early state, while fluid accumulates intracellularly within the Mueller cells, it can be reversed. However, if the accumulation continues, or remains chronic, then at some point death of the Mueller cells occurs and may result in the formation of large cystoid cavities, or CME. The cavities are formed following necrosis of the Mueller cells. As suggested by Yamamoto, these histopathologic findings explain why those eyes with CME may be associated with worse visual outcomes than other subgroups of DME.

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**FIGURE 6-4:** OCT image showing diffuse retinal thickening with reduced intraretinal reflectivity and expanded areas of lower reflectivity, especially in the outer retinal layers. (Courtesy: Dr Nazimul Hussain, Al Zahra Pvt Hospital, UAE)
The change in central foveal thickness (CFT), which the OCT so importantly highlights, is that of the central fovea only. This CFT may not be indicative of response to therapy if it remains unchanged even though the therapy has worked on reducing the parafoveal thickening. Hence, a change in total macular volume (i.e., macular area × average thickness) is a more sensitive indicator of response to therapy. The raster scans that Fourier domain OCTs are now taking at extremely rapid rates can actually help in performing the above volumetric analysis of the scanned area.

A further refinement while performing thickness or volume analysis is calculating the change in the same after standardizing or adjusting for baseline OCT thickness or volume of normative data where ever available or the patient’s other normal eye. A simple formula to calculate the above is given as:
Standardized change in foveal thickness = \( \frac{(\text{Initial thickness} - \text{baseline thickness})}{(\text{Final Thickness} - \text{baseline thickness})} \). The higher the above ratio, the better is the response to therapy.

**Laser Therapy**

The ETDRS showed that focal/grid photocoagulation reduced the rate of moderate visual acuity loss by 50% in patients with CSME, from 24 to 12%. This means that 12% of the patients with CSME do still undergo moderate visual loss at 3 years. This also means that focal/grid photocoagulation does not aim at improving vision. The ETDRS study showed a visual acuity improvement in only 3% of the cases. Moderate visual loss is defined as a doubling of the visual angle, e.g. from 20/40 to 20/80. Laser treatment of DME should precede panretinal photocoagulation (PRP) by at least 6 weeks because PRP before this has been known to worsen DME. PRP should not be delayed in patients with very severe nonproliferative diabetic retinopathy or high-risk proliferative diabetic retinopathy.

**TREATMENT**

Area(s) of leakage can be identified by examination (areas of retinal thickening) and leakage by fluorescein angiography. Laser photocoagulation parameters:

- **Burns**—100 microns in diameter
- **Power**—100 mW, or the kind that gives a just visible burn
- **Duration**—100 ms
- **Focal leakage**—Treatment of leaking microaneurysms
- **Diffuse leakage**—Grid pattern photocoagulation
- **Important to avoid foveal avascular zone**, that is, 500 microns from the centre, 500 microns from the disk margin but can laser the papillomacular bundle
- **Argon green, krypton yellow, or 532 frequency upconverted diode-laser** to treat focal lesions
- **Argon green, krypton red or 532 frequency upconverted diode-laser** to treat diffuse lesions
- **Focal leaks** 300-500 mm from the foveal center causing retinal thickening and hard exudates that persisted after a first treatment and a visual acuity of less than 20/40 provided that the perifoveal capillary network will not be destroyed can be treated

However, while laser photocoagulation reduced the rate of progression of visual loss, but once visual acuity was reduced, eyes treated with laser were unlikely to improve to 20/40 or better. Also, the degree of visual gain following laser is moderate, and may take months to occur.

**Intravitreal Triamcinolone Acetonide**

The mechanism of action of corticosteroids in the treatment of macular edema has yet to be well defined, their action may rely on their ability to inhibit the arachidonic acid pathway and downregulate the production of vascular endothelial growth factor. Corticosteroid treatment has shown to have beneficial effect on DME. The probable mechanisms are an increase in tight-junction proteins, which diminish vessel leakage by a local vasoconstrictive effect, and angiostatic properties through inhibition of Vascular Endothelial Growth Factor (VEGF). These phenomena result, collectively, in the reduction of overall vascular permeability.

Many studies have described the effects of intravitreal triamcinolone acetonide (IVTA) although only two randomized controlled trials have presented data, of which one has been published. In the
published prospective randomized control trial 69 eyes of 43 patients received either 4.0 mg of IVTA or placebo. Two-year data were available for 60 of 69 (87%) eyes. An improvement of greater than or equal to five ETDRS letters BCVA occurred in 19 of 34 (56%) eyes treated with IVTA, compared with nine of 35 (26%) eyes treated with the placebo (P=0.006), with mean improvement in visual acuity of 5.7 letters (95% CI, 1.4–9.9) more in the IVTA-treated eyes than in those treated with the placebo. Increased intraocular pressure (IOP) of at least 5mmHg was observed in 23 of 34 (68%) treated versus three of 30 (10%) untreated eyes (P<0.0001). Two eyes in the IVTA-treated group required trabeculectomy. There was one case of infectious endophthalmitis in the treatment group. Cataract surgery was performed in 15 of 28 (54%) treated versus 0 of 21 (0%) untreated eyes (P<0.0001). The authors concluded that IVTA improves vision and reduces macular thickness in eyes with refractory diabetic macular edema.

Some studies using IVTA have suggested that higher doses are more efficacious. Sixty-three eyes of 63 patients were randomized to 4, 6 or 8 mg of IVTA. All groups showed improvements of BCVA and central foveal thickness. The mean BCVA improvement at 6 months was significantly higher for the 8 mg group compared with the 4mg group, with 9.9 and 3.1 improvement of ETDRS letters (P=0.047) respectively. Ocular hypertensive responses (>21 mmHg) occurred in 39, 30 and 55% of eyes in the 4, 6, and 8 mg groups, respectively (P=0.27) (Figure 6-6).

Role of Anti-VEGF Injections

The advent of anti-VEGF agents marks a major advancement in the treatment of various ocular diseases. VEGF-A has many effects that may contribute to other physiologic and pathophysiologic

FIGURE 6-6: Showing pre-injection and post-injection of intravitreal triamcinolone in a recalcitrant diabetic macular edema. Please note the gross reduction in macular thickness and maintenance of foveal contour and central macular thickness (Courtesy: Dr Nazimul Hussain, Al Zahra Pvt Hospital, UAE)
processes, including vascular permeability, chemotaxis and inflammation, and mitogenesis. In addition to stimulating neovascularization, VEGF serves as a survival factor for existing vessels and for neuronal cells. Hypoxia and oxygen-free radicals are known inducers of VEGF expression. This would be rightly so, as VEGF is expressed constitutively at low levels by the retinal pigment epithelium, where it plays a physiologic role by providing trophic support to the neuroretina and choriocapillaris, facilitating the exchange of oxygen and nutrients.

Considering the key role of VEGF in the pathology and physiology of diabetic retinopathy, a VEGF blockade drug though appearing to be an attractive therapeutic approach in reducing DME as an anti permeability agent, may also turn out to be an anti trophic agent, in which case, caution needs to be exercised in the use of this potential double edged weapon. It is possible to block all VEGF isoforms using bevacizumab or ranibizumab. However, there is evidence to support that selective blockade of the VEGF-165 isoform (pegaptanib sodium) may reduce the VEGF mediated pathologic effect while preserving VEGF mediated normal physiologic functions. In contrast, nonselective VEGF blockade has been shown to impair VEGF-mediated normal physiologic functions, causing regression of normal vasculature as well as reduction of VEGF-mediated neuroprotection.

PEGAPTANIB SODIUM
A published randomized, controlled, double-masked phase II multicentre trial evaluated the efficacy and safety of three doses of pegaptanib sodium (Macugen) (0.3 mg, 1 mg and 3 mg) versus sham injection in 172 subjects with centre-involving DME. Injections were given on three visits, 6 weeks apart. Additional injections or focal laser photocoagulation were given as needed for another 18 weeks. Final assessments were conducted at week 36. The 0.3 mg dose was found to be most efficacious, with median visual acuity (20/50 versus 20/63 (sham), P=0.04). A larger proportion of those receiving 0.3 mg gained visual acuities of 10 letters or more (two lines) (34% versus 10%, P=0.003). Mean central retinal thickness decreased by 68 mm with 0.3 mg, versus an increase of 4 mm with sham (P=0.02). It is unclear why the 0.3 mg dose was most efficacious. Laser photocoagulation was necessary in fewer patients in each pegaptanib arm. There was one case of endophthalmitis from 652 injections (0.15%), which was not associated with severe visual loss.

BEVACIZUMAB
The anti-VEGF agent bevacizumab, approved for the treatment of metastatic colon cancer, appears to show similar efficacy in the treatment of wet age-related macular degeneration to ranibizumab, and its effect on DME is being studied.

Haritoglou et al published a prospective, noncomparative case series of 51 patients with diffuse DME treated with 1.25 mg bevacizumab. Follow-up was short (6–12 weeks) and although injections were repeated if there was persistence of macular edema, most received just one injection. There was a significant reduction in macular thickness at 12 weeks (P=0.001) and although mean visual acuity improved significantly at 6 weeks (P=0.02), this was not sustained at 12 weeks, which may reflect the drug’s duration of effect.

Arevalo et al reported a multi-center uncontrolled retrospective study of 78 eyes of 63 patients with DME treated with at least one injection of intravitreal bevacizumab of dose 1.25 mg or 2.5 mg. Follow-up ranged from 6 to 9 months. Again, most eyes received just one injection (56 of 78 or 72% of eyes). In this study, however, there was a statistically significant improvement in BCVA and
43 (55%) improved 10 or more ETDRS lines of vision. Central macular thickness also decreased significantly, from 387 microns to a mean of 276 microns at end of follow up (P<0.0001).

Diabetic Retinopathy Clinical Research Network studied the short-term effect of intravitreal bevacizumab for diabetic macular edema. They compared a control group receiving focal photocoagulation with both the 1.25 and 2.5 mg bevacizumab. The treated eyes had a greater reduction in central retinal thickness at 3 weeks. Eyes in the photocoagulation group demonstrated improvement in these parameters with longer follow-up. As a result, there were no meaningful differences in central subfield thickness observed for bevacizumab relative to photocoagulation after the 3-week time point. Combining photocoagulation with bevacizumab resulted in no apparent short-term benefit or adverse outcomes.20

Reports in the literature note individual cases of short-term improvement in VA and reduction in OCT measured retinal thickening after intravitreal injection of an anti-VEGF drug (bevacizumab, pegaptanib, or ranibizumab). None of these reports included subjects concurrently randomized to focal photocoagulation.18, 19

**RANIBIZUMAB**

Chun et al21 reported a nonrandomized case series with 10 eyes of 10 patients who received three intravitreal injections of ranibizumab (either 0.3 mg or 0.5 mg) administered on day 0, month 1, and month 2. The mean improvement in visual acuity was 10 letters and at month 3 there was a significant decrease in retinal thickness (122 microns).

A second nonrandomized clinical trial by Nguyen et al22 studied 10 patients with chronic DME who received intraocular injections of 0.5 mg of ranibizumab at baseline and at 1, 2, 4, and 6 months. Intraocular injections of ranibizumab significantly reduced foveal thickness (from mean 503 microns...
Role of Combination Therapy in Diabetic Macular Edema

to 257 microns at 7 months) and improved visual acuity (from 28 ETDRS or 20/80 to 40 ETDRS letters or 20/40) in 10 patients with DME. The injections were well tolerated with no reported ocular or systemic adverse events. A phase II randomized control trial (RESOLVE) is underway which should hopefully yield better information (Figure 6-7).

Combination Therapy

It was shown that macular photocoagulation (MPC) resulted in laser scars, which showed tendency to increase with time, and thus decreased the likelihood of vision improvement. For diffuse DME, MPC has even more limited results. Lee and Olk 23 demonstrated that with modified grid MPC, visual acuity was stabilized in 60.9%, decreased in 24.6%, and increased in only 14.5% of eyes with diffuse DME. Therefore, alternative or adjunct treatments for DME such as IVTA and anti–VEGF therapy have been the focus recently.

COMBINATION OF POSTERIOR SUB-TENON TRIAMCINOLONE INJECTIONS AND MACULAR GRID

Theoretically, adverse effects may be presumed to be lower than those of intra-vitreal steroids. A peribulbar corticosteroid injection is of particular interest for eyes with DME that have good visual acuity where the risks of an intravitreal injection of corticosteroid may not be justified.

Diabetic Retinopathy Clinical Research Network studied the safety and efficacy of anterior and posterior sub-tenon injections of triamcinolone either alone or in combination with focal photocoagulation in the treatment of mild diabetic macular edema and found it unlikely to be of substantial benefit.23

COMBINATION OF IVTA AND MACULAR GRID

The advantages of combining both IVTA and macular grid are:
1. Decreased foveal thickness after IVTA may enhance the effects of grid laser photocoagulation.
   Without IVTA, markedly increased foveal thickness, subfoveal fluid, and retinal opacity due to diffuse DME might interfere with adequate laser delivery to the retinal pigment epithelium (RPE) and photoreceptor layers. However, after IVTA, the decreased foveal thickness and restoration of retinal transparency achieved by the treatment would facilitate the delivery of the laser energy selectively to the photoreceptors and RPE.25
2. The possibility exists that steroids might act beneficially in the process of mature laser scar formation. It has been established that 2 or 3 weeks should elapse for the formation of a mature laser scar, and laser treatment itself frequently induces the aggravation of macular edema or inflammation during this period. The presence of intravitreal steroids might exert certain protective effects against the initial deleterious events that follow grid laser treatment and might also modulate RPE remodeling after grid laser treatment.26-27

An interval of 3 weeks for the separation of macular grid laser treatment from IVTA was chosen empirically because this is when the therapeutic effects of IVTA were found to reach maximum values in most previous studies.7-10, 12

Eighty-six eyes of 74 patients with diffuse DME were randomized into these two groups. The logMAR visual acuities were not significantly different between the two groups at baseline and at 3 weeks after IVTA but were significantly better in the laser group at 3 (P=0.02) and 6 months (P<0.001) after IVTA.28
Severe vision-threatening complications, such as endophthalmitis, that are inherent to intraocular injection can be avoided by periocular injection. However, a more potent protective effect on breakdown in the blood-retinal barrier is expected with IVTA than with posterior sub-tenon injection of triamcinolone.

However, Lam et al showed that combined treatment of IVTA plus grid laser did not yield better Central Foveal Thickness reduction or BCVA improvement at 6 months than IVTA alone. Grid laser alone was significantly worse than the 2 other treatment modalities. Hence it has to be catered separately for each patient.10

The general consensus is that if the edema is significant with cystoid macular changes and a mean central foveal thickness of > 400 microns, then IVTA may be used as an adjunct to grid laser, but if only mild spongy thickening is present, either of the modalities, grid or IVTA have equally good effect.

**COMBINATION OF IVTA + AVASTIN VS AVASTIN ALONE VS MACULAR GRID PHOTOCOAGULATION**

Sohelian M et al in a randomized three-armed clinical trial studied the efficacy of a single intravitreal bevacizumab injection alone or in combination IVTA versus macular laser photocoagulation as primary treatment of DME. They concluded that up to 12 weeks, intravitreal bevacizumab treatment of patients with DME yielded better visual outcome than laser photocoagulation, although it was not associated with a significant decrease in central macular thickness. No further beneficial effect of IVTA could be demonstrated.29

**SUBTHRESHOLD DIODE MICROPULSE (SDM) LASER PHOTOCOAGULATION**

Conventional photocoagulation protocol is effective for treating CSME, but it does result in collateral damage in the form of visible laser scars that can enlarge postoperatively,30, 31 and complications that include choroidal neovascularisation (CNV),32 subretinal fibrosis and Scotomas.33 Besides, conventional photocoagulation could be painful at times.

It is to be realized that the basic aim of conventional macular photocoagulation is to stimulate (and not burn) the retinal pigment epithelium, outer and inner retina as is so with conventional panretinal photocoagulation. Subsequently, this ‘stimulated’ RPE that forms the outer blood retinal barrier in conjunction with capillary endothelium that forms the inner blood retinal barrier modulates vasopermeability-effecting molecules like the VEGF, which causes resolution of CSME.

However, we cannot be sure of this RPE and retinal stimulation unless we burn a bit of RPE and retina with visible or supra-threshold burns. It is this visible burn, which in the form of neural protein coagulation or whitening causes the collateral damage. A ‘threshold’ burn is thus one that is visible 50% of the times and a ‘sub-threshold’ burn is one that is not visible at all clinically or, in fact even angiographically at times.

It could intuitively mean from above that supra-threshold burns will deliver greater energy than threshold which will, in turn deliver greater energy than sub-threshold burns. Certainly then, the lesser the burn intensity or energy, the lesser will be the collateral damage. However, we do not know whether this lesser burn will retain the same ‘stimulating effect’.

It can be concluded from above that it would be best if we could somehow not lessen the laser intensity or energy to retain the same ‘stimulating effect’ but avoid collateral damage at the same time. This has been attempted by way of micropulses. The temperature rise of RPE depends upon the duration of continuous exposure. Also the spread of energy from the RPE to the structures around depends upon the duration of continuous exposure. Hence, if the same amount of energy is
given in pulses, the RPE will ‘cool’ down sufficiently before the next pulse so as to not result in heat induced denaturation of its proteins and cell death. Also, if the same pulse is given of 100-micron duration, it will travel only 4 microns along the length, breadth and width of RPE before it ‘dies’ down. The cuboidal RPE cells, sized at 10 microns length, can easily bear the brunt of this pulsed energy without allowing dissipation.\textsuperscript{34}

To put the above mathematically,
Conventional Green laser: 532 nm
Power: 100 mW
Duration: 100 ms
Spot size: 125 microns
Energy per burn = Power × time = 100 × 100 = 10000 mJ
SDM: 810 nm
Power: 700 mW
Duration: 300 ms
Spot size: 125 microns
Duty cycle: 5\% in 2 ms pulse, i.e. 100 microsecond on, 1900 microsecond off
Effective Duration: 100 × 150 pulses = 15 ms
Energy per burn = Power × time = 700 × 15 = 10500 mJ

From above, we see that the energy given in SDM is in fact higher than conventional green laser, but its micropulse effect will prevent collateral damage. The same has also been ascertained in terms of PE or Permissible Energy. PE stands at 1.46 PE for PDT, 9.36 PE for TTT, 376 PE for conventional green laser and 476 PE for SDM.\textsuperscript{34}

The above math gives energy per burn. With SDM laser, greater number of burns could be given, that too, confluent or even overlapping at times, in the macular region without causing any collateral damage. It also implies that greater number of sessions could be tolerated with SDM laser as opposed to conventional laser.

In a retrospective study by Lutrull et al of 95 eyes of 69 patients, SDM laser resulted in an overall unchanged postoperative visual acuity (plus or minus two Snellen lines) in 76.8\%, worsening by three or more lines in 14.7\%, and improvement in 8.4\%.\textsuperscript{34} In another uncontrolled series by Sivaprasad et al\textsuperscript{35} of 25 eyes with the longest follow-up of 3 years, visual acuity stabilized or improved in 84\% of treated eyes by the end of the first year. The result was maintained in the second year and by the third year, 92\% maintained vision. However, more patients needed supplementary grid laser in the third year than in the second year. CSME decreased in 92\% of the eyes and resolved in 88\% in the first year. By the second year, 92\% showed complete resolution. However, in the third year, recurrent CSME was noted in 28\% of patients.

In conclusion, SDM laser photocoagulation does show promise not only in the resolution of CSME but also in prevention of the adverse effects of conventional photocoagulation. These effects may still translate into mere visual stabilization or prevention of moderate visual loss as was the outcome measure of clinical relevance in the ETDRS, rather than visual improvement, but the qualitative aspects of vision such as contrast, color and fields may show a definite improvement. We require studies using SDM laser and suitable control arms with the above visual criteria as outcome measures in order to ascertain our hypothesis. The only randomized controlled trial that compared SDM laser to conventional green laser had visual acuity as the outcome measure, where both the groups had similar outcomes. Hence, conventional green still remains the standard of care as far as laser therapy is concerned. Also, SDM laser and conventional laser may do equally well in mild to moderate macular edemas. SDM perhaps has a questionable role in severe diabetic macular edema.
The Role of Surgery for DME

If damage to the endothelium and pericytes due to glycosylated products and other mediators such as Insulin Like Growth Factor (IGF1), VEGF and histamine is the common pathogenic pathway to capillary leakage and hence DME\textsuperscript{36}, performing a pars plana vitrectomy with or without an Inner Limiting Membrane (ILM) peeling itself provides no scientific rationale to treating DME, leave alone the complications that may be incurred in the process, such as development of retinal breaks and retinal detachment, lens opacification and so on.

However, one can safely argue upon the fact that removal of a taut posterior hyaloid by vitrectomy can alter anteroposterior or tangential tractional forces on the fovea resulting in resolution of foveal thickening.\textsuperscript{37,38} But, as we all know OCT documents anatomy and not pathophysiology, a posterior hyaloid that may look taut even on an OCT may not actually be taut and the one looking not so taut may actually be taut. Hence, more often than not, the decision is made by circumstantial evidence, viz, those DMEs with diffuse edemas that have not responded to laser or anti-VEGF in single or multiple sittings could have a taut posterior hyaloid, which the OCT may not necessarily document. Thus, performing a vitrectomy in a refractory or persistent diffuse DME may actually begin making scientific sense.

This brings us to the next quintessential question, viz, why peel the ILM then? Diabetics have been shown to have a much thicker ILM compared to others\textsuperscript{39} and removal of the ILM prohibits proliferation of astrocytes that could have otherwise contributed to membrane formation and subsequent traction.\textsuperscript{40} Secondly, a vitrectomised eye, preferably with an ILM peeled may pose a lesser barrier, not only to the diffusion of oxygen from the vitreous cavity to within the retina, but also to vaso permeability enhancing molecules such as VEGF from the retina into the vitreous cavity causing a faster washout.\textsuperscript{41}

Now that we have rather successfully argued out the scientific and intuitive basis for a possible surgical remedy, let us put our hypothesis to test. When reviewing literature, most studies have noted an improvement in terms of a significant decrease in foveal thickening, but the same has not really translated into a significant improvement in visual acuity. However, there are a few studies that do also report an improvement in visual acuity. The discrepancies could simply arise due to differences in the severity of DME, duration of DME, coexistence of ultrastructural anatomical variations on OCT such as cystoid changes, coexistent or coupled laser/anti VEGF therapy and systemic parameter control. All in all, majority of the studies were retrospective, lacked suitable control arms and lacked a long-term follow-up.\textsuperscript{42-46} The surgery may do better if done earlier as a primary procedure in diffuse edemas, or before significant cystoid changes may set in. We do require at present a suitable randomized controlled masked clinical trial to confirm any benefit, if at all by surgery.

A comparison of studies where vitrectomy was not associated with ILM peeling is as follows:

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. eyes</th>
<th>Hyaloid</th>
<th>OCT</th>
<th>VA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Preop to postop</td>
<td>Improved</td>
</tr>
<tr>
<td>Yamamoto\textsuperscript{42}</td>
<td>2003</td>
<td>65</td>
<td>N/A</td>
<td>464 to 225 microns</td>
<td>45%</td>
</tr>
<tr>
<td>Parolini\textsuperscript{43}</td>
<td>2004</td>
<td>59</td>
<td>N/A</td>
<td>463 to 327 microns</td>
<td>17%</td>
</tr>
<tr>
<td>Yamamoto\textsuperscript{44}</td>
<td>2001</td>
<td>30</td>
<td>N/A</td>
<td>478 to 264 microns</td>
<td>43%</td>
</tr>
<tr>
<td>Hartley\textsuperscript{36}</td>
<td>2008</td>
<td>24</td>
<td>N/A</td>
<td>Change of 141 microns</td>
<td>25%</td>
</tr>
</tbody>
</table>
Role of Combination Therapy in Diabetic Macular Edema

A comparison of studies where vitrectomy was associated with ILM peeling is as follows:

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. eyes</th>
<th>ILM peel</th>
<th>OCT Preop to postop</th>
<th>VA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kralinger</td>
<td>2006</td>
<td>51</td>
<td>Yes</td>
<td>No difference</td>
<td>No difference</td>
</tr>
<tr>
<td>Bahadir</td>
<td>2005</td>
<td>17</td>
<td>Yes</td>
<td>N/A</td>
<td>52.9%</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>No</td>
<td></td>
<td></td>
<td>56.1%</td>
</tr>
</tbody>
</table>

The issue of surgery on DME still remains questionable as far as visual acuity is concerned. However, an obvious taut posterior hyaloid needs to be intervened by surgery as early as possible. If the tautness of the posterior hyaloid is of questionable certainty, perhaps alternative therapies (laser/VEGF) can be tried and response noted before intervening in them surgically.

The Concept of Triple Therapy

This applies only to select cases, such as those with diffuse intractable DME. Intractable DME is one which has not responded to prior laser or intravitreal injection therapy or both either biomicroscopically, angiographically or tomographically. Diffuse DME has been defined previously. The visual acuity criteria is that it should be lesser than 20/50.

The triple therapy involves vitrectomy with ILM peeling followed by IVTA injection and MPC conducted sequentially at one and 14 days after vitrectomy. IVTA can be combined with vitrectomy and laser photocoagulation can be performed slightly later (but within 3 weeks), as the half-life of IVTA in vitrectomized eyes is shorter than usual.

The rationale behind triple therapy is that although IVTA therapy has been shown to reduce temporarily the permeability of retinal capillaries or to downregulate vascular endothelial growth factor (VEGF), it does not alleviate macular hypoxia, the underlying cause of the disease. Thus, the recurrence of DME approximately four months after IVTA has been implicated as the primary limitation of IVTA, and the long-term efficacy of repeated IVTA also requires further evaluation. Anti-VEGFs have also been tried. However, because of the neuroprotective functions of VEGF, the long-term effects on vision after repeated injections of anti-VEGF agents should also be evaluated.

In a prospective, interventional masked case series including twenty-four eyes from 24 subjects with intractable DME of non-tractional origin, 12 month follow up showed a significant visual improvement from 0.88 (+0.37) to 0.48 (+0.28), which also reflected in an OCT change of mean macular thickening from 514 microns to 197 microns. Sclerotic cataracts (8/12 phakic eyes) and elevation of intraocular pressure (8/24 eyes) were the adverse effects noted.

Other Agents

RUBOXISTAURIN

Ruboxistaurin is an orally administered selective protein kinase C b-inhibitor which was developed to reduce the permeability of the blood–retinal barrier. An initial 18-month randomized placebo-controlled, double masked trial of 41 patients with DME found a reduction of retinal vascular leakage when assessed by vitreous fluorometry. Further it was found that ruboxistaurin (32 mg/day) in
685 patients with moderately severe to very severe nonproliferative diabetic retinopathy reduced the rate of sustained moderate visual loss (15 letters or greater decrease in ETDRS visual acuity score maintained at 6 months) from 9.1% of placebo-treated patients versus 5.5% of ruboxistaurin-treated patients (40% risk reduction, \( P = 0.034 \)). When a study was designed to investigate macular edema specifically, however, results were disappointing. This multicenter, double-masked, randomized, placebo-controlled study assessed patients with edema further than 300 microns from the center of the macula, without prior photocoagulation. Over 30 months, 686 patients received placebo or ruboxistaurin orally (4, 16, or 32 mg/day). The primary study outcome was progression to sight-threatening DME or application of focal/grid photocoagulation for DME. There were no statistical differences between the groups. Secondary analysis after adjusting for treatment-site related variations showed that 32mg of ruboxistaurin per day reduced progression, compared with placebo (\( P = 0.02 \)).

**FLUOCINOLONE ACETONIDE**

Pearson et al\(^5\) presented a series of 197 patients randomized to either sustained release, fluocinolone acetonide intravitreal implant (Retisert; Baush and Lomb, Rochester, New York, USA) or standard care (ETDRS laser). Although the implant resulted in reduced DME (58% compared with 30%) and a trend toward better acuity, there were significant side effects which have limited its widespread use. These included 28% requiring a filtering procedure and 5% needing to be explanted to manage intraocular pressure.

**Conclusion**

The pathogenesis of DME is multifactorial. Though the above therapies, either singly or in combination, may help in the resolution of CSME, the role of systemic parameter control cannot be underestimated. Insulin use, systemic hypertension, cardiac and renal failure, obesity, proteinuria, high glycosylated hemoglobin, lipid profile and anemic status play an important role in the causation/aggravation of CSME.\(^1,57,58\)

**References**

Role of Combination Therapy in Diabetic Macular Edema

Hemorrhage at the Macula: Classifications and Treatment Options
Introduction and Classification

Hemorrhage at the macula may cause a sudden deterioration of visual acuity. These hemorrhages vary in shape, location, size and color. Hence, the origin as well as the pathophysiology is of importance. Principally, the anatomic location enables a classification of sub-, intra- and preretinal hemorrhage.

Subretinal hemorrhages are localized beneath the neuroretina and/or retinal pigment epithelium (Figure 7-1). The typical cause for such a bleeding is age related macular degeneration (Figure 7-2). Such hemorrhages are also typically seen secondary to choroidal rupture after trauma.

Intraretinal hemorrhages are localized within the neuroretina (Figure 7-3). The origin of such hemorrhages is from blood vessels in the neuroretinal layer. The typical anatomical finding is the radial fomation following the nerve fiber layers. These are seen in vascular diseases, e.g. diabetes mellitus, hypertension, leukemia as well as in venous occlusive diseases like central retinal vein occlusion (Figure 7-4).

The description of preretinal hemorrhage is correct only when the cleavage plane is between the hyaloid and the internal limiting membrane (ILM). In the past, sharply demarcated, dome-shaped
hemorrhages located at the macula (Figure 7-5) were thought to be subhyaloid hemorrhages. Therefore preretinal hemorrhage was the exact description. But Figure 7-5 does not allow a differentiation between subhyaloid or sub-ILM hemorrhage.

Although, subhyaloid hemorrhage nomenclature was used in most cases, the exact localisation of the blood, i.e. subhyaloid or macular, is often not known. Today we know that location of hemorrhage between the hyaloid and the ILM (Figure 7-6) is preretinal and the sub-ILM location (Figure 7-7) is anatomically a retinal hemorrhage as the ILM is a part of the neuroretina. Nevertheless, many different descriptions are found in the literature, as: hemorrhagic detachment of the ILM, submembranous hemorrhage, hyphema posterior, subhyaloidal hemorrhage, sub-ILM hemorrhage, premacular hemorrhage, macular hematoma, hemorrhagic macular cyst, macular cyst, macular hemorrhage or preretinal hemorrhage. The term hemorrhage at the macula does not need to differentiate between subhyaloidal or sub-ILM hemorrhage. De Maeyer et al has actually identified the sub-ILM cleavage plane as the site of hemorrhage in their consecutive case series of 5 patients. During vitrectomy an intraoperative verification of the exact localization was possible.

Different causes of subhyaloidal or macular hemorrhage have been stated, i.e. the most common being Valsalva retinopathy and Terson syndrome. Additionally, it may occur secondary to vascular...
FIGURE 7-5: Hemorrhage at the macula, the fundus image does not allow differentiating between subhyaloidal hemorrhage ( preretinal hemorrhage) or sub-ILM hemorrhage (intraretinal hemorrhage).

FIGURE 7-6: Schematic diagram of a subhyaloidal hemorrhage.

FIGURE 7-7: Schematic diagram of a sub-ILM hemorrhage.
diseases like arteriosclerosis, hypertension, retinal artery or vein occlusion, diabetic retinopathy, blood disorders, shaken baby syndrome, retinal macroaneurysm, chorioretinitis, age-related macular degeneration, trauma or spontaneously.\textsuperscript{7,14}

Although some authors identified a sub ILM hemorrhage by glistening reflexes and surface striae,\textsuperscript{15,16} others, however, disputed the reliability of biomicroscopy in locating the plane of hemorrhage.\textsuperscript{7,17,18} Several authors were able to demonstrate the localization of hemorrhage as sub-ILM. In these cases the cleavage plane could be identified by ophthalmoscopy due to already detached vitreous at the area of the sub-ILM hemorrhage, by echography, optical coherence tomography (OCT) or by histological analyses of the surgically removed anterior wall of the hemorrhage.\textsuperscript{4, 7–9, 17–28}

The lack of a definitive differentiating biomicroscopic characteristic emphasizes the difficulty in detecting clinically the location of tissue separation. But this distinction could have an implication for eventual treatment regimen. In selected cases OCT may be helpful. In general an OCT scan through the center of a hemorrhage at the macula does not illustrate whether the hemorrhage is

![Figure 7-8A](image1.png)

**FIGURE 7-8A:** Hemorrhage at the macula, the fundus image does not allow differentiating between subhyaloidal hemorrhage (preretinal hemorrhage) or sub-ILM hemorrhage (intraretinal hemorrhage); the white arrow demonstrates the area, length and direction of the OCT scan that is shown in Figure 7-8B

![Figure 7-8B](image2.png)

**FIGURE 7-8B:** Corresponding OCT scan; The scan through the center of the hemorrhage does not allow to state the exact location of the hemorrhage
subhyaloidal or sub-ILM. Moreover, it does not even allow the differentiation between pre- or subretinal hemorrhage as the underlying structures are severely attenuated (Figures 7-8A and B). Shukla et al. performed the OCT scans just above the level of sedimented blood and in case of partial detached vitreous these scans displayed two distinct membranes. A single highly reflective band corresponded to the ILM and an overlying membrane with low optical reflectivity demonstrated the posterior hyaloid. Previously we demonstrated a selective A-scan analysis and identified numerous hyper-reflective spikes whereas a highly reflective band corresponded to the anterior wall of the prior hemorrhage corresponding to the ILM. In cases where OCT did not allow to differentiate between subhyaloidal and sub-ILM location we performed OCT after performing argon laser puncture to release the hemorrhage into the vitreous. When the optical media cleared up – in most cases one or two days after laser puncture – OCT was performed. Hereby, the anterior wall of the hemorrhage could be visualized as there was a hyporeflective area beneath, representing the cavity of prior blood accumulation. The reflectivity of the A-scan was measured (Figure 7-9A) and compared to the reflectivity of the posterior hyaloid (Figure 7-9B).

**FIGURE 7-9A:** OCT scan and measurement of A-scan reflectivity in a case of subhyaloidal hemorrhage. The OCT scan is performed in the upper part of the hemorrhage. The distinct membrane is marked with cursor 2 and the surface of the neuroretina is marked with cursor 1. The difference is 1.1 dB. Therefore the distinct membrane represents a high reflective membrane.
Hemorrhage at the Macula: Classifications and Treatment Options

**FIGURE 7-9B:** OCT A-scan measurement of a posterior vitreous detachment. Cursor 1 represents the posterior hyaloid, whereas cursor 2 demonstrates the surface of the neuroretina. The difference of these two spikes is 15.4 dB. The posterior hyaloid appear with low reflectivity

**Treatment Options**

Treatment options should consider the underlying disease.

In the natural course of history, spontaneous reabsorption of the hemorrhage may occur slowly within one to two months. The possible complications of persistence of blood may cause irreversible retinal damage and permanent visual loss due to preretinal tractional membrane formation and proliferative vitreoretinopathy. Moreover, the toxic effect of longstanding preretinal blood is a concern which is even more toxic in macular hemorrhage. It should be considered in the decision of treatment that the hemorrhage beneath the ILM tends to remain longer than the subhyaloid hemorrhage.

Laser drainage, introduced in 1973 by Heydenreich, can be used to provide the entrapped blood, by creating a focal opening, into the vitreous cavity which may result in accelerated clearing and visual improvement. As a complication of this procedure epimacular membrane (ERM) formation has been described. The hemorrhage contains growth factors stimulating proliferation of entrapped cells along the outer ILM and retinal surface. Probably, this occurs in cases where the hemorrhage is located beneath the ILM so that laser drainage requires disruption of the basal lamina of sensory retina with a consequent gliotic wound healing response.
Vitrectomy allows the effective removal of the hemorrhage without any delay. By this method the surgically removed anterior wall of the hemorrhage cavity can be analyzed and the location definitely stated. However, even though vitrectomy is a routine procedure, it is associated with numerous risks and side effects. Formation of a nuclear sclerotic cataract is a well-known and relatively common complication, especially in patients over the age of 50 years. Intraoperative retinal breaks, postoperative proliferative vitreoretinopathy that may result in retinal detachment and severe loss of visual function and endophthalmitis are possible side effects.

Summary
First, the synonym “premacular hemorrhage” was used in the literature for the subhyaloidal as well as the sub-ILM hemorrhage, as in most cases a differentiation was not possible. The term “subhyaloidal” actually describe the location between hyaloid and retina. If the hemorrhage is located beneath the ILM, sub-ILM hemorrhage, macular hemorrhage or macular hematoma seems to be an adequate description. If the exact location can not be determined, “hemorrhage at the macula” represents an appropriate description.

Second, in consideration of the exact location of the hemorrhage, in selected cases we differ these by ophthalmoscopy (evaluation of the vitreous and surface of the retina), echography, OCT, staining with dyes intraoperatively and histological analyses postoperatively. Third, the period of waiting for the natural course and the time point of intervention as well as the best treatment option is speculative. Fourth, laser drainage has shown very good functional results, nevertheless secondary membrane formation has also been reported in selected cases and required additional surgery with vitrectomy. For these cases the location of hemorrhage has been demonstrated beneath the ILM. Further studies are necessary to clarify whether laser drainage is more eligible for subhyaloidal hemorrhage and vitrectomy for sub-ILM hemorrhage.

References
Retinal Stress by Vitreous Traction
Introduction

The vitreous body with a total volume of about 4 ml makes up two-thirds of the intraocular space and consists of 98% water and 2% hyaluronic acid and collagen-fibers. The collagen-fibers form a scaffold, which is arranged loosely in the vitreous and condenses preretinally to form the posterior vitreous cortex. This structure is especially dense in the area of the ora serrata, the so-called vitreous base. The collagen-fibers also insert into the inner retinal layer, the so-called internal limiting membrane (ILM). This connection seems to be very tight at the posterior pole, around the optic disc as so-called Weiss-ring and in the foveal area. In the periphery, this connection is especially adherent at the vitreous base.1

The Adherence of Retina and Vitreous Cortex: Interdependence Diseases

The tight adherence of retina and vitreous cortex is the reason why, changes of the vitreous can also influence the retina and vice versa. The normal vitreous is subject to degeneration. As a consequence this leads to a condensation of collagen-fibres. Finally, water-filled lacunae develop, that can pass through the posterior vitreous cortex and separate it from the retina. This characteristically happens at the central retina and is called “posterior vitreous detachment (PVD)”. Influencing factors include higher age, myopia, after cataract removal, trauma and intraocular diseases, such as uveitis. This physiological ageing process may be complicated by the fact that posterior vitreous detachment may remain incomplete, thus leading to anterior-posterior traction to the retina.

Tangential retinal tractions can also be found in cases with adherent posterior vitreous, when vitreous condenses and shrinks.2 A completely or partially attached vitreous may be the cause of many diseases of the central retina, such as the macular traction syndrome, or it may influence the course of the disease, such as in diabetic maculopathy.3,6

Examination of the Vitreous by Biomicroscopy Ultrasound and OCT

The vitreous is examined biomicroscopically with a 90 or 78 diopter lens, by ultrasound or optical coherence tomography (OCT). If the optical media are clear, a floating peripapillary ring (Martegiani) is a sign for PVD. Preretinal traction may either be recognized by a condensed posterior vitreous or a distortion of the underlying retina.

With ultrasound (USG), different vitreous densities can be demonstrated (Figures 8-1A and B). The border between vitreous-cortex and posterior hyaloid are characterized by a fluctuating structure particularly in cases of PVD where cellular precipitates are enhancing this border. Vitreous tractions inserting in the retina in retinal detachments can be visualized by ultrasound even in the presence of cloudy optical media (Figure 8-2).

The OCT yields high resolution images of retinal structures. Clear optical media and cooperative patients are required in order to perform this examination. With this technique retinal thickness and ultra-structure of the retina with its different layers can be demonstrated as well as the posterior vitreous and vitreo-retinal tractions (Figure 8-3).

Additionally, the posterior vitreous is also visualised during pars plana vitrectomy (Figure 8-4) using a white angle viewing system such as the binocular indirect ophthalmoscope (BIOM) which
Retinal Stress by Vitreous Traction

FIGURES 8-1A AND B: (A) Ultrasound: opacification of the vitreous cavity, the vitreous is attached, but no focal vitreous traction is visible; (B) Ultrasound: focal vitreoretinal traction

FIGURE 8-2: Fundus image; due to vitreous hemorrhage the retina is not visible in detail

allows good fundus overview.

The posterior pole can be examined using a Kilb contact lens which has only a small viewing angle but greatly enhances fine preretinal structures, such as a Martegiani ring and tractions induced by suction with a vitreous cutter. The extent of a posterior vitreous detachment can thus easily be recognized. Furthermore, dyeing of the border layers using triamcinolone can help judging whether a posterior vitreous detachment is present or not (Figure 8-5).

Posterior Vitreous Adherence in Proliferative Diabetic Vitreoretinopathy

Since 1999, the presence or absence of a PVD was documented in all 3300 vitrectomies performed at
the Marburg eye clinic. It turned out that a complete PVD was found only in those 600 eyes with a rhegmatogenous retinal detachment. The posterior vitreous was found to be most adherent in patients with a proliferative diabetic vitreo-retinopathy. Here, tight connections were frequently found between the posterior vitreous and tractions along the great vessel arcades. The membranes were partially vascularized and had to be removed from the retina surgically with vitreous scissors. In some patients, a PVD was found over the macular area, in others, a second membranous structure was found beneath that was removed as well. If fine folds of the internal limiting membrane (ILM) were recognized, the ILM too was removed in an area with a radius of about two disc diameters around the fovea. If the membrane could not be clearly visualized, it was colored with indocyanin-green (ICG). It could be observed, that ICG only precipitated on the preretinal vitreous structures

**FIGURE 8-3**: Optical coherence tomography: macular traction in a case of exudative age related macular degeneration with choroidal neovascularization (female, 85 years)

**FIGURE 8-4**: Intraoperative fundus image during vitrectomy: preretinal proliferations and tactional vitreous adhesions are visible
Retinal Stress by Vitreous Traction

Patients demonstrating a persistent diabetic maculopathy following focal laser coagulation and intravitreal triamcinolone injection or anti-VEGF (vascular endothelial growth factor) injection underwent vitrectomy and there showed an almost completely attached posterior vitreous even if extensive panretinal photocoagulation had been performed prior to the surgery. In such cases, a PVD is induced surgically by applying suction and traction over the optic disc with a vitreous cutter. However, the posterior vitreous is often very adherent in the foveal area and there leads to a rupture of foveal cysts and formation of macular holes. To avoid this, vitreous adherences must be cut surgically with scissors. If the macula appears thickened and the ILM has folds, a removal of the ILM following ICG-staining is indicated.

Age-related Macular Degeneration

In age-related macular degeneration (AMD) with choroidal neovascularisation (CNV) mostly an attached posterior vitreous was found. In 190 patients with an exudative AMD and CNV an attached posterior vitreous was found in virtually all cases during vitrectomy. Even in those 20 eyes with a floating Martegiani ring adherent vitreous remnants attached to the macula were found. There was no difference between untreated patients and prior treatment by photodynamic therapy (PDT), laser treatment, or intraocular anti-VEGF injection (Figures 8-6A and B). In 25 eyes that had undergone intravitreal r-TPA (recombinant tissue-plasminogen-activator) and gas injection due to subretinal hemorrhages, the posterior vitreous could easily be removed intraoperatively.

Idiopathic Macular Holes

Eyes with stage I through stage III macular holes characteristically have an attached posterior vitreous. These preoperative findings could be verified intraoperatively. The vitreous is especially adherent
around the optic nerve head and very difficult to identify due to its transparency in these patients. Some eyes show a tangential traction inserting at the rim of the macular hole. These patients frequently complicate with intraoperative retinal break formation because of peripheral tractions, which is treated by cryopexy or endolaser intraoperatively.

The posterior vitreous was often attached even in those eyes described as stage IV macular holes preoperatively, probably because vitreous clouding was interpreted as PVD. In all those eyes ICG-assisted ILM-peeling was performed apart from inducing a PVD.

It was noted that the ILM appeared thinner than in diabetics but could be removed more easily than in an edematous macula. As already mentioned above, the ILM is especially adherent to the rim of macular holes and most likely itself a component of tangential traction. In stage I macular holes a perforating hole can be induced accidentally by the surgical procedure.

Patients with a cystoid macular edema following cataract surgery (Irvine-Gass-Syndrome) or recurrent inflammation presented with increased local vitreous adherence and incomplete PVD similar to a macular traction syndrome. This is also the case in patients with epiretinal gliosis, where the gliosis comes off together with the posterior vitreous.

Retinal Vein Occlusions

We performed pars plana vitrectomy with sheathotomy (separation of the common adventitial sheath of retinal arteries and veins in the area of occlusion) in patients suffering from branch retinal vein occlusion and neurotomy (cutting of the scleral ring at the optic nerve head) in those suffering from central retinal vein occlusion. None of these eyes presented with a PVD intraoperatively. Routine ILM removal proved more difficult in these cases with edematous retina, because the ILM seemed to be more adherent to the other retinal structures and at the same time more fragile. It could therefore not be removed in one piece.

Vitrecomy is Helpful in Many Retinal Diseases

The close neighborhood between retina and vitreous may explain the interdependence of disease
Retinal Stress by Vitreous Traction

processes of both structures. Schepens already described that a rhegmatogenous retinal detachment is only possible if the vitreous is liquefied and detached.\textsuperscript{7} A PVD becomes more likely with increasing age and is seen in over 50\% in patients 65 years and older.\textsuperscript{1,8,9}

It is all the more amazing that this physiologic process is missing in many diseases of the posterior retina.\textsuperscript{10}

Traction components may interfere with retinal physiology and metabolism by an adherent, thickened posterior vitreous attached to the retina thus negatively influencing diffusion between anterior and posterior areas in the eye. Several studies could show that vitrectomy may improve various retinal diseases. A PVD induced during surgery might be the key effect of vitreous surgery similar to the vitreous liquefaction found in diabetics following panretinal photocoagulation for proliferative diabetic vitreoretinopathy (PDVR).\textsuperscript{11}

Many pathologies such as macular edema disappears after surgically induced PVD.\textsuperscript{12,13} Macular holes may close spontaneously following surgically induced PVD. ILM-peeling could increase the closure rate, but a sole vitrectomy may be sufficient in some patients.\textsuperscript{14}

In AMD patients previously treated without success by PDT and intravitreal injections, the posterior vitreous was found attached during subretinal surgery.\textsuperscript{10} The reason could be that permanent macular traction causes an increased release of inflammatory parameters and VEGF into the subretinal space. This in turn might be responsible for the persistence, the growth, or even the induction of choroidal neovascularisation.

These observations by authors suggest that in the future more attention should be given to the vitreous when treating retinal pathology. If the posterior vitreous remains attached following minimally invasive procedures such as laser or intraocular injections, a surgically induced PVD by pars plana vitrectomy may be considered.

In future, a PVD or vitreolysis might be induced pharmacologically, i.e. by plasmin or microplasmin. Prospective, randomized, controlled, clinical trials are necessary to see whether a vitrectomy as primary treatment is reasonable in cases where there is no obvious traction and to assess the value of adjunct measures such as neurotomy, sheathotomy, and ILM-peeling.

Summary

Due to the immediate neighborhood of vitreous and retina, retinal diseases are frequently associated with changes is the vitreous. During the last years, the condition of the vitreous and posterior vitreous adherence were diagnosed biomicroscopically, my ultrasound and OCT. The results were then compared with findings during vitrectomy. In almost all vitrectomies for macular and retinal diseases we found an attached posterior vitreous intraoperatively, which seemed especially adherent at the posterior pole. This correlated only partly with preoperative findings, where a posterior vitreous detachment was described frequently. The literature describes a high percentage of complete posterior vitreous detachment in patients, increasing with age. In patients who undergo vitreoretinal surgery for macular or retinal diseases, an attached posterior vitreous is found frequently. We postulate that this finding, which is atypical for that age group, may be a causative agent for retinal or vascular disease and prevents a successful treatment of AMD and other diseases because of macular traction. An early removal of the posterior vitreous may support treatment of these
diseases.

References

Introduction

Polyoidal choroidal vasculopathy (PCV) has been recognized since the 1980s. It was first described by Stern et al. and Perkovich et al as “multiple recurrent retinal pigment epithelial detachments in black women”.1,2 Later, it was classified as “posterior uveal bleeding syndrome” by Kleiner et al and Blumenkranz et al.3,4 In 1990, Yannuzzi and colleague designated it “idiopathic polyoidal choroidal vasculopathy” in order to characterize it as a distinct clinical entity of unknown etiology with a peculiar network of choroidal vessels, polyoidal subretinal choroidal nodular lesions, and recurrent serous and hemorrhagic detachments of the retinal pigment epithelium (RPE) and neurosensory retina.5 Using indocyanine green angiography (ICGA), Spaide et al confirmed that PCV has two basic choroidal vascular components: a branching network of vessels in the inner choroid and aneurysmal vascular dilations in a polyoidal configuration.6

More than two decades after the original report, knowledge about PCV has increased rapidly, thus allowing us to understand the demographic profile, clinical manifestations, clinicopathological correlation, natural course, modalities of treatment, and the visual prognosis in patients with PCV with greater detail and precision. The natural history of PCV is reported to be more favorable than that of neovascular age-related macular degeneration (AMD),7 however, half of all patients may suffer from severe visual loss due to massive hemorrhage or severe RPE atrophy after a longer follow-up period.8 Possible treatments include laser photocoagulation, photodynamic therapy (PDT), intravitreal anti-vascular endothelial growth factor (anti-VEGF), and surgical removal of the fibrovascular membrane with or without macular translocation.9-17

Epidemiology

PCV previously was thought to be a rare disease. However, although the true incidence of PCV is still unclear, improvements in diagnostic techniques have shown that PCV is actually more common than originally believed. The clinical presentations of PCV can mimic those of AMD; therefore, many patients may have received a diagnosis of AMD before PCV was well-recognized. Currently, ICGA is the diagnostic choice in differentiating PCV from AMD. Yannuzzi et al reviewed 167 patients initially diagnosed with AMD in the US, and found that 13 (7.8%) of them had PCV.18 Similar results were obtained by Sforzolini et al, in which 19 (9.8%) of 194 Italian patients presumed to have AMD actually had PCV.19 Kwok et al performed ICGA in 204 Chinese patients with provisional diagnoses of AMD, and found that 22 eyes of 19 patients (9.3%) had PCV.20 This percentage is even higher in the Japanese population. Sho et al performed fluorescein angiography (FA) and ICGA in 471 eyes with presumed neovascular AMD, and diagnosed PCV in 110 eyes (23%).21 Thus, PCV might actually be quite common among patients previously thought to have AMD.

PCV was once believed to occur primarily in middle-aged to elderly black women. In 1997, Yannuzzi et al expanded the clinical spectrum of PCV and demonstrated that it affects various ages, both genders, and several racial populations.18 Later reports showed that demographic data may vary widely among different patient populations, as summarized in Table 9-1.8,19-23

AGE

The mean age at diagnosis was between 60 and 70 years of age in previous reports.7,13,18,20-22 However, although it has been suggested that patients affected by PCV were younger than those with AMD,7 the age at diagnosis can range from the 20s to 80s.
Polypoidal Choroidal Vasculopathy

Table 9-1: Comparison of demographic features in different PCV studies

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<th>Authors</th>
<th>Ethnicity, %</th>
<th>No. of patients</th>
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<th>Male sex, %</th>
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GENDER

In the earliest reports, it was thought that PCV affected women exclusively, but it was later shown that both genders could be affected. Yannuzzi et al reported a female to male ratio of approximately 4.7:1 in their series. However, in a later report from the same group, both genders were equally involved. Other reports from Asian countries such as Japan, Hong Kong, and Taiwan showed a predominance of men by a ratio of approximately 2:1.

RACE

Black patients seemed to be preferentially affected in the earlier reports, further expansion of the clinical entity indicated that the disease is prevalent in all races although the incidence and demographic features of PCV do vary in different ethnic groups. Clinical experience suggests that the incidence of PCV is higher in blacks, Japanese, and other Asians than in whites. This is in contrast to the incidence of AMD, which is high in whites, moderate in Asians, and very low in blacks. Yannuzzi et al reported that most white patients with PCV were women with bilateral involvement and peripapillary location of the PCV. However, there was a preponderance of men with unilateral involvement and macular location of abnormal vessels reported in Japanese patients. Kwok et al and Yeung et al reported that the findings in the Chinese population were similar to those in the Japanese population. The reason for these epidemiologic differences in gender, laterality, and location of lesions in the different ethnic groups is not known.
SYSTEMIC FACTORS

Some studies found that 20%-30% of patients with PCV had a history of hypertension.21,25,29 Ross et al had suggested that certain subgroups of PCV and retinal arterial macroaneurysm might be pathophysiologically related as analogous hypertensive insults to the choroidal and retinal vascular beds.30 However, a relationship between PCV and hypertension could not be shown in other studies.20,24

Pathophysiology

The peculiar abnormality of PCV is believed to originate in the inner choroid, external to the choriocapillaries.7 It consists of 2 fundamental elements: a dilated network of vessels and multiple terminal aneurysmal protuberances in a polypoidal configuration.7 These polypoidal lesions appear to account for the episodic leakage and bleeding under the RPE and neurosensory retina that can occur in these patients. The exudative changes can lead to variably sized serosanguineous pigment epithelium detachments (PEDs).5,7 Some patients may also experience bullous retinal detachment and vitreous hemorrhage.1-3,5,7

HISTOPATHOLOGY

Few specimens of PCV have been studied histopathologically. Most reports describe a collection of dilated thin-walled vessels derived from choroidal vessels beneath the RPE in Bruch’s membrane. Lafaut et al examined submacular tissue from an eye with PCV and found a thick fibrovascular membrane with drusen and dilated thin-walled vessels that appeared saccular in serial sections. The authors noted that the aneurysmal vessels appeared to be of venular origin and were probably the pathological counterpart of the PCV lesion in ICGA angiography.31 Okubo et al also found tortuous, unusually dilated venules in a submacular polypoidal vascular lesion that had been surgically removed.9 However, Rosa et al examined an enucleated eye and proposed that the network of peripapillary vessels seen on FA and ICGA derived from branches of posterior ciliary arterties.32 Terasaki et al examined two neovascular membranes obtained during macular translocation surgery for PCV.15 They found polypoidal structures within Bruch’s membrane, which were composed of clusters of dilated, thin walled blood vessels surrounded by macrophages and fibrin material. They showed positive immunohistochemical staining for vascular endothelial growth factor (VEGF) in the RPE and the vascular endothelial cells. In two enucleated eyes with rubeosis iridis and acute angle block glaucoma due to massive subretinal hemorrhage,33,34 extensive fibrovascular proliferation was noted within Bruch’s membrane and between Bruch’s membrane and the RPE. This disciform scar may reflect the end stage of the disease (Figures 9-1 and 9-2).

PATHOGENESIS

The pathogenesis of PCV is unknown. PCV was once proposed to be a variant of choroidal neovascularization (CNV) and to represent a subtype of neovascular AMD.7,31,32,35 However, it is now believed to be an abnormality of the inner choroidal vessels.9,36,37 PCV and wet AMD share some pathologic similarities: serum C-reactive protein levels are significantly elevated,38 VEGF concentrations in the aqueous humor are significantly increased,39 and positive immunohistochemical staining is similar in surgically excised PCV lesions.15 However, PCV had distinct demographic features, clinical presentations, angiographic characteristics, natural course, and visual prognosis when compared to AMD.1-3,7,8,10,12,13,16,18,21,23,25-28,40,43 Yuzawa et al used confocal scanning laser ophthalmoscopy to study
Polypoidal Choroidal Vasculopathy

**FIGURE 9-1:** (A, top left) Color photography of the fundus of a patient with peripapillary PCV demonstrates hemorrhagic pigment epithelial detachment and subretinal hemorrhage. (B, top right) ICGA angiography reveals a cluster of actively leaking polypoidal choroidal lesions and abnormal vessels over the peripapillary area. (C, bottom left) Color photography of the fundus of a patient with macular PCV demonstrates subretinal exudates and fluids. (D, bottom right) ICGA angiography reveals two actively leaking polypoidal choroidal complexes over the macular area

45 eyes with PCV. They found that vessels comprising branching networks began to fill simultaneously with the surrounding choroidal arteries in 38 eyes. Vessel pulsation, not a feature of CNV, was seen in 24 eyes. These authors concluded that PCV is caused by inner choroidal vessel abnormalities, not CNV.

Kondo et al recently published two genetic analyses of PCV using single nucleotide polymorphisms (SNPs). They found that the LOC387715/HTRA1 variants are associated with both PCV and wet AMD in the Japanese population. However, the odds ratios and population-attributable risks were higher for the patients with AMD than for the patients with PCV. In another study, they showed that the elastin gene (ELN) variant was significantly associated with susceptibility to PCV, but not to AMD. Their findings might implicate ELN as a susceptibility gene for PCV, and suggest that a different pathogenic process may be involved in the phenotypic expression of wet AMD and PCV.
Clinical Features

CLINICAL MANIFESTATIONS

The most common presenting symptom of PCV is blurring of vision.\textsuperscript{20} Other symptoms included metamorphopsia, floaters, and central scotoma. Patients can also be asymptomatic and found to have PCV on routine examination. The presenting visual acuity is highly variable. Sho et al studied...
110 eyes with PCV, in which the presenting vision was equally distributed across 3 gradients of 0.2, 0.3-0.7, and 0.8, respectively. The mean visual acuity was 20/60.

PCV is characterized clinically by the presence of dilated, choroidal vascular channels ending in orange, bulging, poly-like dilations in the peripapillary region or macular area. It is associated with multiple, recurrent, serosanguineous detachments of the RPE and neurosensory retina secondary to leakage and bleeding from these peculiar choroidal vascular lesions. The common findings in the fundus are serous macular detachment, subretinal hemorrhage, serous or hemorrhagic RPE detachment, and retinal exudation. Other manifestations included RPE degeneration, subretinal fibrovascular proliferations, and breakthrough vitreous hemorrhage. Disiform scarring is uncommon in PCV.

Studies in Asian populations showed that unilateral involvement was found in most patients (80-90%) when they received their initial diagnosis of PCV. Many of them demonstrated no evidence of PCV in the fellow eye after more than 10 years’ follow-up. However, in the white population, PCV could present either as a unilateral or bilateral disease.

PCV lesions can develop at any part of the fundus, although peripapillary lesions were more common in Yannuzzi et al’s series. Macular lesions were predominant in most later studies. The lesion can also be located over the mid-peripheral and peripheral fundus.

**DIAGNOSTIC TESTS**

The clinical diagnosis of PCV is made on the basis of ophthalmoscopic identification of subretinal reddish-orange spheroidal lesions arising from choroidal vessels. Multiple recurrent serosanguineous RPE or neurosensory retina detachments indicate the possibility of PCV. Definitive diagnosis should be confirmed by the typical features of PCV on ICGA. PCV has two basic choroidal vascular components: a branching network of vessels in the inner choroid and aneurysmal vascular dilations in a polypoidal configuration. The polyps could be one or more focal vascular dilatations in the inner choroid. A cluster of grapelike polypoidal vascular dilations may be observed. These characteristic features are shown at the early phase on ICGA. The majority of polyps and localized hyperfluorescent lesions with terminal branching are seen within the first minute after injection of ICG dye. In the late phase, the core of the polypoidal lesions may become hypofluorescent because of washout of the dye and show a ring-like staining of the polyps. This might not be seen if there has been active leakage from the polyps.

As most components of PCV are located beneath the RPE, they appear typically as occult CNV on FA. However, other fluorescein patterns can also be found. Gomi et al reported 36 eyes with PCV treated with PDT, in which the FA pattern was predominantly classic in 8% eyes, minimally classic in 33% eyes, and occult in 58% eyes. PCV may sometimes accompany type 2 (subretinal) CNV, most of which is shown to be classic CNV on FA. However, leakage from active polypoidal lesions can result in subretinal fibrinous exudation, which may also mimic classic CNV on FA. The visual prognosis of subfoveal type 2 CNV is usually poor. However, it is difficult to differentiate the pure fibrinous exudation from type 2 CNV using FA and optical coherence tomography (OCT). Tamura et al studied 38 PCV eyes with classic CNV patterns on FA. They concluded that when subretinal material corresponding to classic CNV is seen in the subfoveal region or is separate from the polypoidal lesions, the eye may actually have type 2 CNV.

OCT is also a useful tool for the diagnosis and evaluation of the response to treatment in eyes with PCV. Using OCT, Iijima et al and Otsuji et al reported steep dome-like elevations of highly
reflective RPE layers with underlying moderate reflectivity within the dome consisting of polypoidal lesions of PCV. Sato et al used third-generation OCT to evaluate 44 eyes with PCV. The OCT showed prominent anterior protrusions of the highly reflective RPE in the polypoidal lesions in all eyes. Double reflective layers that consisted of the RPE and another highly reflective layer beneath the RPE (“double-layer sign”) could be seen in area of branching network vessels in 59% of the eyes. These authors suspected that the space within the double-layer sign reflects fluid accumulation between the basement membrane of the RPE and the inner boundary of the Bruch’s membrane/choriocapillaries complex.

The OCT-ophthalmoscope is a new device that can capture cross-sectional (longitudinal, B-scan) and en face (transverse, C-scan) images of the posterior fundus. The en face OCT could detect round protrusions of the RPE that corresponded to the polypoidal lesions seen on ICGA. PEDs were seen as round protrusions of the RPE and were often accompanied by adjacent smaller round protrusions of the RPE, consistent with polypoidal lesions. The branching vascular networks seen on ICGA often induce slight elevation of the overlying RPE, which typically assumed a geographic shape.

**NATURAL COURSE**

The disease often follows a remitting-relapsing course; and clinically, it is associated with chronic, multiple, recurrent serosanguineous detachments of the RPE and neurosensory retina. Yannuzzi et al proposed three mechanisms of disease progression. The lesion may be enlarged by simple vessel hypertrophy, by conversion of the lesion into the advancing edge of a vascular channel, and by unfolding of a cluster of aneurysmal elements and subsequent transformation into enlarging, vascular, tubular components. New lesions may also develop at a different location within a given eye.

PCV was generally reported to have a better natural course than AMD. Patients who have had multiple polypoidal bleeds with spontaneous resolution of the associated detachments can preserve good central vision, particularly when the bleeding was from the peripapillary area. Some patients even experience dramatic involution or even autoinfarction of the membrane. However, Uyama et al and Sho et al also observed that one-third to half of patients with PCV may experience severe visual loss (visual acuity of 20/100 or worse). The causes of severe visual loss could be (1) persist submacular hemorrhage or serous retinal detachment of the macula, which leads to atrophy of the RPE and sensory retina in the macula; or (2) subretinal fibrovascular proliferation, which markedly damages macular function. Kwok et al stated that the overall visual prognosis for PCV is guarded in the Chinese population. They followed 13 eyes with PCV in a non-laser treated group for 28.2 months (range, 4–60 months). The median initial visual acuity was 20/40 (range, 20/25 to 1/60). Only one eye (7.7%) had improvement of two or more Snellen lines, while nine eyes (69.2%) had a gradual decrease of visual acuity of two or more Snellen lines. The mean loss of vision for this group was 3.1 Snellen lines. Ten eyes (76.9%) had a final visual acuity of 20/200 or worse. From our experience, the location of the lesions may be one of the important factors affecting final visual outcome. Extrafoveal PCV was usually associated with a relatively good prognosis. The visual outcome could be expected to be poor if the abnormal choroidal vasculature, retinal exudation, or hemorrhagic detachments involved the subfoveal area. In contrast to the white population, the polypoidal lesions are more likely to located in the macular region than the peripapillary region in Japanese and Chinese populations. This may explain why worse prognoses were reported in the studies from these Asian populations.
Differential Diagnosis
The clinical presentations of PCV may resemble those of AMD. A measurable number of elderly patients with findings suggestive of neovascular AMD and serosanguineous macular manifestations will instead have PCV. Yannuzzi et al suggested that PCV is associated with a lower incidence of significant drusen in the fellow eye, occurs more commonly in the peripapillary area, more frequently has large serous PED, and is more prevalent in non-white patients as compared with AMD. However, both PCV and AMD can occur simultaneously in the same eye. It was also reported that PCV lesions developed after the therapeutic irradiation of neovascular AMD. PCV may also mimic central serous chorioretinopathy (CSC) in some patients. Yannuzzi et al reported that 13 patients initially thought to have CSC were ultimately given a diagnosis of PCV. CSC can be easily differentiated from PCV in most patients; however, in CSC with persistent and/or recurrent exudation, a myriad of retinal pigment epithelial changes may evolve that make it difficult to differentiate from PCV. In such patients, ICG angiography is useful in differentiating CSC from PCV. Although choroidal vascular hyperpermeability on ICGA is a characteristic feature of CSC, it can also appear in some patients with PCV.

The differential diagnosis of a reddish orange lesion under the retina includes choroidal hemangioma or metastasis from carcinoid syndrome or, more rarely, renal cell carcinoma, posterior scleritis, and choroidal osteoma. ICGA is useful in differentiating PCV from other lesions by showing dilated inner choroidal vessels and polypoidal vascular elements beneath a PED.

Management
There is no consensus about the best treatment for PCV. Some asymptomatic polyps have been managed conservatively and were noted to resolve spontaneously over time with preservation of good vision. Possible treatments for symptomatic PCV include argon laser photocoagulation, photodynamic therapy (PDT), intravitreal anti-VEGF, and surgical removal of fibrovascular membrane with or without macular translocation.

Observation
Because there is no proven treatment for PCV and the general prognosis is believed to be better than that of AMD, close observation may be a reasonable way to manage those lesions that are located away from the macular region. An Amsler is grid should be provided to patients to monitor any possible progression of lesions into the macular region.

Laser Photocoagulation
ICGA-guided argon laser photocoagulation is one of the potential treatments for polypoidal lesions in selected PCV patients. Photocoagulation of the leaking polypoidal lesion may resolve the associated serosanguineous complications and restore vision. Laser photocoagulation can also be performed after surgical removal of the thick submacular hemorrhage in some cases. Lafaut et al treated 14 eyes with PCV with laser photocoagulation to the polyps. In the five peripapillary lesions they treated, all the polyps regressed with resolution of the fundal lesions. However, among the nine eyes with polyps in the macula or along major vascular arcades, similar success was only achieved in five eyes. Uyama et al performed laser photocoagulation in 17 eyes in which 12 (71%) showed clinical improvement with a decrease of haemorrhage and subretinal fluid. Four eyes (24%) worsened
with two of them developed disciform scars. However, compared with the untreated group, the latter had a better visual outcome. Kwok et al treated 9 eyes with PCV with laser, and five (56%) of them had stable or improved vision, while only four of the 22 untreated eyes (31%) achieved the same result. However, the difference was not statistically significant. Recurrence of polyps subfoveally and subsequent CNV can also occur after laser treatment. However, ICGA-guided argon laser photocoagulation is suggested if the PCV is located extrafoveally.

**SURGERY**

Some authors suggest surgical treatments. Shiraga et al suggested surgical removal of subretinal hemorrhages to minimize iron toxicity and blockage of nutrient diffusion, which could cause irreversible damage to the outer retina. However, there was a high incidence (37%) of RPE tears after surgery. Morizane et al reported on 7 eyes with subfoveal PCV that underwent limited macular translocation. Five of them improved 2 lines or more on the Snellen chart. However, there is lack of controlled studies to determine the benefit of surgical treatments over the natural history of the disease.

**PHOTODYNAMIC THERAPY (PDT)**

Recently, an increasing number of reports have shown encouraging results from PDT. PDT with verteporfin is an effective treatment for maintaining or improving visual acuity in patients with symptomatic PCV with macular lesions. Stable or improved vision was achieved in 81% to 95% of eyes after PDT. Chan et al reported that the use of PDT resulted in the complete absence of leakage on FA and total regression of polypoidal lesions on ICGA in 91% and 95% of patients, respectively. There is no consensus as to whether FA or ICG should be used to guide the PDT treatment in eyes with PCV, although most studies adopted ICGA-guided treatment. The size of the laser spot was chosen to cover the polyps and the surrounding abnormally dilated choroidal vessels shown on ICGA plus an extra margin of 1000 μm. In contrast to the treatment of AMD, the adjacent PED or hemorrhage in eyes with PCV was not included with the lesion. The number of PDT sessions necessary to treat PCV was less than that for typical AMD. Gomi et al showed that PDT is more efficacious for PCV than for AMD in Japanese patients. However, recurrent or new PCV lesions may develop after successful treatment. Subretinal hemorrhage is another common complication after treatment with PDT in eyes with PCV; a few patients may have severe visual loss because of extensive subretinal hemorrhages and vitreous hemorrhage. Hirame et al reported that postoperative subretinal hemorrhage was seen in 30.8% of eyes after treatment with PDT for PCV. Most of the hemorrhage was seen within 1 month after PDT, but some might occur after more than 3 months. Lesions needing larger sized spots of laser irradiation might have such hemorrhagic complications. The subretinal hemorrhage was absorbed without treatment in most of the eyes; however, vitreous hemorrhage in some eyes might require pars plana vitrectomy. If the location of the lesion is subfoveal or very close to the fovea, PDT may be the best current choice for treating the patient.

**ANTI-VEGF THERAPY**

VEGF concentrations in the aqueous humor were markedly increased in patients with PCV when compared with normal controls. The specimens from the eyes with PCV also showed strong expression of VEGF in the vascular endothelial cells and the RPE cells. These data support the
potential rationale for the use of anti-VEGF treatment in PCV. A few uncontrolled studies using intravitreal bevacizumab in PCV eyes have been reported recently. The preliminary data showed that intravitreal anti-VEGF may stabilize the vision and reduce subretinal fluid; however, it seems ineffective for resolving the polypoidal lesions. Further studies are required to elucidate the long term efficacy of different kinds of anti-VEGF therapies.

**COMBINATION THERAPY**

Combination therapy using agents with different mechanisms may, theoretically, provide a synergic effect in the treatment. Possible combinations could consist any of the anti-VEGF, intravitreal steroid, PDT, and laser photocoagulation therapies. The benefits of different combination therapies are worthy of further study.

**OTHER TREATMENTS**

Vedantham et al reported a case of PCV that was successfully treated with transpupillary thermotherapy (TTT). However, Mitamura et al showed that TTT was less effective and required more treatments than PDT in patients with PCV. Vitreous hemorrhage developed in 2 of the 11 eyes treated with TTT.

**Conclusion**

In summary, PCV is a distinct disease characterized by recurrent serous hemorrhage or detachments of the RPE and neurosensory retina. ICGA is used to confirm the diagnosis by showing the typical branching network of vessels in the inner choroid and aneurysmal vascular dilations in a polypoidal configuration. The incidence and demographic characteristics vary among patients with different ethnicities. Although the visual prognosis is believed to be better than AMD, half of the patient may suffer from severe visual loss because of atrophy of the RPE and sensory retina in the macula or subretinal fibrovascular proliferation. Possible treatments include laser photocoagulation, anti-VEGF therapy, PDT, and surgical removal of the subretinal fibrovascular membrane with or without macular translocation. Recent studies of treatment using PDT showed promising visual outcomes. In addition, a trend towards combination therapy may develop in the near future.

**References**

Chapter 10

Vitreous Hemorrhage: Recent and Future Management
Introduction

Vitreous hemorrhage is defined as the presence of extravasated blood within the vitreous cavity. The vitreous cavity is outlined by the zonular fibers and posterior lens capsule anteriorly, the nonpigmented epithelium of the ciliary body laterally, and the internal limiting membrane of the retina posteriorly and posterolaterally. Vitreous hemorrhage can present with sudden visual loss, the development of vitreous floaters or sometimes no symptoms at all, depending on severity and localization. This condition can have many etiologies, the nature of which will determine the precise treatment required.

Etiology

Various etiologies cause vitreous hemorrhage (Table 10-1). The blood originates mostly from retinochoroidal pathology. Vitreous hemorrhage can develop in three ways, firstly from abnormal retinal vessels (i.e. neovascularization); secondly, from avulsed retinal vessels or breaks; and thirdly, by breaking through the retina from the subretinal space. For the first two processes, most vitreous hemorrhage occurs during posterior vitreous detachment.

Neovascularization of the retina is common to some of the etiologies such as diabetes, retinal vein occlusion and sickle-cell anemia, and usually results from retinal ischemia. Angiogenic factors, such as vascular endothelial growth factor (VEGF), have been suggested to be the most important biological cytokines for retinal neovascularization. It has been reported that between 6% and 54% of vitreous hemorrhage resulted from proliferative diabetic retinopathy.

<table>
<thead>
<tr>
<th>TABLE 10-1: Causes of vitreous hemorrhage</th>
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<tbody>
<tr>
<td><strong>Vascular diseases</strong></td>
</tr>
<tr>
<td>Proliferative diabetic retinopathy</td>
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<tr>
<td>Retinal vein occlusion</td>
</tr>
<tr>
<td>Sickle cell retinopathy</td>
</tr>
<tr>
<td>Retinal arterial macroaneurysm</td>
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<tr>
<td><strong>Mechanical</strong></td>
</tr>
<tr>
<td>Trauma</td>
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<tr>
<td>Shaken baby syndrome</td>
</tr>
<tr>
<td>Child abuse</td>
</tr>
<tr>
<td>Eyeball rupture</td>
</tr>
<tr>
<td>Blunt ocular injury</td>
</tr>
<tr>
<td>Posterior vitreous detachment</td>
</tr>
<tr>
<td>Retinal break</td>
</tr>
<tr>
<td><strong>Maculopathy</strong></td>
</tr>
<tr>
<td>Age-related macular degeneration with choroidal neovascularization</td>
</tr>
<tr>
<td>Polypoidal choriovasculopathy</td>
</tr>
<tr>
<td><strong>Tumor</strong></td>
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<tr>
<td>Retinal hemangioma</td>
</tr>
<tr>
<td>Choroidal hemangioma</td>
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<tr>
<td>Choroidal melanoma</td>
</tr>
<tr>
<td>Vasoproliferative choroidal tumors</td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>Valsalva retinopathy</td>
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<tr>
<td>Terson syndrome</td>
</tr>
</tbody>
</table>
Vitreous hemorrhage combined with avulsed retinal vessels and/or breaks has a high risk of retinal detachment because blood itself is a risk factor for proliferative vitreoretinopathy. Determination of the cause of the hemorrhage is crucial for visual recovery and timely management. Vitreous hemorrhage from retinal avulsion should be considered more likely if the patient has a history that includes:
1. A previous history of retinal break or detachment;
2. Myopia;
3. A previous history of trauma;
4. No systemic history of diabetes, hypertension or sickle cell anemia.

Age, sex and race ethnicity should also be considered whilst defining the cause of vitreous hemorrhage. For example, age-related macular degeneration is rarely seen below the age of 40. Sickle cell anemia-related proliferative retinopathy should be considered among black patients. Similarly, trauma is a common cause of vitreous hemorrhage among young patients. The natural history and prognosis depend on the underlying etiology of the vitreous hemorrhage.

**Evaluation and Differential Diagnosis**

A review of systems and complete medical history taking are crucial for establishing the causes of vitreous hemorrhage. Specifically, histories of diabetes, hypertension, sickle cell anemia or trauma are the most important considerations. Retinal macroaneurysm is commonly associated with hypertension, which is often under-diagnosed.

A complete ocular examination can provide important clues. The other eye can provide useful insights into the affected eye. For example, retinal break should be highly suspected if the other eye presents myopia or has a history of retinal detachment. Drusen of the other eye should be apparent if macular degeneration is suspected as the cause of vitreous hemorrhage. Tobacco dust in the anterior vitreous (Schaffer’s sign) indicate retinal break or posterior vitreous detachment. Rubeosis iridis can be seen in vascular retinopathies such as diabetic retinopathy or retinal vein occlusion. It is often hard to see the fundus and find the source of blood. Although clearance of the blood is slow, all means should be taken to establish the cause of the bleeding on each office visit. Although ophthalmoscopy can seldom visualise the fundus, this procedure should always be carried out anyway. Indirect ophthalmoscopy is more effective at finding the source of bleeding, for example, if the vitreous hemorrhage is not too dense, a retinal break could be seen before retinal detachment arises.

Echography is a useful tool to evaluate the fundus if the vitreous hemorrhage occludes the view. A-scans (one-dimensional view of the eye) and B-scans (two-dimensional, cross-sectional view of the eye) are valuable tools that are widely used in preoperative evaluation. For example, B-scans are very effective at detecting mass lesions, which may develop into tumors. High internal echogenicity from an A-scan can be seen in vascular tumors such as retinal hemangiomas, whereas low internal echogenicity suggests the presence of a melanoma. V-shape topographic finding and after-movement can differentiate between simple vitreous hemorrhage and retinal detachment. However, in a longstanding vitreous hemorrhage after open globe injuries, it is usually too late to perform a vitrectomy once serial echographic examinations have documented retinal detachment. Hence planning when to perform the vitrectomy may depend on the exact nature of the etiologies.
Grading of Vitreous Hemorrhage

There is no single accepted standardized scale for grading vitreous hemorrhage. The scale depends on the entity and purpose of each specific study. Most studies grade the vitreous hemorrhage in a qualitative (mild/moderate/severe) or quasi-quantitative (1+ to 4+) approach. Vitreous hemorrhage is usually graded on the basis of the fundus, as visualized by ophthalmoscopy. Bhavsar et al. developed a grading scale by dividing the fundus into twelve divisions like a clock face and designating a score between 0-4 for each division. The twelve scores are summed to give a
Vitreous Hemorrhage: Recent and Future Management

FIGURE 10-2: B-scan showed suspected tractional retinal detachment (upper) and A-scan confirmed the tractional retinal detachment, which has high reflectivity (bottom)

Some patients, for instance after ocular trauma, may present with corneal opacity, hyphema, dense cataract or other anterior segment pathologies which can interfere with this grading procedure. In these cases, ultrasonography may provide an alternative approach.

Generally, vitreous hemorrhage can be graded as either localized or diffuse by its extent. It can also be graded according to the visibility of the fundus. Table 10-2 shows the grading system used.

<table>
<thead>
<tr>
<th>Grading scale</th>
<th>Visibility of funds</th>
</tr>
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<tbody>
<tr>
<td>None</td>
<td>No vitreous hemorrhage.</td>
</tr>
<tr>
<td>Mild</td>
<td>Most of the optic disc or retinal vessels are visible.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Optic disc or retinal vessels are barely visible.</td>
</tr>
<tr>
<td>Severe</td>
<td>Optic disc and retinal vessels are not visible.</td>
</tr>
</tbody>
</table>
in most of our studies which involved evaluation of the severity of vitreous hemorrhage. Most vitreous hemorrhage can be graded in a reasonably reproducible manner by providing both its extent and the visibility of the fundus. Figures 10-3A to D illustrates four different severities of vitreous hemorrhage.

Current and Future Treatments of Vitreous Hemorrhage

The natural history of vitreous hemorrhage depends on the underlying cause, and the clinical outcome is generally more favorable in eyes without any underlying disease. Treatment is directed at the underlying cause, such as laser photo-coagulation against proliferative diabetic retinopathy or retinal breaks. Occasionally, the hemorrhage does not resolve itself spontaneously and vitrectomy surgery
is necessary and beneficial. New strategies for the treatment of vitreous hemorrhage, such as pharmacologic vitreous liquefaction, may become important in the future.

**CURRENT TREATMENTS**

*Observation*

Restricting patient activity and elevating the head of the patient’s bed are conservative measures that are usually initially recommended. Patching and bed rest might help the blood to settle sufficiently to allow the superior peripheral retina to be examined for scleral depression within 24 hours. Ultrasonography could be performed regularly to see if there is development or concomitant presence of retinal detachment. Urgent vitrectomy is needed if retinal detachment has developed in combination with vitreous hemorrhage. For those patients where the blood is not surgically removed, a careful and frequent follow-up using serial B-scan ultrasound improves the reliability of the diagnosis at each visit, until such time as the vitreous hemorrhage resolves itself sufficiently to allow a full and proper examination of the retina. A confirmed retinal tear, retinal detachment or other fundus pathology are most appropriately treated by laser treatment or by vitrectomy. In children, observation (50.0%) was the most common treatment modality for those with vitreous hemorrhage.16

*Pan-retinal Photocoagulation (PRP)*

Whenever the fundus is adequately visualized, Pan-Retinal Photocoagulation (PRP) is always performed to stabilize the vitreous, or to achieve neovascularization regression, despite vitreous hemorrhage in diabetic retinopathy or in other retinal ischemic diseases with retinal neovascularization.17 This procedure may hasten the resorption of vitreous hemorrhage and reduce complications in the vitrectomy surgery subsequently performed.

*Cryotherapy*

Retinal cryotherapy against vitreous hemorrhage secondary to diabetic retinopathy and other etiologies has been reported with varying success.18-23 Benedett et al. reported 238 eyes with vitreous hemorrhage secondary to diabetic retinopathy when followed up after 6 months. Fifty percent of these eyes had reduced vitreous hemorrhage, 33% had no change, and 17% had increased vitreous hemorrhage.24 Postoperative retinal detachment occurred in 4% of eyes. Seventeen percent of eyes had recurrent vitreous hemorrhage and 15% eventually underwent vitrectomy. Visual acuity 6 months post cryotherapy had improved in 44%, was unchanged in 23% and had decreased in 33% of eyes. Cryotherapy treatment did not improve the visual outcome in comparison with vitrectomy and might have increased the breakdown of the blood retinal barrier and worsened ocular inflammation.25 With the wide availability of vitrectomy machines nowadays, cryotherapy is only rarely used.

*Pars Plana Vitrectomy*

Pars plana vitrectomy is the standard treatment for nonclearing vitreous hemorrhage. Diabetic vitreous hemorrhage remains a major indication for pars plana vitrectomy despite the worldwide use of PRP. Clinical information for the treatment of diabetic vitreous hemorrhage has mostly been derived from a single randomized clinical trial known as the Diabetic Retinopathy Vitrectomy Study (DRVS).11,26-28 This study evaluated the timing of vitrectomy for vitreous hemorrhage. The DRVS enrolled and managed patients between 1976 and 1980, during the early days of vitrectomy surgery. The first report was published in 1985.28 The study demonstrated that in type 1 diabetic patients
with vitreous hemorrhage, vitrectomy performed within 6 months gave a more favorable outcome than if surgery was referred for 1 year or longer. For the type 2 patients however, the results at these two different intervals were essentially the same. It is noteworthy that the DRVS recruited patients before the endolaser had been widely used.\textsuperscript{29-32} Pars plana vitrectomy outcomes improved with the introduction of the endolaser and modern instrumentation.\textsuperscript{33-37} Therefore, the indications of surgery were not limited by the results from DRVS.

The use of long-acting gas after diabetic vitrectomy has been found to reduce recurrent post-operative vitreous hemorrhage.\textsuperscript{38} Recently, using smaller gauge cutters (23 or 25 gauge) during vitrectomy has been found to shorten total surgical time, reduce surgical trauma, and fasten wound healing.\textsuperscript{39-42} Injecting an anti-VEGF antibody, bevacizumab (Genentech, San Francisco, CA), resulted in rapid regression of retinal neovascularization and fast resolution of vitreous hemorrhage in some eyes that had diabetic retinopathy.\textsuperscript{43} Pre-vitrectomy application of bevacizumab (Genentech, San Francisco, CA) has also induced fibrovascular tissues to regress, thereby reducing the likelihood of bleeding during surgery or of recurrent vitreous hemorrhage post-surgery.\textsuperscript{44,45} Although these anti-VEGF agents appeared to be well tolerated within diabetic eyes, it is noteworthy that these agents are still off-label for this particular application. The potential benefits and complications of these anti-VEGF agents need to be verified by more studies. Nowadays, vitrectomy for severe diabetic vitreous hemorrhage is performed within 3 months for type 1 diabetics and within 6 months for type 2 diabetics. Even more rapid vitrectomies have been advocated recently. Surgical goals include removal of vitreous hemorrhage to provide a clear medium, excision of the posterior hyaloid and epiretinal membrane to relieve vitreoretinal traction, and applying endolaser photocoagulation to achieve regression of proliferative tissue.

Post-vitrectomy, patients with nondiabetic vitreous hemorrhage have a better visual prognosis than patients with diabetic vitreous hemorrhage.\textsuperscript{46-48} Vision improved in 80\% of cases with vitreous hemorrhage secondary to retinal or choroidal vascular disease.\textsuperscript{47} Vision improved in 98\% of patients with non-vascular etiologies.\textsuperscript{46} The prognosis of patients after vitrectomy for vitreous hemorrhage secondary to retinal venous occlusive disease depends on the type of the occlusion. Patients with branch retinal vein occlusion were reported to experience improved visual acuity in 88-100\% of cases after vitrectomy.\textsuperscript{47-49} The prognosis is worse in patients with central retinal vein occlusion with improvement of visual acuity occurring in one third of these cases.\textsuperscript{47,49} The visual prognosis does not depend on the vitreous hemorrhage and its clearing, but more on the damage to the retina done by the vein occlusion. Vitrectomy for vitreous hemorrhage secondary to sickle cell anemia is rarely necessary and is associated with many complications.\textsuperscript{50}

Vitrectomy for vitreous hemorrhage resulting from Terson’s syndrome has a very good prognosis, with improved visual acuity in most patients.\textsuperscript{46} Vitrectomy for nonclearing vitreous hemorrhage has been successfully performed in many other underlying conditions, such as retinal tear,\textsuperscript{46,48} avulsed retinal vessels,\textsuperscript{46,48} leukemia and anticoagulant therapy,\textsuperscript{48} Eale’s disease,\textsuperscript{48} Behcet’s disease,\textsuperscript{48,51} uveitis,\textsuperscript{47,48} and surgical trauma.\textsuperscript{46,48}

Most surgeons will agree that immediate vitrectomy is indicated for vitreous hemorrhage with IOFB, but timing the vitrectomy for vitreous hemorrhage in the management of open globe injury remains a controversial issue. Proponents of performing vitrectomy between 4 and 14 days after injury argue that the uveal congestion which develops after trauma may increase the risk of uncontrollable hemorrhage; furthermore, a lack of separation of the posterior vitreous makes complete removal difficult.\textsuperscript{52-54} Experimental evidence points toward heightened fibrous proliferation when surgery is delayed by 2 weeks, which can inflict further retinal damage and make the operation
Vitreous Hemorrhage: Recent and Future Management

more difficult. However, some authors have argued that vitrectomies performed 14 days after penetrating ocular injury are associated with improved visual outcomes.

**FUTURE TREATMENTS**

*Hyaluronidase (Vitrase)*

Hyaluronidase hydrolyzes hyaluronic acid by splitting the glucosaminidic bond between C1 of the glucosamine moiety and C4 of glucoronic acid, thereby causing the breakdown of organized proteoglycan structures and liquefaction of the vitreous. Purified ovine hyaluronidase, Vitrase (ISTA Pharmaceuticals, Irvine, CA), induces breakdown of the vitreous structure by acting on hyaluronan and chondroitin sulfate. Purified ovine hyaluronidase has been studied in the “Vitrase for Vitreous Hemorrhage Study” consisting of two clinical trials. These Phase III clinical trials randomized patients to a single intravitreal injection of a 7.5 IU, 55 IU, or 75 IU dose of Vitrase versus saline injection. These studies enrolled 1,306 patients with a BCVA worse than 20/200 and with severe vitreous hemorrhage due to almost any etiology that obscured visualization of the fundus and was present for at least 1 month. The primary efficacy endpoint was the clearance of the vitreous hemorrhage sufficient for laser photocoagulation complete to at least 6 pm (on the retina clock), with photographic documentation of hemorrhage clearance. Evidence that treatment was not necessary after 3 months was not found. However, the secondary endpoints including reduction in vitreous hemorrhage density, improvement in BCVA, and clinical assessment of therapeutic utility (hemorrhage clearance sufficient to allow treatment to begin or for the decision that treatment was not necessary) were met and were statistically significant and in favor of Vitrase. For primary efficacy, statistical significance was reached in the 55 IU dose group by months 1 and 2. At the 55 IU dose, 13.2%, 25.5%, and 32.9% of patients reached primary efficacy by months 1, 2 and 3 versus 5.5%, 16.2%, and 25.6% of saline-treated patients. In addition, all of the endpoints (both primary and secondary) were met for the subset of patients with vitreous hemorrhage due to diabetic retinopathy who were treated with the 55 IU dose of Vitrase (unpublished). The major adverse events in the entire study population included typically self-limited iritis which occurred in 59% (55 IU) and 62% (75 IU) of treatment eyes versus 33% of saline control eyes. Hypopyon occurred in 2% (55 IU) and 5% (75 IU) of treatment eyes versus 0.0% of the saline control eyes. The rate of retinal detachment was similar between the groups and in most cases was due to tractional detachments.

*Plasmin*

Plasmin enzyme is a nonspecific protease that acts on laminin, fibronectin, and fibrin and may act on the matrix between collagen fibrils. The vitreoretinal junction is mainly composed of laminin and fibronectin, and therefore plasmin could act on the vitreoretinal junction. Plasmin has been used in humans to cleave the vitreoretinal junction and allow less traumatic detachment of the posterior hyaloid from underlying retina. Plasmin enzyme also produces vitreous liquefaction which may contribute to faster blood resorption; this may be beneficial in managing patients with vitreous hemorrhage. Previous clinical studies with plasmin have shown an excellent safety profile when applied to human eyes. No major complications were found when plasmin was used in these trials. Plasmin (Bausch & Lomb, Inc.) and microplasmin (ThromboGenics) have been developed and are either approved or currently undergoing phase II clinical trials for treatment of vitreomacular traction.

Vitreous hemorrhage is a manifestation of varying etiology that often has systemic associations. A detailed ocular and systemic history, thorough clinical and laboratory evaluation and meticulous
and often repeated ocular ultrasonography can help to make an etiological diagnosis. Prompt and judicious laser photocoagulation (where indicated) can prevent visual loss in the majority of eyes. Early surgery (in eyes with retinal detachment) can salvage many of these eyes from going irreversibly blind. In other cases, where laser treatment is not possible or does not cause adequate resolution of the pathology, vitreous surgery can be performed as an elective procedure. With careful attention to the principles of vitreous surgery and regard for the underlying pathology, surgery can successfully rehabilitate sight in patients who have suffered from vitreous hemorrhage.

References


Suprachoroidal Hemorrhage
Introduction

Suprachoroidal hemorrhage (SCH), an accumulation of blood within the suprachoroidal space, can be a devastating complication of ophthalmic surgery. The term expulsive hemorrhage was first coined in 1894 to denote an acute hemorrhage of the choroid resulting in poor visual outcome and partial or total loss of vision. Verhoeff reported the first successfully managed case of expulsive choroidal hemorrhage in 1915. Since then, the etiology, risk factors and management of this condition have been studied in detail.

Anatomic Considerations

The suprachoroidal space is a potential space situated between the choroid and the sclera. When filled with blood or fluid, it becomes a true space, the boundaries of which are the scleral spur anteriorly and the optic disc posteriorly. The choroid is firmly attached to the sclera at the vortex vein ampullae, and these attachments are responsible for the typical lobular appearance of a large choroidal detachment. The outer surface of the ciliary body and the choroid are closely attached to the sclera by a series of fine collagen fibrils arranged in tangential sheets. The suprachoroidal space normally contains approximately 10 ml of fluid.

Definitions

Choroidal detachment and SCH represent two distinct entities. A choroidal detachment is defined as a separation of the uvea from the sclera and may occur secondary to effusion of serous fluid within the suprachoroidal space. Both hypotony and inflammation appear to be causative factors responsible for this accumulation of fluid.

Suprachoroidal hemorrhage is defined as blood within the suprachoroidal space. Suprachoroidal hemorrhages can be categorized with respect to size and the extent of hemorrhage. They may be classified by their relationship to intraocular surgery, or categorized by precipitating events. SCHs can vary from a small area of involvement to massive involvement. Suprachoroidal hematomas represent small loculated collections of blood within the suprachoroidal space. These lesions are benign, may resolve spontaneously, and are distinct from SCH associated with intraocular surgery. Hoffman et al have defined small areas of suprachoroidal blood in patients who have undergone intracapsular cataract extraction as limited choroidal hemorrhage. On the other hand, a massive hemorrhage into the suprachoroidal space can be sufficiently large to force the inner retinal surfaces into direct apposition within the center of the posterior chamber, defined as a kissing SCH.

Suprachoroidal hemorrhage may develop at the time of intraocular surgery, representing intraoperative SCH. This is usually associated with a massive degree of hemorrhage and may result in the expulsion of intraocular contents through the surgical wound. Such a forceful SCH is categorized as an expulsive SCH. Suprachoroidal hemorrhages that develop in the postoperative period are termed either postoperative SCH or delayed SCH. Since delayed SCHs occur in a closed system, they are not typically associated with expulsion of intraocular contents. Nevertheless, they may be extensive enough to result in a kissing-type configuration.

SCHs may also be categorized by precipitating events. In particular, they can occur in the setting of either penetrating or blunt trauma. Traumatic SCH behaves differently from SCH associated with intraoperative surgery and should be considered as a distinct entity.
Suprachoroidal Hemorrhage

Pathophysiology

Several theories have been postulated to explain the mechanism whereby SCHs develop in nontraumatized eyes. Hypotony appears to be the major precipitating factor, resulting in a rupture of a necrotic long or short posterior ciliary artery. Another theory is that hypotony causes a choroidal effusion that stretches and ruptures a long or a short posterior ciliary artery. Experimentally, hypotony has been linked to enhanced aqueous humor outflow from the anterior chamber into the suprachoroidal space. Obstruction of venous outflow from the vortex veins may precipitate a cascade of events leading to an SCH. Beyer et al have suggested four sequential stages in the development of expulsive SCH:

1. Engorgement of the choriocapillaris.
2. Serous effusion into the suprachoroidal space.
3. Stretching and tearing of the vessels and attachments at the base of the ciliary body as the effusion enlarges.
4. Resultant massive extravasation of blood from torn ciliary body vessels, which leads to SCH and expulsion of intraocular contents through the surgical wound.

The long posterior ciliary arteries appear especially vulnerable to rupture during separation of the choroid from the sclera—because their connections between the scleral exit and the outer choroid are short.

Incidence

Suprachoroidal hemorrhage has been reported to occur in the setting of all types of intraocular procedures. The actual incidence of SCH is somewhat difficult to reliably estimate, because it occurs so infrequently. With older methods of cataract surgery, the overall incidence of expulsive SCH has been widely regarded to be approximately 0.2%. Furthermore, secondary intraocular lens implantation surgery appears to carry a similar risk of expulsive SCH. The advent of phacoemulsification lens extraction, topical anesthesia, and clear corneal incision techniques has lowered the incidence of SCH secondary to cataract surgery to 0.03% to 0.06%.

These newer techniques of cataract extraction can be carried out more rapidly with less manipulation of the globe. In addition, phacoemulsification cataract extraction can be performed with less pronounced fluctuations of intraocular pressure (IOP). One can postulate that fewer oscillations of IOP circumvent the development of ocular hypotony during surgery, thereby preventing the inciting event in the development of SCH.

The incidence of expulsive SCH during glaucoma filtering surgery has been reported to be approximately 0.15%. It is not surprising that the incidence of delayed SCH is approximately 10-fold greater than that of expulsive SCH. The opportunity to develop a delayed SCH after glaucoma surgery appears to be particularly great.

Expulsive SCH has been rarely reported after both penetrating keratoplasty and vitreoretinal surgery. Typically, prolonged intraocular hypotony does not occur during vitreoretinal surgery. Expulsive SCH in these cases may therefore be related to direct trauma to the choroid during drainage of subretinal fluid or creation of pars plana sclerotomies, or to compression and trauma to vortex veins during placement of scleral buckling elements.
Patient Characteristics

Numerous systemic findings have been implicated in the development of SCH, including fragility of choroidal vessels associated with advanced age, systemic hypertension, and arteriosclerosis. Generalized atherosclerosis has been reported to be a significant systemic risk factor.  

Various ocular conditions have been reported to be associated with SCH, including glaucoma, elevated IOP, aphakia, axial myopia, and inflammation.  The mechanism by which these ocular risk factors are believed to have an impact on the development of SCH is similar. These ocular conditions are presumed to weaken the integrity of the long posterior ciliary arteries by promoting vascular necrosis. This, in turn, would make these vessels more susceptible to rupture. In the case of surgical aphakia, the absence of the lens and zonular support is believed to allow more stretching and separation of the uvea from the sclera during ciliochoroidal effusions. Loss of scleral rigidity and/or choroidal vascular fragility are also believed to be responsible for the association between SCH and axial myopia.

Certain intraoperative maneuvers have been anecdotally implicated in the development of SCH. Numerous authors have cautioned that general anesthesia may be a risk factor for SCH.  Coughing, straining, nausea, vomiting, and Valsalva-type maneuvers are believed to increase episcleral venous pressure, resulting in an increased pressure gradient across the wall of necrotic ciliary vessels, thereby promoting their rupture.

Hypotony in the postoperative period has been reported to help contribute to the development of delayed SCH. In addition, the hypotonous eye may be more susceptible to episcleral venous pressure fluctuations induced by Valsalva maneuvers and, therefore, be more vulnerable to rupture of ciliary arteries.

Spontaneous SCH has also been reported in cardiac patients undergoing treatment of acute myocardial infarction with systemic thrombolytic agents. These potent agents promote a systemic hemolytic state and thus greatly increase the risk of severe hemorrhaging.

Clinical Considerations

PROPHYLACTIC MEASURES

A thorough preoperative examination should be performed with particular attention to both systemic and ocular risk factors for SCH. A complete medical evaluation should be undertaken, looking for evidence of cardiovascular disease, such as hypertension and arteriosclerosis. Also, patients should be screened for evidence of liver disease or the use of digoxin which may precipitate SCH. Any underlying blood dyscrasia or coagulation defect should be addressed. Patients should be encouraged to avoid the use of aspirin or other nonsteroidal anti-inflammatory agents. Diabetic patients should have their blood glucose level under satisfactory control.

Preoperatively, the physician should be alerted to the high-risk patient by the presence of certain findings in the ophthalmic history. Indeed, patients at highest risk for the development of SCH usually have a history of chronic glaucoma and are either aphakic or pseudophakic. Other risk factors include severe myopia, choroidal arteriolar disease, recent intraocular surgery, and the presence of SCH in the fellow eye.

Aggressive medical management of high IOP be undertaken before surgery. Softening of the eye with intravenous hyperosmotic agents or carbonic anhydrase inhibitors at the beginning of the
operative procedure should be considered. Compressive maneuvers, however, should be avoided, and they may contribute to choroidal hyperemia and/or may facilitate the rupture of a weakened artery. Recently, an anterior chamber maintainer has been advocated to reduce intraoperative hypotony, which may lower the chance of SCH in high-risk cases. Hypertension and increased intraoperative heart rate have also been implicated as risk factors for SCH. In patients with hypertension and tachycardia, efforts should be made at the time of surgery to lower the heart rate and blood pressure. Labetalol has been suggested for use in such high-risk patients. The use of preoperative phenylephrine should also be restricted to help avoid systemic hypertension.

General anesthesia may also be a risk factor for SCH. Performing surgery under monitored local anesthesia rather than under general anesthesia should be considered. A protective effect of epinephrine added to the lid block has been reported and therefore may be considered when this form of anesthesia is administered. Both during and after surgery, Valsalva maneuvers should be avoided. Laxatives and antiemetics are therefore recommended for high-risk patients. Postoperatively, the patient must be instructed to avoid any eye trauma or eye pressure, as this may precipitate the rupture of ciliary arteries. Postoperative inflammation must be vigorously controlled because inflammation may contribute to serous fluid accumulation in the suprachoroidal space, thereby starting the cascade of events leading to SCH. In cases of glaucoma filtering surgery, every effort should be made to avoid postoperative hypotony.

Intraoperative Diagnosis and Management

A favorable outcome after expulsive or delayed SCH requires early recognition and expeditious management. If an expulsive SCH occurs during intraocular surgery, the surgeon must be prepared to react quickly and decisively. Clinically, early signs of an intraoperative SCH include a sudden increase in IOP with firming of the globe, loss of a red reflex, and shallowing of the anterior chamber with forward displacement of the iris and lens or lens implant, with or without vitreous prolapse. If an intraoperative SCH is suspected, immediate tamponade of the open globe is required. This can be accomplished by either direct digital pressure or rapid suturing of all surgical incisions. Closure of the eye allows the IOP to rise to a sufficient level to tamponade the bleeding vessel. If intraocular contents are expelling, they should be repositioned as quickly as possible. If the intraocular contents cannot be replaced in the globe, the eye can be softened by performing posterior sclerotomies. The long-term benefit of performing posterior sclerotomies acutely at the time when SCH occurs remains debatable.

Blood in the suprachoroidal space clots extremely rapidly, and often the SCH has already clotted by the time the emergency sclerotomy is performed. If the hemorrhage has not clotted, the eye will usually soften enough to allow for the repositioning of intraocular tissue. With the acute drainage of a SCH, however, the tamponading effect of increased IOP in a closed eye is lost and frequently the SCH will recommence hemorrhaging. Lakhanpal reported that creation of immediate sclerotomies during SCH is detrimental to eyes.

Several other maneuvers may be performed acutely. Reformation of the anterior chamber by saline or air injection is recommended. This can prevent entrapment of vitreous into the surgical wound, which increases the risk of development of retinal detachment. Intravenous hyperosmotic agents, sedation for agitated patients, and lowering of systolic blood pressure may be helpful. Removal of the lid speculum may also decrease direct pressure on the globe, preventing further extrusion of intraocular contents.
Postoperative Diagnosis and Management

Delayed or postoperative SCH behaves somewhat differently from expulsive SCH. This type of SCH usually presents after uncomplicated glaucoma filtering surgery. Typically, patients experience a sudden onset of severe ocular pain with a subsequent loss of vision. Headache, nausea, and vomiting may also accompany the ocular pain. These symptoms may occur after a Valsalva-type maneuver or may be severe enough to arouse a patient from sleep. Clinically, patients with delayed SCH can have markedly decreased vision. The appearance of the eye can mimic that of an acute retrobulbar hemorrhage.28

On slit-lamp examination, there may be shallowing of the anterior chamber, vitreous prolapse into the anterior chamber in aphakic and pseudophakic eyes, and loss of a red reflex. On funduscopic examination, dark elevated dome-shaped lesions are seen occupying the equatorial fundus, and may also be seen to extend posteriorly. These lesions do not transilluminate well. Intraocular pressure may be low, normal, or elevated.

Regardless of the cause of the SCH, whether expulsive or delayed, the immediate postoperative management is similar. If the IOP is elevated, aggressive medical therapy with a topical beta-blocker and an oral carbonic anhydrase inhibitor is advocated. Inflammation should be controlled by liberal use of a topical steroid. Oral prednisone may be necessary in cases of severe intraocular inflammation. Pain can be considerable in this condition, because of stretching of ciliary nerves. Pain can be managed with adequate cycloplegia and analgesics. Aspirin and nonsteroidal agents, however, are contraindicated, as they may contribute to further hemorrhaging.20,28

Echography and Radiologic Evaluation

Standardized echography can be extremely useful in the diagnosis and in making decisions about management.29 Suprachoroidal hemorrhage may be difficult to diagnose in the presence of opaque media. Corneal changes, breakthrough vitreous hemorrhage, and/or a kissing configuration may make adequate visualization of the posterior chamber impossible.

Differentiation between hemorrhagic choroidal detachment and serous choroidal effusion can be made by A- and B-scans.30 Echo graphically, on B-scan, patients with SCH exhibit highly elevated choroidal detachments with a typical dome-shaped appearance. In severe cases, broad central retinal apposition can be seen, illustrating a kissing type configuration (Figure 11-1). On A-scan evaluation, a steeply rising, double-peaked wide spike is seen, characteristic of choroidal detachment, with lower reflective spikes in the Suprachoroidal space, indicating clotted hemorrhage. Echography is an excellent way to follow up patients, with or without opaque media, for the liquefaction of the SCH (Figure 11-2). Once liquefaction of the hemorrhage has occurred, the height of the choroidal detachment will be seen to slowly diminish with time. This reduction in height should be watched for in clinical follow-up. If early surgical drainage of a massive suprachoroidal hemorrhage is warranted, echography may be a helpful adjunct in determining the optimal time for drainage. By allowing for complete liquefaction of the SCH, one can minimize probing of the suprachoroidal space for residual clots, a maneuver that may cause further bleeding or retinal damage, yet facilitate the evacuation of the hemorrhage and restoration of normal ocular anatomy. It would appear that surgical intervention is most effective when clot lysis is near completion; whether complete liquefaction of the hemorrhage is absolutely necessary for successful drainage of the hemorrhage remains unknown. The mean time for clot lysis was 14 days, as determined by echography.31,32
Suprachoroidal Hemorrhage

Delaying drainage of an SCH for 7 to 14 days has therefore been advocated. Serous and hemorrhagic choroidal detachment can be differentiated on computed tomography because of differences in attenuation values. On average, fresh hemorrhagic lesions have higher attenuation values than serous choroidal detachments. In addition, the use of magnetic resonance imaging has been shown to be helpful in the evaluation of suprachoroidal hemorrhage.

Indications for Secondary Surgical Management

The decision to re-operate a case of postoperative SCH is controversial. Specific clinical features may influence the decision to consider surgical drainage, including the presence of a retinal detachment, central retinal apposition, vitreous incarceration into a surgical wound, or a breakthrough vitreous hemorrhage; increased IOP; retained lens material during cataract surgery; and intractable eye pain. A retinal detachment may be identified in the postoperative period, either on funduscopic examination or by echography. A distinction must be made, however, between retinal detachments of a serous origin and retinal detachments of a tractional or rhegmatogenous cause. The presence of a rhegmatogenous retinal detachment in the postoperative period remains a common indication for surgical intervention. Serous retinal detachments should be observed closely for regression or progression. Central retinal apposition has traditionally been considered to be an absolute indication for surgical intervention. Retinal incarceration is strongly associated with a poor prognosis.
SURGICAL TECHNIQUES

When reoperation is considered in patients with SCH, the surgical approach can be one of two choices: (i) drainage procedures to remove the SCH and to reestablish normal IOP; and (ii) vitreoretinal surgery in combination with a drainage procedure to remove vitreous hemorrhage and/or retained lens material, to relieve vitreoretinal traction, and to reestablish the normal anatomic configuration of the posterior segment.

Drainage Procedures

When a drainage procedure is considered, the optimal time for intervention can be critical for success. It is recommended that drainage procedures in patients with SCH be deferred for 1 to 2 weeks, preferably with clot lysis confirmed by echography. Verhoeff recommended the use of drainage sclerotomies at the time of expulsive SCH to enable closure of the surgical wound and to reduce IOP.38 He advocated the use of scleral punctures with a Graefe knife; furthermore, he suggested that scleral punctures be made as quickly as possible at the time of expulsive SCH, and that the scleral...
Suprachoroidal Hemorrhage

opening be V-shaped with excision of the apex of the “V” to facilitate postoperatively the continued escape of blood.

Drainage sclerotomies are created in the quadrant(s) of the involved SCH. The IOP is then maintained by continuously injecting a vitreous substitute into the globe. Usually, an anterior chamber approach is recommended, as the majority of these eyes are aphakic or pseudophakic. The reestablishment of IOP by these methods facilitates the egress of lysed blood through the drainage sclerotomies in a controlled fashion. These methods are ideally suited for management of SCH in which there is little remaining vitreous in the eye, when vitreoretinal traction is absent, and no retinal detachment exists.

Several vitreous substitutes have been recommended for reestablishing IOP. Both balanced saline solution and viscoelastic solutions have been advocated as vitreous substitutes.\textsuperscript{39,40} Balanced saline solution can be instilled via a limbal approach with a gravity infusion system. Drainage sclerotomies are created posteriorly, in a radial fashion, before engagement of the infusion system. The anterior and posterior chambers are maintained with balanced saline solution as the choroidal blood is drained from the sclerotomies. The sclerotomies are then held open with forceps, allowing drainage of the suprachoroidal space as the eye is reformed with solution. A cyclodialysis spatula can also be gently introduced into the suprachoroidal space to facilitate removal of persistent blood clots.

A gravity infusion system for balanced saline infusion is preferable; however, care must be taken not to allow the globe to become hypotonous (which may lead to recurrent SCH) or for the IOP to become too great (which may result in retinal incarceration). Instead of balanced saline solution or viscoelastic agents, sterile air can be used to hydraulically aid in the draining of suprachoroidal blood. Again, radial incisions are made in the sclera into the suprachoroidal space. The eye is then insufflated with sterile air by using a continuous-infusion air pump through a 25, 27, or 30 gauge needle inserted through the limbus. The air pump insufflation pressure is preset to 20 to 30 mm Hg. A major advantage of this technique is the use of a continuous-infusion air pump rather than a syringe. The IOP can be maintained at a predetermined level, thereby preventing both hypotony and excessive pressure. A potential disadvantage of this technique is the loss of detailed visualization of the posterior segment because of air-fluid interface reflections. This method may therefore make it difficult to identify peripheral retinal tears and persistent vitreoretinal traction at the time of surgery.

Vitreoretinal Surgical Approaches

When retinal detachment, vitreoretinal traction, vitreous hemorrhage, and/or dislocated lens fragments are present in the setting of SCH, vitreoretinal surgery at the time of the SCH drainage procedure is usually advisable. When vitreoretinal surgery is planned in combination with a drainage procedure, the sequence of surgical maneuvers is extremely important. Typically, in the presence of a SCH, the normal anatomic location of the pars plana, anterior retina, and vitreous base is distorted. Entry into the posterior segment of the globe via a pars plana approach can be dangerous and can result in iatrogenic damage to the anterior retina. Drainage of hemorrhage from the suprachoroidal space is therefore initially required before any pars plana incisions are created. Both balanced saline solution and viscoelastic agents can be used to accomplish drainage of suprachoroidal blood. Recently, perfluorocarbon liquids have been recommended as a new surgical adjunct in cases of complex vitreoretinal pathology.\textsuperscript{40}
Unlike the above-mentioned methods, when a perfluorocarbon liquid is used, the drainage sclerotomies should be placed anteriorly, approximately 4 mm off the limbus. A 30-gauge needle attached to a syringe containing perfluorocarbon liquid is then introduced through the limbus. This liquid material is then slowly injected, whereby it will immediately move posteriorly. As it fills the posterior chamber, the per fluorocarbon liquid will flatten the posterior pole while displacing suprachoroidal blood anteriorly, thereby allowing more complete removal of liquefied blood through anteriorly placed sclerotomies (Figures 11-3 and 11-4).

Prognosis

EXPULSIVE SUPRACHOROIDAL HEMORRHAGE

In cases of expulsive SCH, in the absence of a rhegmatogenous retinal detachment, both early surgical intervention and observation and medical management have been advocated. It does not appear that all patients suffering from an expulsive SCH should be subjected to a secondary surgical procedure. Secondary surgery, however, should be contemplated on an individual level, based on clearly defined indications or intervention.

DELAYED SUPRACHOROIDAL HEMORRHAGE

Abrams et al reported the greatest success with early surgical drainage in patients with delayed SCH.41 In their study, three of seven patients maintained prehemorrhage visual acuity, and two of seven patients actually had a final visual acuity that was better than their prehemorrhage visual acuity.

FIGURE 11-3: Showing egression of dark colored suprachoroidal blood through the sclerotomies under infusion through the anterior chamber maintainer. Surgery was performed after liquefaction of suprachoroidal blood seen on B-scan as shown in Figures 11-1 and 11-2 (Courtesy: Dr Nazimul Hussain, Al Zahra Pvt Hospital, UAE)
Suprachoroidal Hemorrhage

FIGURE 11-4: Fundus photograph of the same patient (Figures 11-1 to 11-3) after vitreoretinal surgery for expulsive hemorrhage. Note the attached retina under silicone oil (Courtesy: Dr Nazimul Hussain, Al Zahra Pvt Hospital, UAE)

New Frontiers

A new treatment modality is the use of intravenous tissue plasminogen activator to accelerate clot lysis. This form of treatment is experimental, and its clinical benefit remains to be proved. Finally, the use of silicone oil tamponade after vitreoretinal surgery for SCH has been recommended, but should be reserved for only the most desperate cases.

References

Chapter 12

Imaging in Posterior Uveitis
Introduction

Posterior uveitis is a group of disorders, which often pose diagnostic and therapeutic dilemma to the treating ophthalmologist. In the management of posterior uveitis it is required to ascertain the cause of the posterior segment inflammation, its stage and extent and also its contribution to the associated visual loss. A number of techniques are used to image the posterior segment in a patient with uveitis.

Imaging techniques in uveitis are used:
1. To determine the presence or absence of specific uveitic diseases with characteristic patterns as seen on imaging.
2. To determine the stage of activity of the specific disease and the extent of involvement of the posterior segment.
3. To determine the cause of the vision loss in the affected eye.

In this chapter, we shall try to understand the basis and the indications for use of imaging techniques in the management of posterior uveitis.

The Technique

The techniques used for imaging the posterior segment in uveitis are as follows:

COLOR FUNDUS PHOTOGRAPHY

The first tool that can be used to document the presence of a fundus lesion at the initial visit and to further judge the extent and progression of the disease in the subsequent follow up visits is digital color fundus photography (Figures 12-1A to D). Digital fundus photography has the added advantage of simple storage and retrieval of images over the conventional film-based colour fundus photography. The construction of a composite montage further enhances the documentation of the extent of the lesion in the peripheral fundus. A good agreement has been found among the uveitis specialists on the interpretation of retinal photographs of patients with presumed Toxoplasma chorioretinitis.

FUNDUS FLUORESCEIN ANGIOGRAPHY (FFA)

In patients with posterior uveitis, FFA is useful to detect and document vasculitis and subsequent areas of peripheral capillary non-perfusion (Figure 12-2) in Eales’ disease, Intermediate uveitis, Sarcoidosis, and also in uncommon conditions like Behcet’s disease. Further it can be used to show leakage of dye from inflamed retinal capillaries at the macula (Cystoid Macular edema—Flower Petal pattern) (Figure 12-3) and in the optic disc (Optic Disc Edema). Lastly, it can also be used to recognize choroidal neovascularization in patients of uveitis.

INDOCYANINE GREEN ANGIOGRAPHY (ICG)

ICG provides visual access to the choroidal circulation and thus provides an insight into the understanding of the pathogenesis of various inflammatory disorders especially the white dot syndromes. The normal background choroidal fluorescence is altered in posterior uveitis as seen in the late phases of the angiogram. Two definite patterns of inflammatory involvement of the choroidal vessels have been reported using ICG. These are Type 1 (Figures 12-4A to D) which appears as hypofluorescence in both the mid and late phases of the angiogram and is seen in the white dot
FIGURES 12-1A to D: Serial color fundus photographs to document the resolution of lesions in a patient with Toxoplasma chorioretinitis. (A) 1st day, (B) 3rd day, (C) 2nd week, (D) 6th week.

FIGURE 12-2: Fundus fluorescing angiography of a patient with Eales’ disease to document perivasculitis, capillary non-perfusion and NVE.
**FIGURE 12-3:** Fundus fluorescein angiography of a patient with cystoid macular edema showing typical 'flower petal pattern' due to leakage of dye from the inflamed retinal capillaries at the macula.

**FIGURES 12-4A to D:** Indocyanine green angiograph of a patient with MEWDS and type 1 choroidal neovascular membrane.
syndrome where there is a selective involvement of the choriocapillaris. Disorders like tuberculosis, sarcoidosis and Vogt-Koyanagi-Harada (VKH) disease, sympathetic ophthalmia, Birdshot chorioretinopathy, Behçet’s disease and posterior scleritis affect the choroids more diffusely demonstrate the type 2 pattern characterized by late leakage of the ICG dye from the inflamed choroidal vessels.

**B-SCAN ULTRASONOGRAPHY AND ULTRASOUND BIOMICROSCOPY (UBM)**

B-scan ultrasonography is useful to image the posterior segment when clinical examination is not possible because of hazy media due to various causes. In uveitis, this may be due to corneal scars, hypopyon, cataract, small pupils, and pupillary membranes. In the presence of ocular hypotony in uveitis it can be used to detect choroidal detachment in the presence of opaque media. UBM uses a higher frequency probe to image the ciliary body and the pars plana region to look for ciliary body effusion or to find the cause of hypotony such as ciliary body thinning, cyclitic membranes or to document exudates in the pars plana region in cases of pars planitis with hazy media or small pupils precluding the view of the pars plana region. Some authors have used UBM to document the peripheral fundus involvement in toxocariasis and to differentiate pars planitis characterized by typical UBM pars plana deposits from Behçet’s disease, which does not show the deposits in the presence of opaque media. In patients who have a clear media like VKH and posterior scleritis, B scan is used to demonstrate choroidal thickening which is peripapillary to begin with (Figure 12-5) and also echolucency in the posterior sub-Tenons space (Figure 12-6).

**OPTICAL COHERENCE TOMOGRAPHY (OCT)**

OCT is best suited for measurement of the foveal thickness in the diagnosis and follow-up of patients with cystoid macular edema. OCT can also be used to document epiretinal membranes and subtle vitreomacular traction and other clinical features which are subtle on clinical examination (Figures 12-7 and 12-8).

Having an overview of the various imaging modalities used in management of posterior uveitis, we can now discuss how each of these modalities is useful to document findings in patients of uveitis with an inflammatory response causing loss of vision. We know that vision loss in a patient with uveitis is due to a myriad of causes including cystoid macular edema (CME) (Figure 12-9), optic disc inflammation, exudative neurosensory detachment, retinal phlebitis, macular retinal vascular
occlusion, peripheral retinal vascular occlusion, neovascularization of the disc and elsewhere, rubeosis of the iris and angle, choroidal neovascularization and posterior scleritis.

**Cystoid Macular Edema (CME)**

FFA and OCT are the preferred imaging modalities to demonstrate the presence of CME in a patient with uveitis. Break down of the blood retinal barrier causing CME is seen in the late phases of the
Imaging in Posterior Uveitis

**FIGURE 12-8:** Optical coherence tomography of the same patient to document resolution of macular hole

**FIGURE 12-9:** Optical coherence tomography to document cystoid macular edema in a patient with pars planitis
FFA as leakage of dye from the macular capillaries with collection of the dye in the cystic intraretinal spaces. The typical appearance of CME on the FFA has been classically described as a flower petal pattern.

This appearance can be graded into 5 grades:\textsuperscript{10}

Grade 0: No perifoveal hyperfluorescence

Grade 1: Incomplete perifoveal hyperfluorescence

Grade 2: Mild 360° hyperfluorescence

Grade 3: Moderate 360° hyperfluorescence with the area of hyperfluorescence being 1 disc diameter across

Grade 4: Severe 360° hyperfluorescence with the area of hyperfluorescence being 1.5 disc diameter across. However, while interpreting the area of dye leakage in relation to the visual acuity, one must remember that the two do not correlate well at times.\textsuperscript{11, 12}

Three basic patterns of macular edema have been described in patients with uveitis.\textsuperscript{13} They are:

1. Diffuse macular edema: Increased retinal thickness, disturbance of the layered retinal structure and sponge like low reflective areas.
2. Clearly defined intraretinal cystoid spaces.
3. Serous retinal detachment seen as a clear separation of the neurosensory retina from the retinal pigment epithelium.

OCT is also helpful in assessing the results of the treatment of CME with intravitreal injection of triamcinolone acetonide.\textsuperscript{14}

\textit{Optic Disc Inflammation}

In cases when the diagnosis of uveitis is doubtful or when there is a doubt regarding disease activity, leakage of the dye from the disc (hot disc) is an important sign (\textbf{Figure 12-10}).

\textbf{FIGURE 12-10:} Fundus fluorescein angiography of a patient with Vogt-Koyanagi-Harada disease showing leakage of dye from the disc in the late phase—‘hot disc’
Imaging in Posterior Uveitis

Exudative Neurosensory Detachments
These are seen on FFA as multiple focal leaks at the level of the RPE, with pooling of dye in the sub-retinal space (Figure 12-11). ICG shows patchy choroidal fluorescence.

Retinal Phlebitis
FFA shows retinal phlebitis as staining of the major retinal vessels in the area of localized inflammation with leakage of dye (Figure 12-12). In the presence of prominent vascular leakage, ICG can also be used to demonstrate choroidal vascular inflammation.15, 16

Macular Vascular Occlusion
FFA is a gold standard in documenting macular vascular occlusion as an enlargement of the foveal avascular zone especially in cases of unexplained loss of vision in patients with long standing uveitic entities like Behçet’s disease and herpetic necrotizing retinitis (Figures 12-13A and B).

Peripheral Retinal Vascular Occlusion
Peripheral retinal vascular occlusion as in Eales’ disease and tuberculosis is seen on FFA as a peripheral capillary dropout with an associated leakage of dye from the tortuous vessels at the border of the perfused and the non perfused areas.

Neovascularization of the Disc and Neovascularization Elsewhere
In cases of intermediate uveitis, sarcoidosis and Behçet’s disease,17 which are complicated with neovascularization of the disc (Figures 12-14 and 12-15) and elsewhere, FFA can be used to demonstrate dye leakage in the vitreous with obscuration of the underlying details during the late phase of the angiogram. When vitreous haemorrhage obscures the retinal view, B scan can be used to assess the condition of the retina.

FIGURE 12-11: Fundus fluorescein angiography of a patient with Vogt-Koyanagi-Harada disease showing pooling of dye in the sub-retinal space in the late phase
Rubeosis of the Iris and the Angle

Iris and angle neovascularization is not an uncommon complication in long standing uveitis (Figure 12-16). Fluorescein angiography of the anterior segment can be used to reveal subtle active iris neovascularization in doubtful cases.

Choroidal Neovascularization Membrane (CNVM)

FFA can be used to differentiate between active choroidal neovascularization and chorioretinal scars. Chorioretinal scars are characterized by hyperfluorescence first in the periphery and then
FIGURES 12-14A AND B: Fundus fluorescein angiography showing leakage of dye in a patient with neovascularization of the disc.

FIGURES 12-15A AND B: Fundus fluorescein angiography of a patient showing leakage of dye from new vessels elsewhere.

FIGURE 12-16: Slit lamp photo of a patient showing neovascularization of the iris—Rubeosis iridis.
spreading to the centre of the scar. In CNVM, hyperfluorescence begins first in the area of the
CNVM and then spreads to the periphery of the lesion. Both show hyperfluorescence of the entire
lesion in the late phase of the FFA. Active CNVM shows leakage of the dye into the overlying serous
retinal detachment. ICG shows CNVM as a ‘hot spot’ of hyperfluorescence in the mid phase of the
study with a late leakage. Chorioretinal scars show hypofluorescence throughout the entire ICG
study. A CNVM on the OCT is seen as a ‘bump’ with a moderate slope extending upward or as a
fusiform thickening with disruption of the reflective band.

**Posterior Scleritis**

FFA, in a case of posterior scleritis shows multiple pinpoint leaks at the level of the retinal pigment
epithelium which evolves in the later phases of the angiogram to fill the subretinal space with
associated optic disc leakage, vascular staining and occlusion. ICG shows choroidal vascular
hyperpermeability and hyperfluorescence in the mid-to-late phases of the angiogram. B-scan
ultrasonography shows the classical ‘T sign’, which is virtually pathognomonic of posterior scleritis.
The ‘T sign’ is due to scleral edema with associated fluid within the Tenon’s space resulting in an
echolucent area just posterior to the sclera. In nodular posterior scleritis there is a localized echoluency
seen.

**Diagnosis of Specific Uveitic Conditions**

Now knowing the different imaging modalities and their applications to pick up various causes for
loss of vision in patients with uveitis, we come to the diagnosis of specific uveitic conditions using
various imaging modalities.

**ACUTE POSTERIOR MULTIFOCAL PLACOID PIGMENT EPITHELIOPATHY (APMPPE)**

FFA of a patient with APMPPE is characteristic and often imaging modality may be essential to
diagnose this disorder. In the acute stage, a fundus fluorescein angiography (FFA) reveals a
characteristic “block early, stain late” pattern (Figures 12-17A to C). The acute lesions are
hypofluorescent due to a grayish white opacification of the retinal pigment epithelium and choroidal
nonperfusion. The acute lesions become hyperfluorescent in the late phase of the angiogram.
Hyperfluorescent lesions in the late phase of the study are lesser in number than the hypofluorescent
lesions seen in the early phase in the acute stage of the disease. In the quiescent stage a varying
degree of hyper or hypofluorescence is seen depending upon the degree of retinal pigment epithelial
derangement. Indocyanine green angiography (ICG) reveals hypofluorescence of the active and
healed lesions and thus highlights the choroidal nonperfusion. The etiology of APMPPE is unclear.
Antecedent viral illness in 1/3rd of the patients points towards a viral etiology. Nonperfusion of the
choroids as demonstrated by ICG may be another possible etiological mechanism. This choroidal
nonperfusion may be secondary to a vasculitis as suggested by its association with systemic vasculitis.

**SERPIGINOUS CHOROIDOPATHY**

FFA is characteristic and shows early hypofluorescence of the active lesions. In the late phase there
is hyperfluorescence of the active border (Figures 12-18A to C), which appears pseudopododal. This
hypofluorescence may extend centrally.
ICG shows hypofluorescence of the lesions in all the stages except in the healing and the subhealing stage where hyperfluorescent lesions are seen.

There may also be localized areas of hyperfluorescence outside these areas. These latter lesions do not correspond to any clinically visible change of the retina, RPE, and choroid, and could represent areas of subclinical choroidal inflammation. ICG angiography may also be useful in distinguishing between new active inflammatory lesions, which are hypofluorescent, and CNVM, which may appear as a localized hyperfluorescent lesion during the mid-to-late phases of the ICG study.\(^\text{23}\)

**BIRDSHOT CHORIORETINOPATHY**

FFA may show active retino-vascular leakage along the large and small vessels and cystoid or diffuse macular edema. The birdshot lesions are seen only if there is a loss of retinal pigment epithelium over them creating a window defect. ICG shows birdshot lesions appearing to line up along the large choroidal veins (**Figures 12-19A and B**) as areas of blockage in the early mid and sometimes in the late phase of the angiogram.\(^\text{24}\) The early appearance of the spots differentiates these lesions with the late spots seen with multifocal choroiditis. Many more spots can be seen with ICG angiography than with either ophthalmoscopy or FA. The hypofluorescent spots on ICG angiography are similar in size to the clinically detectable lesions.

**FIGURES 12-17A TO C:** Patient with acute posterior multifocal placoid pigment epitheliopathy (APMPPE). Fundus fluorescein angiography showing 'block early, stain late' pattern.
FIGURES 12-18A TO C: Patient with serpiginous choroidopathy. Fundus fluorescein angiography showing early hypofluorescence of the active lesions and hyperfluorescence of the active borders in the late phase.

FIGURES 12-19A AND B: Patient with birdshot chorioretinopathy. Fundus fluorescing angiography showing hypofluorescent spots along the major chroidal vessels with leakage of dye from the disc.
These hypofluorescent ICG spots are larger than the lesions seen with multifocal choroiditis and multiple evanescent white spot syndrome, and are usually smaller than the hypofluorescent plaques seen in AMPPPE and VKH disease. The hypofluorescent spots have a predominant distribution along the major choroidal vessels. Sometimes, hyperfluorescent spots appear during the mid phase of the ICG study and persist into the late phase. These hyperfluorescent areas seem to correspond to localized areas of retinal vasculitis seen clinically. Despite hyperemia or frank swelling of the optic nerve head seen clinically and confirmed by FFA, disc abnormalities are seldom noted on ICG study, and there is no convergence of hypofluorescent spots in the peripapillary area, as seen in multiple evanescent white spot syndrome and multifocal choroiditis. OCT and the retinal thickness analyzer can both be used to measure the retinal thickness in the macular area and in the typical fundus spots in patients with birdshot retinochoroidopathy.

**MULTIPLE EVANESCENT WHITE DOT SYNDROME (MEWDS)**

FFA shows early and late hyperfluorescence of the dots in a wreath like pattern (Figure 12-20) around the fovea with a late disc staining. ICG shows more numerous hypofluorescent round spots in the posterior and midperipheral fundus. During the convalescent phase there is disappearance of the hypofluorescent spots, and sometimes an appearance of hyperfluorescent spots of uncertain significance.

**VOGT-KOYANAGI-HARADA DISEASE**

Typically the early stages of the FFA show multifocal pinpoint areas of leakage originating from the RPE. This leakage increases in intensity during the recirculation phases, filling overlying serous
pigment epithelium detachments and neurosensory retina elevations (Figures 12-21A to C). Optic nerve leakage is usually seen, and occasionally perivenous retinal staining is observed as well. ICG of VKH disease shows multiple hypofluorescent spots scattered throughout the fundus. In the posterior pole they coalesce and the filling of the large choroidal vessels cannot be visualized. The hypofluorescent spots correlate with the Dalen–Fuchs-like nodules seen clinically. Presumably they represent blockage of underlying fluorescence by inflammatory infiltration of the choroid and by overlying RPE changes. Sometimes ill-defined areas of hyperfluorescence not necessarily correlating with the pattern of hyperfluorescent spots or neurosensory detachments representing a more diffuse type of choroidal staining are seen. After treatment, with resolution of the leaks and the neurosensory detachment, both the abnormal hypofluorescence and hyperfluorescence fades.28

**Conclusion**

The importance of imaging tools in the evaluation and management of posterior uveitis cannot be over emphasized. The information afforded by these techniques provides insight into various aspects of inflammation of the posterior segment.
References

Optical Coherence Tomography in Age-related Macular Degeneration
Introduction

Optical Coherence Tomography (OCT) is a new diagnostic tool in the diagnosis and management of Age-related macular degeneration (AMD). It uses light waves (near infrared laser-820 nm) to give cross-sectional images of retinal tissue with a resolution of 10 microns (Stratus OCT). It provides tomographic image and simulates in vivo histopathology. ¹

Technique

The scan protocols used in AMD are the fast macular thickness map, macular thickness map, radial lines, line scan and raster lines. Any two of the protocols would provide adequate information. The fast macular thickness map is done first as the protocol takes 1.92 seconds.¹ This is very important in patient with ARMD as they have problems in fixation.

OCT complements clinical examination and fundus fluorescein angiography (FFA) in the management of AMD. It aids in the following:
1. Diagnosis and disease categorization:² It can identify neovascular AMD, primarily understanding the level of lesion characteristic, thus identifying classic and occult choroidal neovascular membrane (CNVM). These are complementary to biomicroscopic examination and FFA.
2. Identify neovascularisation in doubtful cases of dry AMD: In symptomatic patients with extensive soft drusen, OCT helps in detecting occult CNVM.² It is a step in diagnosis between FFA and Indocyanine green (ICG) angiography.
3. Detects associated changes like Pigment epithelial detachment, Cystoid macular edema and subretinal fluid.³⁻⁵
4. Response to treatment: OCT can demonstrate the response to treatment of CNVM viz. PDT or anti VEGF drugs like ranibizumab, bevacizumab, etc.³⁻⁹
5. Can monitor treatment response and aid in decision making for re-injection of anti VEGF drugs. Presently this is the most important implication, which has radically changed the treatment approach in AMD. It has evolved the variable dosing of drugs.¹⁰,¹¹

Disease Categorization

**DRY AMD**

Drusen appear as bumps or focal elevations of the RPE. There is no shadowing (Figure 13-1).

**Classic CNVM**

There is disruption of the RPE with an area of increased reflectivity in the foveal center. There is increase in the retinal thickness with a cystoid space (Figure 13-2).

**Occult CNVM**

There is an elevation of the RPE layer with an area of enhanced reflectivity under it. There is increase in the retinal thickness suggestive of Occult CNVM. The ICG angiography demonstrates the large plaque lesion (Figures 13-3 and 13-4).
**Optical Coherence Tomography in Age-related Macular Degeneration**

**FIGURE 13-1:** OCT image showing RPE-CC modulations (arrows) suggestive of Drusen

**FIGURE 13-2:** Shows OCT image of a classic choroidal neovascularization (arrowhead) and associated intraretinal cystic change (arrow)

**FIGURE 13-3:** ICG angiogram showing occult CNVM
DETECTING CNVM IN DRY AMD
OCT is very useful in detecting CNVM in patients with symptomatic dry AMD. Patients with large number of soft drusen pose a challenge to the diagnosis of occult CNVM. Here OCT plays an important role between FFA and ICG angiography. OCT has excellent sensitivity (1.0) and reasonable specificity (0.65) in detecting CNVM.

DETECTS ASSOCIATED CHANGES
The associated morphological changes seen with CNVM, on OCT are presence of subretinal fluid, retinal pigment epithelial detachment (PED) and intraretinal cystic changes. Associated presence of retinal angiomatous proliferation (RAP) lesions can also be seen.

Figure 13-5 shows subretinal fluid and cystoid spaces indicating activity of the CNVM. Presence of significant scarring seen as hyper reflective areas with shadowing would indicate poor visual prognosis. Hence, treatment decision revolves around the findings on OCT.

RAP lesions appear as focal area of hyper reflectivity within the neuroretinal layers frequently associated with Pigment epithelial detachment (75.6%). Surrounding these areas are areas of low reflectivity due to retinal edema. Occasionally serous retinal detachment is seen.

Response to Treatment
The usefulness of OCT was demonstrated while studying the response to treatment. It plays an important role in monitoring the changes observed following treatment, either with photodynamic
therapy (PDT) or anti-VEGF drugs. Immediately following PDT, usually there is increase in subretinal fluid while some may show increase in the intraretinal fluid. This resolves between 15-30 days following treatment. The response to PDT has been staged on OCT with initial response being stage-1 and resolution grouped in stage-2. The subsequent changes either inactivity or recurrence are staged as 3 and 4 and finally scarring as stage-5. These changes are thought to be due to the initiation of the inflammatory response and up-regulation of VEGF and prompted the use of combination therapy of PDT with triamcinolone and later anti-VEGF drugs.13

Any change in the OCT picture especially reappearance of fluid after the macula was dry, would be a strong indication for retreatment (Figures 13-6 and 13-7).

The response to treatment is better appreciated in occult CNVM and gives information regarding activity. The activity of the Occult CNVM is detected by the presence of subretinal or sub RPE fluid. This is not clearly seen on FFA. OCT clearly demonstrates the presence of fluid and helps in decision making. OCT is more informative than FFA in some patients (Figures 13-8 and 13-9).

Sahni et al.8 reported that OCT was superior to clinical examination in detecting cystoid macular edema and subretinal fluid in patients undergoing PDT for CNVM. It has been reported that the inter observer agreement to the presence of leakage was good with OCT and moderate for FFA in patients undergoing PDT. Hence ineffective retreatment could be reduced from 35 to 20%.
OCT-guided Treatment of AMD

Approach towards treatment of AMD has undergone paradigm shift over time. OCT-guided management has become the standard of care in the era of VEGF inhibitors. Presently the treatment of AMD is with the use of two drugs—ranibizumab, a fully humanized antibody fragment has short half life and greater affinity for VEGF. Bevacizumab is the other drug which is off-label; full length monoclonal antibody with long half-life.
In MARINA and ANCHOR\textsuperscript{16,17} studies, with monthly injections of ranibizumab, the mean change of visual acuity over time showed a 17 letter difference between the treated group and the sham group. Further 25-34\% patients showed visual improvement of 15 or more letters.

In clinical practice, replicating clinical trial methodology is not possible. Moreover, the drug is expensive and may show variable response. In addition, the possible risks of systemic side effects also exist.

The treatment could be based on the following:
1. Empiric dosing
2. Visual acuity
3. Anatomic characteristics.

**EMPIRIC DOSING**

The PIER trial\textsuperscript{18} was started to evaluate whether quarterly dosing of ranibizumab would have the same result as the MARINA trial. The mean change of visual acuity over time showed a drop in the curve to just below the base line compared to +6-7 letters in the MARINA study. The 3-line gainers dropped to 13\%. Hence, empiric dosing is not the right approach. It was further observed that the initial gain (3 month data) was similar to the MARINA trial as both the studies had the initial three monthly injections.
VISUAL ACUITY

The functional change could be used to decide on treatment and retreatment. However this has been shown to be unreliable as the ETDRS chart recording, necessary for using visual acuity as a guide for treatment, is not available in many clinics. Further, there is a variation in vision in patients of AMD and the functional change is not reflected in the anatomy of the macula. Hence this would be quite unreliable, though could be an additional parameter in the decision to retreat.

ANATOMIC CHARACTERISTICS

This is a true reflection of the activity and OCT is the best tool to evaluate.

The OCT could be assessed in the following ways:

**Quantitative**

Here the analysis is done by averaging the retinal thickness using the various scans. The two commonly used measurements are the central macular thickness and the central subfield. The problem with this method is that patients with AMD have improper fixation leading to various errors. Therefore, boundaries are incorrectly placed by the instrument leading to errors in retinal thickness.

*FIGURE 13-9B: Post-treatment FFA and OCT showing good resolution of CNVM following treatment*
Presence of subretinal fluid, retinal pigment epithelial detachment (RPED) and eccentric CNVM leads to significant errors when using the standard analysis protocols. Errors in central macular thickness can occur in 62.2% patients with macular pathology. Incorrect boundaries and off center artifacts contribute to these errors. Measurements of retinal thickness with the analyzed images are significantly lower than when measured on the original image in patients with AMD.

**Qualitative**

The OCT image is evaluated for the following features:

1. Intraretinal cysts (*Figure 13-10*)
2. Diffuse retinal edema (*Figure 13-11*)
3. Subretinal fluid (*Figure 13-11*) and
4. Sub-RPE fluid. (*Figure 13-11*)

All the OCT scans should be evaluated for the above four findings, which would indicate activity. Goff et al\(^3\) used a combination of quantitative and qualitative assessment when using bevacizumab as monotherapy or in combination with PDT. They reported resolution of the subretinal fluid and retinal edema following treatment but the RPE detachment took longer time. Emerson et al\(^9\) used the presence of intraretinal or subretinal fluid as a guide for retreatment with bevacizumab in AMD. The PRONTO study\(^11\) on 40 patients using OCT as guide to treatment with Ranibizumab showed the mean change in visual acuity was 9.1 letters, similar to the outcome of MARINA and ANCHOR
studies. The three line gainers were 35% but the number of injections could be reduced to 9.9 injections in 2 years.

**Variable Dosing of anti-VEGF Drugs using OCT**

Presently, the most important use of OCT in AMD is to guide the treatment with anti-VEGF drugs. Fung et al\(^{10}\) reported the use of OCT in the treatment of AMD. A drop in visual acuity by 5 letters, an increase in macular thickness by 100 microns or presence of new fluid were indications for retreatment. Using these parameters, the number of injections were 5.5 in one year. This appeared to be a practical guideline. Hence, increase in thickness by 100 microns, presence of new fluid or persistence of fluid—intraretinal, subretinal or sub-RPE would necessitate re-injection of anti-VEGF drugs. A patient with Occult CNVM was injected with the loading dose of 3 injections of Ranibizumab. Re-injections were based on OCT findings (Figures 13-12 to 13-14). There was recurrence of subretinal fluid and sub RPE fluid at 6 months and hence was re-injected with ranibizumab.

Using a combination of assessments which include OCT (both quantitative and qualitative) and vision, would prevent inadequate treatment. Figures 13-15 to 13-19 shows a patient with significant subretinal hemorrhage secondary to AMD. He underwent pneumatic displacement following which observed to have a CNVM. He underwent intravitreal injections with ranibizumab. The quantitative analysis showed normal central macular thickness however on qualitative assessment there was persistence of sub retinal fluid for which he was re-injected with ranibizumab. On follow-up, subretinal fluid was absent and he was advised follow-up.

**FIGURE 13-12:** Pre-treatment fundus picture, FFA and OCT of an occult CNVM
FIGURE 13-13: Post-treatment fundus photo, FFA and OCT at 3 months showing regression of CNVM

FIGURE 13-14: Fundus photo and OCT of the same patient at 6 months showing recurrence of subretinal fluid and sub-RPE fluid
**FIGURE 13-15:** OCT image of submacular hemorrhage due to AMD

**FIGURE 13-16:** Quantitative OCT (Retinal thickness map) prior to treatment with ranibizumab showing increased central macular thickness
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**FIGURE 13-17**: Quantitative OCT (Retinal thickness map) post-treatment following loading dose of ranibizumab showing normal central macular thickness

**FIGURE 13-18**: OCT image showing persistence of subretinal fluid even after injection of ranibizumab
**Figure 13-19:** OCT image showing normal macular contour and resolution of subretinal fluid after retreatment.

**Figure 13-20:** Showing the biphasic response of AMD to ranibizumab. (Courtesy: Novartis Ophthalmics, India. Lucentis product monograph first edition 2007, Novartis, Basel Switzerland)

**Figure 13-20** demonstrates the present role of OCT in the maintenance phase when anti-VEGF drugs are used in the management of AMD. The goal is to sustain the visual gain with the least number of injections.

**Future**

The use of ultra-high resolution OCT in dry AMD had showed its ability to detect early neovascular changes not visible clinically or by angiography. The ultra-high resolution OCT defines the outer retinal layers better.

Spectral domain OCT would play a major role in the management of AMD as it has the ability to provide different layers for analysis and provide a 3-D rendering of the image (Figure 13.21). It has higher resolution and faster acquisition time. The higher resolution is due to the increased bandwidth of the existing laser (50 nm) as well as Fourier domain transformation eliminating the mechanical mirror. This allows 20,000-30,000 A scans per minute compared to 400 A scans in Time domain OCT.
Optical Coherence Tomography in Age-related Macular Degeneration

**FIGURE 13-21:** Spectral OCT showing the 3-D rendering of the retinal image

### References

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Newer Advances in Retinal Lasers
Introduction

The retinal burn was first produced by Meyer-Schwickerath using sunlight in 1960. This was followed by the introduction of Xenon-arc photo coagulators. However due to intense retinal burns of large size, these were replaced by the laser based systems in the 1970s. Over the next 30 years, few changes were seen in the laser systems. Some of the notable changes were the change from gas based lasers to solid state lasers with the advantage of portability and lower maintenance. The most commonly used lasers are the Frequency doubled Nd-YAG laser (532 nm) and the infrared diode laser (810 nm). There has been a constant endeavor for better technology to overcome the problems of the presently available lasers.

Photocoagulation—Conventional Laser

Though the effect of the laser is on the RPE there is concurrent damage to the choriocapillaris and the neural retina. There is an increase in the size of the burn over time. Maeshima  reported an annual increase of size of the laser burn by 12.5% and this was observed to be more in the posterior pole and with the use of longer wavelength lasers (Figure 14-1). The retinal laser burn is surrounded by an area of latent thermal damage which manifests over time. Some of the reported side effects are loss of visual field, contrast sensitivity and night blindness. Some of the research has been focused on the use of lasers which has minimal side effects while maximizing therapeutic effect.

The options are (1) Change in the method of treatment: Light photocoagulation and Minimum intensity photocoagulation (MIP) or Micropulse laser and (2) Change in instrumentation: PASCAL laser.

CHANGE IN THE METHOD OF TREATMENT

Light Photocoagulation

Studies have shown that when the power is adjusted to produce a barely visible burn, the effects on the retina appear to be similar to standard burns. Bandello et al reported no difference in the visual outcome or reduction in high risk proliferative diabetic retinopathy characteristics in pan retinal photocoagulation from either the light burns or classic burns. Similar findings were observed in macular focal or grid laser. The reduction in macular edema and improvement in vision were similar in both the groups. The complication rate was reported to be less. Larger multicentre trials would provide us an answer whether reducing the iatrogenic damage to the retina can achieve beneficial effect on the disease control.

Minimum Intensity Photocoagulation

Dorin suggested that the standard photocoagulation is a photo-thermal reaction and effects results in release of more biologic agents from an area adjacent to the burnt tissue. This area is partially affected and hence is biologically active. The area of burn ends up as an atrophic scar and is an inactive area (Figures 14-1 and 14-2). So, the purpose of iatrogenic damage caused by present techniques appears inappropriate. Hence, use of non lethal thermal burns without visible end point during the treatment would be desired. This happens to be the principle behind Minimum Intensity photocoagulation theoretically sparing the retina and thus incurring minimal side effects.
FIGURE 14-1: Argon laser done 9 years back. The scars show significant enlargement and tend to become confluent

Micropulse Laser

The effect on the Retinal pigment epithelium (RPE) appears to be the most important laser-tissue reaction.\textsuperscript{5,7} It has been postulated that the effect on RPE would improve oxygen diffusion from the choriocapillaris to the inner retina, release of factors which inhibit neovascularization and improve absorption of edema at the macula.

As the name suggests, micropulse laser has duration in microseconds compared to milliseconds in conventional laser. Since one laser spot cannot produce a biological effect, a train of pulses is used. The laser used is 810 nm laser and in pulse duration of 2000 microseconds (2 milliseconds) the laser is on for 100 to 300 microseconds and the frequency is about 400-500 pulses per second. As shown in Figures 14-3 and 14-4 as the energy per spot get reduced the effect gets more and more confined and in micropulse laser is confined to the RPE.\textsuperscript{5,8}
Figure 14-2: Large pigmented laser scar at the macula

Figure 14-3: Autofluorescence images of Micropulse laser (810 nm) for a patient with diabetic macular edema. It is seen as hypofluorescent spots in infero-temporal part of macula

**Therapeutic Effect**

The effect is confined to the RPE compared to the extent of retinal damage in conventional laser. The lateral spread of energy is confined (Figures 14-5 and 14-6). There is comparable though slower therapeutic effect. In view of lack of pain or discomfort there is better patient acceptance and cooperation. The only drawback is the lack of visible endpoint. Evidence also suggests that variable response of RPE due to heterogeneity may occur.

**Terminology (Figure 14-7):** In a laser pulse of 5000 µs, if the laser on time is 100 µs and the duty cycle is 2% (100/5000), then the repetition rate is 1/5000 (200 Hz).
1. **Technique (step-1 test burn):** To begin the treatment, a test burn is placed. Ideally a test burn with the micropulse parameters is best but not possible as there is no visible lesion. Hence a test burn with 200µ spot size with 200ms duration is used and power adjusted to produce a barely visible burn. This is applied nasal to the disc avoiding edematous area and areas with intra retinal or sub retinal blood. This would determine the threshold power (P). Then it is changed to micropulse mode with same power setting. At 25% to 5% duty cycle there is isolation or thermal confinement. Enucleated eyes have shown that 10-25% duty cycle at the threshold power consistently produces sub-clinical damage to the RPE visible only on light microscopy and electron microscopy.
2. **Technique (step-2—Treatment):** The treatment is carried out with 200µ spot size and 200ms duration and power adjusted to:

1. Same as threshold power \( P \) when using 10% duty cycle (200 µs on and 1800 µs off) or in 15% duty cycle (300 µs on and 1700 µs off).
2. 2-3 times threshold power \( P \) when using 5% duty cycle (100 µs on 1900 µs off).

**Outcome:** Ideally there is no visible reaction. However, autofluorescence (AF) changes could be observed after 1 hour after the procedure.\(^1\) RPE changes and window defects could be seen on FFA after 90 days. It could be visualized as hyper reflective areas on infrared imaging after 1 week (Figure 14-3).\(^1\) Change on OCT and clinical picture with respect to edema and neovascularization could be observed. However the therapeutic effect from laterally and axially confined thermal damage would require longer response time.

**Coverage:** A 200 µm spot with duration 100 ms conventional laser burn could expand up to 500 µm. Whereas, a micropulse laser spot of 200 µm would only expand up to 220 µm. Hence, up to 5 micropulse spots would be required to cover the same area of RPE.
Clinical results: The use of micropulse laser in clinically significant macular edema (CSME) in patients with non proliferative diabetic retinopathy (NPDR) has shown stabilization or improvement in vision in 85% of treated eyes with a mean follow up of 12.2 months. Further macular edema decreased in 96% and resolved in 79% of treated eyes. Reports also suggest reduction or elimination of diabetic macular edema in 74% of treated eyes with a follow up of 24 months, however there was an increase in the treatment sessions from 1 to 5. Studies have compared the threshold laser with sub threshold micropulse laser in the treatment of diabetic macular edema and found no significant difference in visual acuity outcomes in the treated eyes. The advantage being its ability to objectively and subjectively reduce the pericentral scotoma and reduction in post treatment scarring and atrophy (Figures 14-1, 14-2 and 14-4).

Studies on the use of micropulse laser in the treatment of macular edema secondary to branch retinal vein occlusion showed that at 6 months the resolution of foveal thickness and total macular volume was significantly better with the conventional laser. However, there was no difference in the foveal thickness and total macular volume in the two (conventional and micropulse laser) groups at one year. The visual gain of two lines was not different in the two groups at 12 and 24 months.

Studies have shown that subthreshold micropulse laser helps in resolution of the serous detachment in 85% of patients with Central serous chorioretinopathy.

CHANGE IN INSTRUMENTATION

PASCAL Laser

PASCAL stands for Pattern Scan Laser Photocoagulator. From the time the first Argon laser machine was built, the instruments delivered one laser spot at a time. This has remained unchanged till now. The PASCAL laser allows multiple spot deliveries, one after another, when the foot switch is depressed. The aiming beam projects the various patterns on to the retina and the laser delivery is along these specified spots. The patterns range from 3×3, 4×4, 5×5, macular grid pattern, partial grid, arcs, etc.

Physical principles: It is a 532 frequency doubled Nd-YAG laser in which the duration is reduced to enable multiple spot delivery. However, the energy delivered per pulse is reduced as Energy = Power × Time. If the power is doubled with pulse duration of 30 ms, the energy delivered would be 1/3rd of the energy if 100 ms duration is used. As the energy per spot is reduced the effect tends to be more confined to the outer retinal layers compared to the involvement of all layers of the retina by conventional laser. This probably would confine laser reaction to and around the RPE.

Advantages: The advantages are:
1. Multiple spot deliveries which would reduce the duration of treatment.
2. Since the energy delivered is reduced, the treatment sessions could be reduced to 1 or 2.
3. As the laser is more confined to the outer retinal layers, the pain fibers in the choroid is not stimulated hence pain is less. This would enable reduction in treatment sessions and increased patient comfort.
4. Since the total energy delivered per treatment session is reduced, the complications of choroidal detachment should supposedly be reduced.
5. The laser spots are more uniformly spaced.
Newer Lasers

Selective Laser Therapy (SLT) with the use of 30 pulses of Nd-YLF laser (527 nm) has been studied with effects being confined to the RPE. There are reports of use of diode red laser 670nm in the treatment of various retinal diseases with promising results.

Summary

These changes in techniques and instrumentation should guide us in the treatment of various retinal diseases. The aim of the treatment should be to produce a minimal burn at the level of the RPE thereby reducing the destruction and scarring of retinal tissue while maximizing the beneficial effects.

References

Role of Biostains in Vitreous Surgery
Introduction

The vitreoretinal surgeon operates with many limitations, the most significant one being the need to visualize the various optically clear components of the surgical field. These components are the vitreous body, the posterior hyaloid, internal limiting membrane (ILM), retina, epiretinal and subretinal membranes. The need to visualize these components stems from the critical roles played by them in the pathogenesis of all the surgical vitreoretinal disorders.

The vitreous body is perfectly transparent and only the obliquity of the endoillumination source can make it visible to the trained eye. Since vitrectomy demands removal of the vitreous, hence it is prudent to visualize this structure to the best extent possible. The same applies to the posterior hyaloid, which is not clearly seen even on oblique illumination and often requires movement with an instrument to be appreciated. To visualize the posterior hyaloid surgeons have traditionally relied on engaging it with an aspirating instrument or silicon tipped cannula (fish strike sign).

The ILM plays a vital role in the causation and management of macular holes and is also perfectly transparent. Some expert surgeons are able to visualize an unstained ILM and manage without any need for making the ILM more distinctly visible. For a large majority, however, visualizing the ILM is not easy and most surgeons would welcome any technique to make the ILM easily distinguishable from the retinal tissue. The benefits would be a reduction of operative time, less iatrogenic damage and a cleaner dissection plane from the nerve fibre layer.

Removal of epiretinal membranes is similarly inconvenient as a result of their transparency as well as their propensity for strong focal adhesions that can easily lead to iatrogenic tears during surgery. As with the ILM some experts are able to carry out this surgery without the help of stains but the surgery can be facilitated by techniques that improve visualization of the ERM selectively.

To improve outcomes in vitreoretinal surgery, a process of continuous experimentation and innovation has resulted in a host of available options to stain the various structures selectively. The currently available aids are grouped together to enable vitrectomy “in colour” – chromovitrectomy. These biomaterials are:

1. Indocyanine green
2. Infracyanine green
3. Trypan blue
4. Patent blue
5. Brilliant blue G
6. Bromophenol blue
7. Sodium fluorescein
8. Triamcinolone acetonide

**Indocyanine Green (ICG)**

The retinal internal limiting membrane (ILM) forms the structural boundary between the retina and the vitreous. It is derived primarily from, and rests upon, sea of Müller cell footplates that separate it from the nerve fiber layer. The pathogenesis of macular holes is debatable but consensus exists that the cause lies at the vitreoretinal interface.

Logically, management of macular hole is surgical and is directed at the vitreoretinal interface. The aims of macular hole surgery are to relieve traction on the edges of the hole and its immediate
surroundings. This may be targeted at anteroposterior traction or tangential traction. Anteroposterior traction is relieved by removal of vitreous and its attachments to the fovea. Tangential traction is exerted by membranes lying on the surface of the retina and can only be relieved by removal of these membranes, namely the ILM and any epiretinal membranes. Thus far there is no controversy.

Even though controversies exist, evidence available in the literature suggests that ILM peeling can enhance the successful closure of macular hole.1,2,3 Hence, various agents are used to enhance the visualization of ILM.

Indocyanine green (ICG) is a watersoluble tricarbocyanine dye. It was FDA approved for study of the choroidal circulation and was later described to enhance visualization and removal of the anterior capsule. The dye has a strong affinity for proteins and is excluded from the intracellular space of living cells by intact cell membranes. It has a photothermal effect resulting in radiation of heat after the absorption of light (Fox et al, 1957) and peaks in absorbance at the wavelength emitted by the endoillumination light source (Fox and Wood, 1960; Van den Biesen et al, 2000) thus increasing the potential for phototoxicity and thermal damage.

ICG is widely used for enhancing visualization of the ILM. According to the 2003 survey of the American Society of Retinal Specialists, 52% of vitreoretinal surgeons then using ICG-assisted ILM peeling had not routinely attempted ILM peeling before the introduction of ICG.

The staining properties of ICG are excellent and uncontested, however a debate rages on the safety of the drug and whether using ICG actually increases closure rates and visual outcomes. The advantages and disadvantages of using ICG are listed in (Table 15-1).

DOES THE USE OF ICG RESULT IN BETTER CLINICAL OUTCOMES

Unfortunately, there are no meta-analyses or systematic reviews on the subject. In a randomized controlled trial by Horio et al reported in 2004, 40 eyes were studied and randomized to surgery with or without ICG. At 12 months a statistically significant difference was reported between the 2 groups (p=0.02) favoring ILM peeling with ICG. However, there was a significant overlap in the confidence intervals of the 2 groups and the study had not clearly defined what they considered a clinically significant outcome. A recent meta-analysis (ophthalmologica 2008) has reported a significantly worse outcome in cases where ICG was used.

Other non randomized prospective studies (Kwok et al)4 have reported marginally statistically significant benefits of ICG use. A number of retrospective studies5-8 have been published with closure rates varying from 88 to 100% and rates of visual recovery >2 lines ranging between 38 to 100%.

SAFETY OF ICG

Initial use of ICG was reported at concentrations up to 5%. Since then, reports have been published regarding the toxicity of ICG in the form of RPE toxicity, visual field defects and persistent fluorescence. These adverse effects assume importance in the light of uncertain benefits of ICG use as far as improvement in visual outcomes is concerned.

The toxicity of ICG on the RPE has been documented experimentally.9-11 The experimental models used have been human donor eyes, rat, rabbit, pig and various cell lines. The results of these studies are often contradictory and influenced by variations in experimental procedure like the removal or preservation of vitreous, the experimental model used and other variables. However, many of these
studies have reported some damage at concentrations ranging from 0.025 to 0.5%. The postulated mechanisms of intravitreal ICG-related toxicity\textsuperscript{12, 13} are:

1. Biochemical direct injury to the ganglion cells/neuroretinal cells, RPE cells, and superficial retinal vessels.
2. Apoptosis and gene expression alterations to either RPE cells or neuroretinal cells.
3. Osmolarity effect of ICG solution on the vitreoretinal interface.
4. Light-induced injury.
5. Mechanical cleavage effect to the internal limiting membrane/inner retina.

There is controversy as to which mechanism is predominant, however the animal models have documented some injury to be attributable to the biochemical, osmolar, phototoxic or air induced
Role of Biostains in Vitreous Surgery

drying mechanisms. Therefore a number of surgeons have resorted to the following precautions while using ICG:
1. Injection while infusion is on—washes off excess dye and prevents concentration of dye in one area.
2. Placing a bubble of PFCL or viscoelastic over the hole to prevent direct contact with RPE
3. Using the lowest effective concentration, the aim being to make the ILM just visible rather than deep staining.
4. Keeping the ICG on the retina for the shortest possible time and completing the surgery in the shortest possible time subsequent to injection of ICG so as to lessen the chances of phototoxicity—this is aided by timing the surgical procedure and completing the ILM peeling within the allotted time span; this avoids unnecessary light exposure of the ICG stained macular region to the endo-illumination light source.
5. Use of the VINCE applicator technique.

The alternatives to ICG in macular hole surgery are Infracyanine green (IfCG) and trypan blue.

Infracyanine Green
Infracyanine green (IfCG) is a green dye with the same chemical formula and similar pharmacologic properties as ICG. It is postulated to be a safer alternative to ICG due to the absence of sodium iodine in its final constituted form. Another advantage is said to be due to the iso-osmotic state of IfCG compared with the hypotonic state of ICG. In a retrospective series comparing 67 eyes with macular hole that underwent surgery with IfCG staining vs 72 eyes operated without IfCG, closure rates and postoperative visual acuity was reported to be similar in both groups. No significant toxicity was reported, leading the authors to conclude that IfCG was safe for intravitreal use. In an experimental study on cultured human RPE cells, there was no difference in the acute or chronic toxicity of indocyanine green or infracyanine green. As of now, infracyanine green use has not become popular in the clinical setting.

Trypan Blue
Trypan blue (TB) may stain a tissue either by binding to degenerated cell elements or being taken in by phagocytosis and was introduced in 1998 to stain the anterior capsule to facilitate capsulorrhexis for cataract surgery. The stain may traverse cell membranes only in dead cells, coloring dead tissues or cells blue. It does not stain live cells or tissues with intact cell membranes as cellular membrane transport does not allow trypan blue binding. While it has been suggested that TB may stain both ILM and ERM, the dye most likely stains primarily the ERM, possibly due to a strong binding affinity to glial-cell elements.

In clinical use, the general impression of surgeons is that trypan blue does not stain ILM as well as ICG, but its side effect profile is better and hence, becomes an attractive alternate to ICG. A drawback is the need for an air fluid exchange prior to injection of the dye. To obviate this requirement a heavy form of trypan blue (10% glucose mixed with membrane blue [DORC]) that can be injected has been proposed.

Stalmans and colleagues described a double staining of retinal structures with both TB (for ERM) and ICG (for ILM) in the treatment of macular pucker. A recently proposed role for trypan blue consists of staining retinal break edges during vitrectomy for rhegmatogenous retinal detachment repair.
**COMPARISON WITH ICG**

Trypan blue, in concentration from 0.06% to 0.20%, stains the ILM but less intensely and uniformly than ICG. However it has been postulated by some to be a safer option than ICG.

A recent randomized control trial\(^{20}\) to test this hypothesis found no difference in the structural or functional outcomes between the two. However, this was a pilot study with a sample size of 20 patients in each arm and no predetermined end point for efficacy, but had the advantage of testing vision, visual field and OCT on all patients. The obvious next step is an adequately sized study for answering this question.

Safety in clinical reports has been established but in vitro studies have shown conflicting results on the safety of intravitreal TB injections. Due to its solubility it has been proposed that TB has less acute toxicity to cultured RPE cells compared to ICG and IICG, however it has been reported to have more chronic toxicity. RPE cell culture studies indicate a potential increase in apoptosis even after application of lower concentrations of 0.05% of Trypan blue for 5 minutes. In contrast, no direct TB-related toxic effects were observed in a postmortem study, in rabbit eyes, and in several clinical trials. Carcinogenic and teratogenic properties of trypan blue have been described in animal models\(^ {21}\) and long-term side effects are unknown in humans, so far.

**Patent Blue**

Patent blue (PB) is an anionic dye and is orange in acid conditions and blue in alkali. It has been used to assist in fungus identification and removal of lymph nodes. The dye has been recently certified for capsule staining during cataract surgery at the concentration of 2.4 mg/ml. The carcinogenic and mutagenic effects described with systemic use of TB in laboratory animals have not been seen for PB.

Patent blue is reported to provide better visualization of the ERM in comparison to the ILM, and no visual field defects or visible RPE-changes were observed postoperatively. In vitro studies have revealed conflicting data on the retinal safety of the dye and the safe dose is yet unknown.

**Sodium Fluorescein**

Sodium fluorescein (SF) is an anionic hydrophilic dye and was found to be highly safe for fundus angiography in a concentration of 5-25% solution, even when leakage through the retina occurred. Because of its hydrophilic properties, SF is highly absorbed by the vitreous gel. The use of sodium fluorescein in vitrectomy was reported by Abrams and co-workers\(^ {22}\) as early as 1978. Das and Vedantham\(^ {23}\) showed that intravitreal SF injectable dye improved the visualization of clear vitreous fibers through a green coloring during chromovitrectomy, and no complications were noticed in their clinical series. To date, the main indication of SF in chromovitrectomy remains in the vitreous, while future clinical investigations should determine its role in ILM staining. There is a lack of data evaluating retinal toxicity of intravitreal sodium fluorescein in human eyes.

**Brilliant Blue G (BBG)**

Also known as Coomassie or acid blue, it is a synthetic dye and a food additive having been used intraocularly for anterior lens capsule staining and chromovitrectomy.
In humans studies, BBG was used in an iso-osmolar solution of 0.25 mg/ml to stain ILM for ERM and macular hole surgery, with 85% of patients improving at least two Snellen lines. No clinical signs of toxicity have been observed in the long-term. In rat and primate eyes no significant retinal toxicity has been reported both structurally and functionally. Due to its high affinity to ILM, BBG is an alternative to ICG and IfCG for ILM staining although toxicity data are presently limited.

**Bromophenol Blue (BrB)**

BrB has been proposed as an alternative biostain for chromovitrectomy. RPE culture studies demonstrated that among six biological stains (light green yellowish, E68, Chicago blue, rhodamine, rhodulinblau-basic), BrB stained better the ERM, ILM, and did not cause RPE toxicity at concentrations of 0.2 and 0.02%. Further studies in rodent and porcine eyes demonstrated that BrB at concentrations of 0.5 and 0.02% promoted less significant retinal toxicity in comparison with three other vital dyes.

**Triamcinolone Acetonide**

Triamcinolone acetonide (TA) is a relatively insoluble steroid that is used for local treatment of several ocular diseases, such as ocular inflammation, macular edema and age-related macular degeneration. TA was added as an alternative stain for chromovitrectomy based on experience from other ophthalmic applications.

TA injections for chromovitrectomy have been performed with 0.5 mL of the 40 mg/ml commercial product. The white steroid is used to visualize the vitreous gel and posterior vitreous cortex. The high affinity of TA to the vitreous particles and the fine ILM was postulated as the result of the steroid precipitation. Besides aiding in the visualization of preretinal tissues, TA application in chromovitrectomy may improve surgical outcomes by decreasing the break down of blood-ocular barrier and reducing the chance of preretinal fibrosis. While TA was proposed for visualization of the ILM and vitreous, further investigation on its exact target tissue during chromovitrectomy is required. Intraoperative identification of the preretinal membranes may be hindered by the deposition of TA particles.

During chromovitrectomy, TA is found to deposit in the macular or submacular space for several days after its intravitreal application, although no clinical signs of retinal damage were observed. Researchers have proposed that the toxic substance in TA is the vehicle, rather than the steroid itself. Probably, to minimize the risks, TA should be filtered to generate a vehicle-poor suspension.

This steroid has shown no toxic effects and complications associated with intravitreal injection such as glaucoma occur less frequently due to the removal of most of the steroid by the end of the surgery in chromovitrectomy. The risk of endophthalmitis associated with intravitreal injection of TA is related to the injection procedure and not an independent complication of triamcinolone in the vitreous. This lack of toxicity remains the most remarkable advantage of staining preretinal membranes with TA.

**Fluorometholone Acetate**

Fluorometholone acetate is a synthetic fluorinated glucocorticosteroid and a creamy ophthalmic suspension that can be prepared for use. Hata et al. investigated the safety of intravitreal or subretinal
Fluorometholone acetate to the morphology and function of the retina in rat and primate eyes for possible use in chromovitrectomy. They concluded it was a useful alternative to triamcinolone acetonide during chromovitrectomy.

**Vitreoretinal Internal-limiting Membrane Color Enhancer (VINCE)**

A new dye applicator named VINCE has been recently released to allow painting of preretinal tissues. The painting brush is constructed of a silicone tube connected to a 20 gauge metal cannula. The dye diluted in fluid is provided by connection to a silicone disposable cartridge containing the vital dye. The flexible dye-filled tip smoothly traverses the retinal surface, enabling the dye to paint with a minimum of dye. The novel approach should enable vitreoretinal surgeons to stain the fine delicate semitransparent tissues on the retinal surface, avoiding an excessive and unselective staining of the entire retinal surface.

**Conclusion**

Visualization of preretinal structures and membranes has become easier due to availability of various dyes. ICG has been the “pioneer dye” for ILM-peeling. Current recommendations for ICG-assisted chromovitrectomy consist of injection in concentrations as low as possible, short incubation times and no concomitant light exposure; a similar approach is warranted for novel vital dyes. Alternatives to ICG are IfCG and Brilliant blue Green. For ERM removal the current preferance is trypan blue, with alternative options being patent blue and Bromophenol blue. Triamcinolone acetonide is preferred for vitreous visualization, while sodium fluorescein and fluorometholone acetate are good alternatives approaches.

**References**

Chapter 16

Wide-angle Viewing System in Vitreoretinal Surgery
Introduction

Modern vitreous surgery was largely the result of pioneering effort of Robert Machemer. During the process of further improvement till today, vitreoretinal surgical techniques and instrumentations has facilitated the surgical management of vitreoretinal pathologies. However, besides surgical instrumentation, optimal viewing of the surgical field is one of the most important factors which can influence the surgical outcome. This viewing system includes a very good operating microscope and a contact or a non-contact optical lens system.

The older contact lens (either assistant held or those fixed to the episclera) does aid in the surgical viewing but limited field of view is the major disadvantage. Peripheral retina can only be seen with indentation. Besides this, difficulty in keeping the lens properly aligned during surgery, limited access to the limbus, air bubble or blood film coming beneath the lens system are the other drawbacks. Limited use in small pupil as well as poor visualization during fluid gas exchange in phakic or pseudophakic eyes are added disadvantages.

Vitreous microsurgery has made a tremendous progress in the last couple of decades. The wide-angle viewing systems provide a panoramic view of the surgical field up to the ora serrata. Though the initial cost may be higher and might demand a steeper learning curve, it has several advantages over the contact lenses. Because of the ease of operation, overall surgical time is less. Besides, it has greater depth of field and easy view during fluid-gas exchanges.

Wide-angle viewing system is mainly of two types:

**NONCONTACT**
- **BIOM with SDI** (Binocular Indirect Ophthalmomicroscope with Stereoscopic Diagonal Inverter)
- **EIBOS** (Erect Indirect Binocular Ophthalmo-microscope System).

**CONTACT**
- **VPFS** (Vitreous Panfunduscope System)
- **CWF** (Contact Wide Field System)
- **AVIS** (Advanced Visual Instrument System)
- **ROLS** (Reinverting Operating Lens System).

Though these contact lens systems can achieve up to 150° field of view and great optical resolution, they might cause change in intraocular pressure, corneal trauma and perform poorly in steep corneal curvature. The noncontact systems can avoid most of the above problems, the trade – off being that the optical resolution is of inferior quality to the contact systems. Moreover, systems like EIBOS cannot be used in all microscopes.

All the above contact or non-contact viewing systems produce an indirect image, hence necessitating the incorporation of image inverter system in the microscope which would reinvert the image in the surgical field. This image inverter system is called the Stereoscopic Diagonal Invertor (SDI).

**Stereoscopic Diagonal Invertor (SDI)**

SDI is an inverter system which is incorporated in the operating microscope to reinvert the inverted image produce by a wide-angle viewing system ([Figure 16-1](#)). This system was first developed by Spitznas and Reiner.¹
The SDI has an internalized prism system with near-zero light escape to achieve maximal illumination and light intensity. It provides stereoscopic erection of the inverted image and can be activated by electrical hand or footswitch or manually. It can be adapted to different types of microscopes.

Indirect Surgical Non-Contact Lens Systems

**BINOCULAR INDIRECT OPHTHALMOMICROSCOPE (BIOM)**

BIOM (Figure 16-2) manufactured by OCULUS, Optikgeraete, GmBH, (Wetzler, Germany) was an invention of Prof Spitznas where he incorporated the principle of indirect ophthalmoscopy in the operating microscope. As BIOM provides an inverted image, it can only be used in conjunction with
SDI. BIOM can be mounted with case on the microscope and can be shifted in to the beam path when required. It has a mounting plate secured to the lower surface of the operating microscope by a flange and a dovetail. There is a condensing lens on the top of an indirect viewing tower and a small objective lens combined to a retractable extension arm. Manual rotation of a knurled-knob attached to the extension arm facilitates upward or downward movement of the objective lens for finer adjustments while focusing.

The advantages of BIOM are:
1. Wide angle of view (90°-110°)
2. Good stereopsis and depth of focus
3. Wide angle of view even with small pupil
4. Non contact system, hence there is no risk of corneal touch.
5. The eye can be rotated allowing the view of the peripheral fundus
6. Good view even in air filled aphakic, phakic or pseudophakic eyes.

**BIOM 3**

It can be installed very fast and can be swung into the path of rays when desired. Advantages are:
1. Large depth and sharpness.
2. Simple to focus.
3. All components can be sterilized.
4. No load on cornea.

**Instrumentation and Maneuvering**

A clear visual axis with a minimum pupillary diameter of 2.5 mm is required. The operating table should be as low as possible with comfortable leg position for the surgeon.

After the standard pars plana ports are made and anterior vitrectomy done under the normal microscope light, the light is turned off and endo-illuminator is switched on. The SDI foot pedal is activated and the microscope slowly lowered. Magnification is achieved by using the zoom system of the operating microscope or by lowering the microscope so that the objective lens is closer to the cornea.

The knurled-knob should be started about an inch below its highest setting. When the knob is rotated anticlockwise the small objective lens moves up but focuses down and a clockwise movement will cause the objective lens to go closer to cornea and will focus upward. To achieve the initial focus, the endo-illuminator in the vitreous should be aimed at the disc. After the surgeon has decided about the adequate magnification, he adjusts the knurled knob to achieve the fine focus. Once the disc and the posterior pole is properly focused, the periphery is also viewed by manipulating the eye and the X-Y movement of the microscope.

During the surgery, if the surgeon wants to shift to a contact lens the assistant has merely to flip the BIOM up to move away from the visual axis.

**Sterilization**

The BIOM can be sterilized with gas or autoclaved. The lenses can be sterilized with ethylene oxide (ETO) or Cidex. The SDI is incorporated into the microscope and is not sterile.
EIBOS

EIBOS (Figure 16-3) is a non-contact wide angle viewing system which works on the same principle as BIOM, except that it has an integrated reversing optics and hence does not require SDI. This has disadvantage that the inverter cannot be used independently with miniature indirect contact lens, unlike BIOM. But, it allows the use of direct contact lenses as it can be flipped up and out of visual axis.

Sterilization

The one piece design does not allow sterilization of the entire unit, and it must be draped with a sterile covering, though the objective lens can be sterilized.

Wide-angle Indirect Surgical Contact Lens Systems

VPFS (VITREOUS PANFUNDOSCOPE SYSTEM)

VPFS is a modified Rodenstock panfundoscope with a portion of the lens trimmed off to allow easy introduction of instruments into the vitreous cavity without disturbing the lens. The system provides an inverted image, and hence SDI is necessary. It gives an observation angle of 130°-150°. It can be stabilized with a handle held by an assistant or a link chain. The major disadvantage is its weight (28 gm), which appears to be heavy compared to other lenses, hence often difficult for the assistant to hold the lens for prolonged period of time.

CWF (CONTACT WIDE FIELD LENS)

These wide field contact lenses (Figure 16-4) provide inverted images, hence have to be used with SDI. It provides surgical field of view of 120°-130°. It is lighter (4 gm) and smaller than VPFS. It can be held by handle or standard lens ring.
AVIS (ADVANCED VISUAL INSTRUMENT SYSTEM, ADVANCED VISUAL INSTRUMENT INC., NEW YORK, USA)

AVI (Figure 16-5) panoramic viewing system consists of:
1. AVI stereo inverter, and
2. Two miniature contact lens

The system provides an inverted image, which is re-inverted by a stereo inverter. There are two miniature contact lenses. The first one gives a 68° field of view with increased magnification for the central fundus. The second lens provides a viewing angle of 130°. The lenses can be stabilized by a handle held by an assistant or by a self-retaining ring.

The advantages are:
1. Smaller and lighter, allowing easy manipulation of the lens.
2. Allows visualization of the fundus through small pupil or air filled eye.
Wide-angle Viewing System in Vitreoretinal Surgery

3. Greater depth of focus than the other lenses
4. Integrated with conventional contact lens system, so that when one lens is removed it can be easily replaced by another.

ROLS (REINVERTING OPERATING LENS SYSTEM)
ROLS (by Volk Optical Inc, Mentor, Ohio, USA; Figure 16-6) is another advanced wide angle viewing system available for vitreoretinal surgery. It has a single element reinverter prism design, the surface

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FIGURE 16-6: Reinverting operating lens system
of which is manufactured to 1/10th wave flatness for perfect image reproduction. The purpose of this reinverter is to correct the inverted image created by the indirect vitrectomy lenses and provides widest field of view. A series of vitrectomy lenses are used along with it, like Super Macula Lens for viewing the macula, the Mini Quad lenses for viewing upto 127° and the Mini Quad XL for viewing upto 134° and Dyna View up to 156° (for full field fundus viewing). These lenses along with the reinverter can provide panoramic field of view from the vascular arcade upto the ora serrata.

This system has the added benefit of decreased working distance. It automatically decreases the working distance when switching from plane concave lens to wide field vitrectomy lens, hence promoting a more comfortable working distance. ROLS system has diode laser safety filter permanently installed.

**Sterilization**

The lenses can be sterilized with ETO at 130° F.

**Conclusion**

The introduction of wide angle viewing system has changed the approach towards vitreoretinal surgery. The major advantages of Wide Angle Viewing System are:

- Easy visualization of peripheral retina and hence better understanding of peripheral vitreoretinal relationships
- Complete, assured and better surgical results can be achieved
- Better monitoring of PFCL injection
- Complete endophotocoagulation is achieved
- Vitreous base excision is easy and hence indentation is often not required as with conventional contact lenses
- Retinal detachments with advance proliferative vitreoretinopathy as well as proliferative retinopathies can be operated with ease.

**References**

Chapter 17

Microincision Vitrectomy
Introduction

Vitreous surgery has evolved significantly since its introduction in 1970. From the introduction of 17 gauge (G) vitreous cutter to 20 gauge, then 25 gauge and now 23 gauge cutters extensive technological innovations have occurred over these years. Along with vast changes in the machinery, it has evolved providing better results in complicated vitreo-retinal surgical management. In the evolution many things got introduced and were called back. When the gauge of the cutter changed new issues came up and surgeons found new solutions.

With the smaller gauge instruments proper case selection became imperative as decreased caliber of the instruments and decreased fluidics work most efficiently when extensive manipulation of intraocular tissue or significant membrane dissection are not required.

In fact, several issues associated with 25-G surgery due to the small calibre led to further innovation of larger 23 gauge instruments and eventually an angled tunnel angled through the wall of the eye evolved.

The history, development, advantages and disadvantages of transconjunctival suture less vitrectomy is reviewed in this chapter. The spectrum of appropriate cases, recent innovations in vitrectomy surgery, long-term outcomes and possible complications are discussed.

History of Vitreous Surgery

In the 1970s, Machemer et al. first introduced a 17 gauge vitreous cutter (1.5 mm diameter) that required a 2.3 mm scleral incision for pars plana vitrectomy (PPV) in an eye with diabetic vitreous hemorrhage. In 1974, O’Malley and Heintz produced a smaller 20 gauge vitrector (0.9 mm diameter) for use with the three-port sclerotomy system. This has become the gold standard for modern PPV. In standard 20 gauge PPV, conjunctival dissection is followed by the creation of three linear 1.4mm sclerotomies. The infusion line is typically sutured into place in the inferotemporal quadrant, while the superonasal and superotemporal sclerotomy sites are used for interchange between a light pipe, vitreous cutter, and other microsurgical instruments. Following completion of vitreoretinal surgery, the sclerotomy sites as well as the overlying conjunctiva are closed with absorbable (e.g vicryl) suture.

The next advance in PPV involved novel techniques for scleral-tunnel based incisions that created sutureless, self-sealing sclerotomies. This method still required conjunctival dissection and encountered significant complications, including difficulty in passing instruments, wound leak, extension or dehiscence, hemorrhage, vitreous or retinal incarceration, retinal tears, and dialysis.

In 1990, de Juan and Hickingbotham developed a 25 gauge vitrector, membrane dissector, and microforceps with a diameter of 0.5 mm that facilitated more precise surgical manipulation. This system was further refined with the introduction of the TSV system along with an accompanying set of instruments in 2002. Several problems associated with 25 G surgery, like flexible instruments, limited functionality of forceps and scissors, decreased flow rates, wound leak etc. were bothering surgeons and instrument manufacturers. Solutions to some of these problems would seemingly involve using slightly larger gauge instruments; the 23 gauge vitrectomy system has thus come into being. 23 G instruments have been in use in pediatric cases for years, and there is a long-term manufacturing experience in this bore size.
Microincision Vitrectomy

Sutureless Vitrectomy System

The idea behind the development of 25 gauge sutureless vitrectomy originated from using 25 gauge needles for transconjunctival, pars plana intravitreal injections that did not require conjunctival dissection or suturing of the sclerotomy. The small gauge microcannula system used in the pars plana wound maintains alignment between the conjunctival and scleral entry sites, allowing for interchangeability of intraocular instruments while minimizing damage to the vitreous base and trauma at entry sites. Each microcannula system contains an extra ocular collar that can be grasped with forceps to facilitate manipulation and provide stability when placing the ports or exchanging instruments during surgery. The infusion line fits directly into the microcannula without suturing, and the tubing can be secured with adhesive to the surgical drape.

The instrumentation for 23 G surgery is exactly the same as for 25 G surgery; it is only the diameter which is different (Figure 17-1).

Available instruments include a vitreous cutter, an illumination probe, microforceps, scissors, retinal picks, micro vitreoretinal blade, soft-tip cannula for aspiration, endolaser, and diathermy. An illuminated endolaser probe has been added recently, which allows for laser with surgeon-controlled scleral depression.

Surgical Technique

23 and 25 gauge vitrectomy are typically performed under local anesthesia with a retrobulbar block and intravenous sedation. While vitrectomy can be done under topical anesthesia alone, the patient may experience discomfort, especially upon insertion of the microcannulae with the trocars and during scleral depression. A retrobulbar block has the added advantage of limiting eye movements during crucial portions of surgery such as membrane peeling. Proper prepping of the surgical field with povidone iodine significantly decreases the risk of postoperative infection, and careful surgical draping must isolate the operative field from the eyelid margins and eyelashes as well as seal off the oral and nasal passages to minimize fogging of the viewing system during surgery.

The first step is to displace conjunctiva with a cotton bud or caliper tip so that there will be misalignment between the conjunctival and scleral incisions upon cannula withdrawal at the completion of surgery. The first microcannula is inserted directly through conjunctiva (3.5-4 mm posterior to the limbus depending on phakic status) with the aid of a beveled trocar in the inferotemporal quadrant and the infusion line is inserted. The other two microcannulae are
inserted in the superotemporal and superonasal quadrants; plugs can be used to close them when needed.

The 23 gauge vitrectomy is started by pushing the conjunctiva 1 mm to 2 mm laterally (i.e. parallel to the corneal limbus) in the inferotemporal, superotemporal, and superonasal quadrants using a special pressure plate to hold it firmly to the sclera. A 23 gauge stiletto blade (45° angle) is then inserted at a 30° to 40° angle through the conjunctiva, sclera, and pars plana 3.5 mm from the corneoscleral limbus (Figure 17-1). To obtain scleral tunnels parallel to the corneoscleral limbus, the scleral incisions are made radial to the corneoscleral limbus. The incision with the 23 gauge stiletto blade is 0.72 mm wide. Constant pressure is applied to the pressure plate while the incision is made and during withdrawal of the stiletto blade to prevent slippage of the conjunctiva against the sclera. Should displacement occur, it would be difficult if not impossible to subsequently locate the incision in the conjunctiva and sclera.

- An angled tunnel through the wall of the eye provides greater transmural wall strength in the area of the incision and has the potential to self-seal with the help of intraocular pressure.
- Moreover, an angled incision does not present a direct perpendicular opening from the vitreous to the external environment.

Microcannula removal at the end of the case is performed by grasping the external collar with forceps and rolling over the opening with a cotton tip to purposefully misalign the conjunctival and scleral openings; this decreases the chance of a direct conduit between the intraocular space and the environment. Towards the end of the surgery the superior microcannulae are removed first while infusion is kept open, to maintain chamber stability, optimize intraocular pressure, and promote vitreous occlusion of the sclerotomies. The infusion line and its attached cannula are then simultaneously removed.

The 0.5 mm sclerotomies is self sealing and heal rapidly, precluding the need for suturing to close sclera or overlying conjunctiva. Postoperative subconjunctival injections of antibiotic and steroid are routinely given as in 20 gauge vitrectomy.

To prevent hypotony a suture should be placed if bleb formation is seen upon cannula removal. Performing intraocular fluid-air/gas exchange at the completion of surgery is also beneficial. But the hypotony usually resolves within one week without any long-term complications.

Ultrasound biomicroscopy (UBM) studies have demonstrated that sclerotomy sites with oblique cannula insertion heal much more rapidly than standard 20 gauge sclerotomies or even those with direct cannula insertion in 25 gauge surgery.7

Case Selection

Success with the Transconjunctival sutureless vitrectomy system requires selection of appropriate cases. Optimal cases for 25 gauge vitrectomy are those that do not require extensive membrane dissection or manipulation of dense intraocular tissues; as the overall smaller scale of 25 gauge vitrectomy leads to decreased vitreous or tissue removal as well as lower infusion and aspiration rates. These situations may be better handled with the full capabilities and instruments of the 20 gauge vitrectomy system or 23 gauge sutureless system. Illumination is also reduced accordingly, but may be maximized with a xenon light source and newer endoilluminators with greater divergence (wide) angles.

Ideal cases for 25/23 gauge vitrectomy (Figure 17-2) includes vitrectomy for macular hole, macular edema, secondary to a taut posterior hyaloid or vitreo-macular traction, macular pucker, vitreous opacities secondary to vitritis or previous endophthalmitis, vitreous opacity in Behçet’s disease and
Microincision Vitrectomy

Vitreous amyloidosis, radial optic neurotomy for central retinal vein occlusion, branch retinal vein occlusion sheathotomy or arteriovenous crossing manipulation, uncomplicated vitreous hemorrhage, removal of dislocated intraocular lens, pars plana membranectomy for posterior capsule opacification, endophthalmitis, submacular hemorrhage secondary to choroidal neovascular membrane (for subretinal injection of tissue plasminogen activator), aqueous misdirection, transretinal choroidal tumor biopsy, etc.

In pediatric patients, when the narrow palpebral fissures and smaller eyes make conventional vitrectomy surgery difficult, 25 or 23 gauge vitrectomy will become the procedure of choice. In retinopathy of prematurity stage 4 and 5, a modified 25 gauge pars plicata vitrectomy with conjunctival dissection is used to treat tractional retinal detachments. It has added advantages of enhanced surgical access to the retrolental space and to the retinal folds.

Certain cases of retinal detachment without proliferative vitreoretinopathy (PVR) or diabetic tractional retinal detachments (TRD) with minimal fibrovascular proliferation may be appropriate. In retinal detachment repair, decreased fluidics may be safer as a small lumen combined with a high cutting rate may lower the incidence of iatrogenic retinal breaks by reducing pulsatile vitreoretinal traction. Removal of vitreous gel and vitreous base shaving is more difficult, however, given the
slow cutting/aspiration ability and the flexibility of 25 gauge instruments, incomplete removal of peripheral vitreous may lead to recurrent retinal detachment with significant PVR and difficult reoperations. However, 23 G instruments is a good balance between microincision of 25 G and versatility of 20 G. For uncomplicated diabetic membrane peeling or TRD repair, the Micro gauge vitrector may facilitate accessing surgical planes and small spaces. The mouth of the vitrector is closer to the end of the cutter than in the 20 gauge cutter, allowing for membrane segmentation and delamination closer to the surface of the retina while minimizing inadvertent trauma.

As with PVR detachments, complex diabetic TRD may be more challenging with the 25 gauge setup. Time saved in ‘opening’ and ‘closing’ will be negated by less efficient vitrectomy due to the smaller port diameter and reduced cutting and aspiration speeds. Certain instruments like lighted pick or scissors, MPC (membrane peeler cutter) scissors are not available, which will be limiting bimanual surgery and extensive membrane dissection. Substantial intraocular manipulation and resultant inflammation will also cancel the benefits from ‘less traumatic’ 25 gauge surgery. Presently, 23 G instruments appears to improve the micro-incision vitrectomy in complicated retinal detachment than 25 G instruments.

Scleral buckle surgery necessitates conjunctival peritomy and dissection, and retained nuclear lens fragments are best removed with the 20 gauge fragmatome. Surgery following trauma is also best approached with 20 gauge PPV, either in intraocular foreign body removal or complicated retinal detachment repair. Silicone oil cases often involve significant intraocular manipulation, and viscous fluid injection or extrusion is extremely slow through available micro gauge instruments, although it is more efficient when using 1000 centistoke oil.

In some of these cases, the small gauge setup can be combined with opening a single superior port for 20 gauge instruments to maximize overall efficiency and time savings. Uncomplicated silicone oil removal can be performed with an 18 gauge angio catheter and viscous fluid extraction through a slightly enlarged sclerotomy. Lensectomy with the fragmatome can remove retained lens material, although caution must be used as aspiration on the fragmatome can easily outpace inflow provided from the 25 gauge infusion line. This can be minimized by increasing the infusion pressure and reducing the suction. Finally, in cases that are initiated as 23/25 gauge vitrectomy, conversion of a single port to 20 gauge to allow for the use of certain instruments is often adequate.

Combining 23/25 gauge surgery with Phacoemulsification and intraocular lens implantation is found to be safe and effective, because of the short time taken for vitrectomy, less chances of post operative astigmatism due to sclerotomies, early scleral wound healing and minimal post operative inflammation. While doing 23/25 gauge vitrectomy with phacoemulsification, microcannula insertion can be performed prior to cataract extraction under physiologic intraocular pressure or after closing the cataract wound with a single 10-0 nylon suture. In cases with a shallow anterior chamber or positive vitreous pressure, limited 25 gauge pars plana vitrectomy (PPV) can be used to remove retrolental vitreous to facilitate cataract extraction. When there is posterior capsular rupture with vitreous loss, 25 gauge PPV can be used to clear the anterior chamber of vitreous and perform anterior vitrectomy.

Advantages of Transconjunctival Sutureless Vitrectomy

The advantages of sutureless vitrectomy are similar to those advantages seen with sutureless, small-incision phacoemulsification for cataract surgery. Intra-operative time, postoperative inflammation and patient discomfort, recovery time may all be decreased (Figures 17-2 and 17-3). When compared
Microincision Vitrectomy

FIGURE 17-3: Showing first day postoperative appearance after 25 G (above) and 23 G vitrectomy surgery (below). Note: micro cannula insertion site (Courtesy: Dr Nazimul Hussain, Al Zahra Hospital, UAE)

to conventional 20 gauge vitrectomy, the greatest advantage of transconjunctival sutureless vitrectomy is the time saved in cutting short the first and last steps in vitrectomy. The initial steps of conjunctival dissection, placement of conjunctival and scleral incisions, cannula insertion, infusion line setup, plug placement, and the final steps of cannula withdrawal and suturing are all bypassed. Omitting conjunctival dissection avoids intraoperative bleeding and possible limbal stem cell damage, which is a great advantage in eyes with preexisting corneal or conjunctival disease. Minimizing conjunctival damage is also ideal in patients with present or future glaucoma filtering procedures. Intraoperative steps such as instrument exchange are easier due to the flared cannula design as well as decreased friction compared with a 20 gauge sclerotomy. Immediately after surgery eyes have a less traumatic appearance, with significantly less redness and intraocular inflammation. Although sclerotomies and scleral tunnels are left unsutured, ultrasound biomicroscopy (UBM) have shown that they heal much more rapidly than conventional sclerotomies. There is minimal wound gape on postoperative day one and the site is undetectable within 2 weeks, compared with a 6-8 week healing time for 20 gauge sclerotomies. Along with this, the advantage of reduced inflammation and no discomfort related to suture material is also there in 25 gauge and 23 gauge PPV.
Disadvantages

Both 23 and 25 gauge vitrectomy involves risks inherent to 20 gauge PPV, including cataract progression, iatrogenic retinal breaks, inadvertent lens touch, and postoperative ocular hypertension.

In 25 gauge vitrectomy the instruments are too flexible and many are too small to be sufficiently effective. Although next generation vitrectomy systems are stiffer, increased flexibility of 25 gauge instruments do not allow as much torsion of the eye itself. By placing a finger on the instrument shaft just above the collar of the microcannula during surgery can help to partially overcome this. Also, due to the smaller port size and inner diameter, the 25 gauge vitrector has a lower aspiration rate by a factor of 6.6 compared with the 20 gauge cutter; the infusion rate in the 25 gauge system is similarly decreased by a factor of 6.9.

Hypotony during aspiration is rarely encountered, but maximum cut settings and increased aspiration power must be employed to achieve reasonable cutting and aspiration rates. This will minimize occlusion of the vitreous cutter with large or dense fragments of fibrous or other intraocular tissue. Flow rates through a tube is related to the radius to the fourth power and so any small increase in the diameter of the “tube” will make a big increase in the flow rates.

Many problems with 23 G vitrectomy relate to the larger wound required. Unlike 25 G, conjunctival displacement is not sufficient to prevent wound leaks. Many surgeons have observed that 23 G wounds leak if the scleral tunnel is too short. Some surgeons have noted intra operative scleral folds extending into the posterior pole if the scleral tunnel is too long. Although tools and technique changes have attempted to address this problem, many surgeons still have difficulty in locating the sclerotome made with the stiletto when subsequently inserting the cannula.

Open sclerotomies or leaking tunnels at the end of surgery can create other complications such as early postoperative hypotony, which develops when the opening is not plugged internally with vitreous or externally by conjunctiva. Hypotony itself will produce more wound gaping in case of the tunnel incisions. This may occur more frequently with significant intraocular manipulation or removal of peripheral vitreous gel. As oblique insertion requires adequate scleral tissue, patients with a history of severe ocular trauma, high myopia, or multiple intraocular surgeries may not be ideal candidates.

A suggested potentially more devastating complication in small gauged vitrectomy is endophthalmitis. Endophthalmitis in transconjunctival sutureless vitrectomy may occur secondary to several mechanisms.

- Direct cannula insertion may inoculate the vitreous with conjunctival flora during trocar insertion.
- Open sclerotomies and wound leaks may allow for increased influx of bacteria.
- Decreased infusion during vitrectomy itself may decrease the amount of fluid that dilutes or flushes out organisms within the eye.

To decrease these risks,
- Carefully prepare and sterilize the surgical field with povidone iodine.
- Ensure purposeful conjunctival displacement prior to cannula insertion to misalign the conjunctival and scleral openings in 25 gauge surgeries.
- Good oblique cannula insertion in 23 gauge surgeries to facilitate scleral wound closure.
- Suture any wound leaks seen following cannula removal.

Postoperative retinal detachment following 25 gauge vitrectomy has been reported, in rates that appear comparable to 20 gauge surgery. The open sclerotomies are plugged by small amounts of vitreous that usually do not exert significant traction to produce subsequent retinal detachment. If there minimal leakage through the sclerotomy, it may lead to formation of a small conjunctival bleb.
Microincision Vitrectomy

There are few limitations that are common to both 23 and 25 gauge vitrectomy. Currently, there is no fragmatome smaller than 20 gauge. Even though cortical and small nuclear lenticular fragments can be removed with a 23 gauge cutter, large nuclear pieces require at least one 20 gauge sclerotomy. The cannulae are more difficult to insert than in 25 gauge systems because of the additional steps required. Lastly, there are fewer 23 gauge instruments commercially available than 25 gauge, as the system has been more recently introduced, although any 25 gauge instrument can be used in 23 gauge surgery, but not vice versa.3,11

Conclusion

Recent advances and successful clinical experience have ushered in a new era of sutureless vitrectomy. As 25 and 23 gauge vitrectomy has evolved, we have seen further improvements in instrument design and function, which in turn have expanded the indications for its use. New innovations in technique, such as oblique insertion of microcannulae to facilitate sclerotomy healing, may help to minimize complications such as hypotony. Certain issues still remain and need to be addressed, like limitations on types of available instruments and probably, a slightly increased rate of postoperative endophthalmitis. When used for appropriate cases, however, these systems allows for less invasive and more efficient surgery. Decreased surgical time, less trauma and inflammation, faster patient recovery all have served to enhance patient care and satisfaction. It is likely that indications for the sutureless, small-incision vitrectomy technique will expand and postoperative outcomes will improve.

References

Update on Retinopathy of Prematurity: Concept and Management
Introduction

Retinopathy of prematurity (ROP) is a potentially blinding eye disorder that primarily affects premature infants weighing 1250 grams or less, that are born before 31 weeks of gestation (A full-term pregnancy has a gestation of 38–42 weeks). The smaller an infant is at birth, the more likely that infant will develop ROP. This disorder develops in both eyes and is among the leading causes of childhood blindness and is recognized as a priority by the VISION 2020: The Right to Sight. In its more severe form it results in severe visual impairment or blindness, both of which carry a high financial cost for the community but also a high individual cost by affecting the normal motor, language, conceptual, and social development of the child which are amplified when a child commences formal education.

There exist a total of 50 million blind people worldwide. Four percent of these are constituted by children i.e. a figure of 2 million. Twenty two percent cases of blindness in children have cause attributable to retinal disease due to Retinopathy of prematurity (ROP). Preventable blindness in children exists in 57% of cases because of ROP.

The incidence and severity of ROP increases with decreasing birth weight and gestational age. In the past two decades, advances in neonatal intensive care have contributed to an increase in the survival of premature infants leading to a concomitant increase in ROP. More than half of the infants with a birth weight of 700 grams survive. These extremely low-birth weight infants are at a greater risk of developing ROP. Not all infants who are premature develop ROP. The incidence of ROP worldwide ranges from 21.3% to 64.5%, and the estimated incidence in India is 38 - 42.3%.

Of the 14,000–16,000, premature infants weighing less than 1250 grams born each year in United States, 9000 to 10,500 are affected by some degree of ROP. The disease improves and leaves no permanent damage in milder cases of ROP. About 90 percent of all infants with ROP are in the milder category and do not need treatment. However, infants with more severe disease can develop impaired vision or even blindness. About 1,100–1,500 infants annually develop ROP that is severe enough to require medical treatment. About 400–600 infants each year in the US become legally blind from ROP.

Cause of ROP

ROP is a multifactorial disease. Low birth weight, low gestational age and supplemental oxygen therapy following delivery have been consistently associated with ROP.

ROP occurs when abnormal blood vessels grow and spread throughout the retina. These abnormal blood vessels are fragile and can leak, scarring the retina and pulling it out of position. This causes a retinal detachment. Retinal detachment is the main cause of visual impairment and blindness in ROP. Two overlapping phases are known to occur in ROP: (a) an acute phase in which normal vasculogenesis is interrupted and a response to injury manifests in the retina and (b) a chronic or late proliferation of membranes into the vitreous wherein detachments of the retina, and scarring of the macula occurs resulting in significant visual loss. Several complex factors may be responsible for the development of ROP. The eye starts to develop at about 16 weeks of pregnancy, when the blood vessels of the retina begin to form at the optic nerve in the back of the eye. The blood vessels grow gradually toward the edges of the developing retina, supplying oxygen and nutrients. During the last 12 weeks of a pregnancy, the eye develops rapidly. When an infant is born full-term, the retinal blood vessel growth is mostly complete (The retina usually stops growing a few weeks to a
month after birth). But if an infant is born prematurely, before these blood vessels have reached the edges of the retina, normal vessel growth may stop. The edges of the retina—the periphery—may not get enough oxygen and nutrients.

Scientists believe that the periphery of the retina then sends out signals to other areas of the retina for nourishment. As a result, new abnormal vessels begin to grow. These new blood vessels are fragile and weak and can bleed, leading to retinal scarring. When these scars shrink, they pull on the retina, causing it to detach from the back of the eye.

**ROP Classification**

An International Classification of Retinopathy of Prematurity (ICROP) is the work of 23 ophthalmologists from 11 countries and is today followed world wide for documentation of ROP findings. They described various aspects of the disease. The anteroposterior extent or the location was divided into 3 zones (zones 1-3), the circumferential extent into clock hours (1-12) and severity of the disease in 5 stages (stage 1-5). The presence of dilated and tortuous vessels denotes an aggressive, potentially sight threatening component and is called the **PLUS** disease.

**LOCATION OF THE DISEASE (ZONES)**

The normal blood vessels of the retina progress from optic nerve posteriorly to the edge of the ora serrata anteriorly. The location of ROP is a measure of how far this normal progression of blood vessels have reached before the disease takes over (Figures 18-1A to C). Three circular zones are defined with the optic disc at the center.

**Zone I:** This is the area around the optic nerve and the macula. The radius of zone I is equal to two times the distance between the disc and the fovea.

**Zone II:** This is up to ora serrata on the nasal side and up to the equator temporally.

**Zone III:** This is the remaining crescent of retina from the equator to the ora serrata temporally.

**EXTENT OF THE DISEASE (CLOCK HOURS)**

The eye is divided into twelve sectors similar to a clock. The extent of ROP is defined by how many clock hours of the eye circumference is diseased.

**Plus Disease**

Plus disease is characterised by abnormal dilated vessels on the iris and/or engorgement and tortuosity of the blood vessels in the retina. Additional findings include retinal haemorrhages, poorly dilating pupil and hazy media.

**STAGES OF THE DISEASE (SEVERITY)**

ROP is a progressive disease, that starts slowly anywhere from the third to the tenth week of life and may progress very slowly or fast through successive stages from stage 1 through 5 (Figures 18-2 and 18-3). It may cease at any stage and finally disappear completely, without affecting the vision.

**Stage 1:** A white line separating the clear normal red retina from the sharply contrasting underdeveloped gray retina characterizes stage 1 ROP.
FIGURES 18-1A to C: Show zone of vascularization
Stage 2: ROP shows a rolled ridge of scar tissue, which may be limited to a small area or encircle the entire inside of the eye, around the middle of the eye.

Stage 3: ROP is characterized by the development of abnormal new blood vessels and fibrous scar tissue on the edge of the ridge seen in stage 2. These vessels are lifted off from the surface and project into the vitreous cavity. Since more than 50% eyes with stage 3 will progress to stage 4 or 5, treatment with laser or cryopexy is considered at this stage.

Stage 4: ROP occurs due to pulling of the retina by the scar tissue. As a result retina separates from the wall of the eyeball. In stage 4 the retinal detachment (RD) is partial, involving only small part of the retina. Depending on the extent of RD stage 4 is further subdivided into stage 4A (sparing macula) and 4B (involving macula).

In stage 4A eyes have reasonably good chance of achieving usable vision, should the retina be re-attached. In stage 4B, the partial RD involves the macula, usually with a fold extending from the optic disc through zones I, II and III.

Stage 5: ROP involves complete RD with the retina assuming a partial or closed funnel configuration. The infants usually develop a white reflex in the eye (leucokoria).

ROP ZONE CLASSIFICATION VS. PROGNOSIS

The severity of ROP is determined by the zone of the retina involved. Figures 18-1A to C show immature retina to complete vascularisation. Zone 3 ROP disease rarely causes blindness and constitutes 30% of ROP cases. Zone 2 ROP constitutes 60% of ROP cases and is a potential cause of blindness. Zone 1 ROP (10% of ROP cases) has a very high chance of causing blindness. Figures 18-2 and 18-3 show the different stages of ROP progression to advanced disease.

ROP NEW CLASSIFICATION-ETROP

The early treatment of ROP study provided a new method of classifying ROP.

Type 1 ROP is defined as:
- Zone I, any stage ROP with plus disease
- Zone I, stage 3 ROP with or without plus disease
- Zone II, stage 2 or 3 ROP with plus disease

Type 2 ROP is defined as:
- Zone I, stage 1 or 2 ROP without plus disease
- Zone II, stage 3 ROP without plus disease

Rush Disease

This is zone I ROP with plus disease. In this, the progression is rapid and fulminant. In this new vessels are initially flat and in groups and later tend to get elevated into the vitreous cavity and may rapidly progress in nasal retina. This is also termed Fulminant ROP/Type II ROP or Posterior Zone I ROP.

Based on the CRYO-ROP Study, threshold ROP is defined as zone I or II ROP stage 3 more than 5 contiguous or 8 cumulative clock hours with plus disease present. Pre-threshold ROP is defined as any stage of ROP in zone I with plus disease or ROP stage 3 with plus disease with 3 contiguous or 5 interrupted clock hours of retinal involvement in zone II but less than threshold.
FIGURE 18-2: Stage 1 to 4 ROP

FIGURE 18-3: Shows white papillary reflex suggestive of stage V ROP
In the ETROP trial, pre-threshold ROP was further subdivided based on the risk of an unfavorable outcome. Eyes with high-risk were defined as having more than or equal to 15% risk, where as eyes with low risk had less than 15% risk of an unfavorable outcome. An unfavorable outcome was primarily based on 1 of 4 categories of visual function as tested with teller Acuity cards. Secondary outcomes were based on structure where poor outcomes were retinal fold or detachment involving the macula, or a retrolental opacity blocking the visual axis.

Type I pre-threshold ROP was defined as zone I, any stage of ROP with plus disease, Zone I, stage 3 ROP with out plus disease, and zone II, stage 2 or 3 with atleast two quadrants of plus disease.

An international group of pediatric ophthalmologists and retinal specialists have developed a consensus that revises some aspects of ICROP. Few modifications were made that are as follows:

A. **Aggressive posterior ROP:** This is most virulent form of ROP observed in the tiniest of babies.
   This is a new terminology for Rush disease or type 2 fulminant ROP in which the posterior pole vessels show increased dilatation and tortousity in all 4 quadrants out of proportion to peripheral retinopathy. It progresses rapidly and does not progress through classic stages 1-3 and may appear only as a flat network of neovascularization at the deceptively featureless junction of vascularized and non-vascularized retina.

B. **Pre plus disease:** This is in between normal posterior pole vessels and frank plus disease. This is defined as vascular abnormalities of the posterior pole that are insufficient for the diagnosis of plus disease but that shows more arterial tortuosity and venous dilatation than normal and may later progress to plus disease. A practical clinical tool for estimating the extent of zone I.

**Incidence and Natural Course**

The incidence of ROP increases with decreasing birth weight and gestational age. Thus, nine out of ten infants with birth weight less than 750 grams will develop some form of ROP while only 4.7 out of ten in birth weight group of 1000-1250 grams will develop ROP. Similarly, the incidence of ROP in infants of gestational age groups of 24-27, 28-31, 32-35 and above 36 weeks is 89, 63, 26 and 19 percent respectively. A study from India quotes an incidence of 38 % for a birth weight less than 1500 grams. The CRYO ROP study has examined the natural history on a cohort of 4099 infants and reported the occurrence of events in the history. Stage 1 ROP occurred at a median age of 34.3 weeks post conceptional age (PCA, Gestational age +chronological age). Stage 2 was seen at a median age of 35.4 weeks PCA. Stage 3 was seen at a median age of 36.6 weeks PCA. Stage 3+ was seen at a median age of 36.3 weeks PCA. Pre-threshold ROP occurred at a median age of 36.1 weeks PCA. Threshold ROP occurred at a median age of 36.9 weeks PCA.

The prevalence of ROP in moderately developed countries (human development index; HDI 30-100) is as high as 60% in premature babies. The prevalence in poorly developed countries, which includes India, is 3 to 13%. The incidence in highly developed countries, those with a HDI of 1-3% is 3-13%. Table 18-1 shows ROP in Asian countries.

**Risk Factors**

The greatest single risk factor for developing ROP is being born prematurely. An important ocular risk factor was zone I. If, at a 32 weeks PCA, incomplete vascularization in zone I was present,
Table 18-1: ROP in Asian countries

<table>
<thead>
<tr>
<th>Name of countries</th>
<th>UNDP rank</th>
<th>Source of data</th>
<th>No. of samples</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaysia</td>
<td>59</td>
<td>Blind school</td>
<td>332</td>
<td>6.0%</td>
</tr>
<tr>
<td>Thailand</td>
<td>76</td>
<td>Blind school</td>
<td>65</td>
<td>16.9%</td>
</tr>
<tr>
<td>Philippines</td>
<td>83</td>
<td>Blind school</td>
<td>179</td>
<td>8.4%</td>
</tr>
<tr>
<td>China</td>
<td>94</td>
<td>Blind school</td>
<td>1131</td>
<td>1.9%</td>
</tr>
<tr>
<td>Srilanka</td>
<td>96</td>
<td>Blind school</td>
<td>226</td>
<td>0.0%</td>
</tr>
<tr>
<td>India</td>
<td>127</td>
<td>Blind school</td>
<td>2360</td>
<td>0.2%</td>
</tr>
<tr>
<td>Pakistan</td>
<td>142</td>
<td>Blind school</td>
<td>760</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

32.8% eyes developed threshold ROP, compared to 9.3% with incomplete vascularization in zone II. Other ocular risk factors for developing threshold ROP included plus disease, stage 3 ROP, more than 6 clock hours stage 3 and iris vessel dilatation. Non-ocular factors associated with development of ROP are oxygen supplementation. Although much has been written about the association of oxygen use and ROP, on the contrary low levels of oxygen and slow weaning from oxygen may help regression of early stages of ROP. Oxygen levels must be well monitored to ensure optimum oxygen saturation of blood (95-98%), since hypoxia is a factor in increasing abnormal retinal neovascularization.

Prenatal steroids administered to women in preterm labor have resulted in reduced infant mortality and morbidity, primarily through improved lung function. There is evidence that prenatal steroids are protective for the development of ROP. Later administered steroids have had an adverse effect or no effect on the incidence of ROP.

Apnea, mask ventilation, respiratory distress syndrome, hyaline membrane disease, asphyxia, sepsis, multiple blood transfusion, exchange transfusion, intraventricular hemorrhage, chronic inutero hypoxia and maternal factors like anemia are other risk factors.

Hence, birth weight and gestational age are the prime risk factors for ROP:
- < 28 wk + < 800 g – high-risk (zone I ROP) – 90%
- < 32 wk + < 1000 g – mod-risk – 60%
- < 32 wk + < 1200 g – low-risk – 30%
- > 32 wk + < 1500 g – low-risk – 10%

**MINOR RISK FACTORS**

1. Oxygen inhalation-
   - the duration and concentration
   - RDS
2. Septicemia
   - A positive factor in ROP development

**MAJOR RISK FACTORS**

1. Gestational age
2. Birth weight
Clinical Signs and Symptoms

There are no symptoms of acute ROP, nor can a specific visual behavior of a premature infant herald a concern for ROP. Therefore, effective screening is essential as premature infant is not born with ROP. The retina is immature but perfectly natural for their age. It is the postnatal development in the retinal vessels that could lead to ROP.

Screening for ROP

Proper planning is a key component of efficient screening in a neonatal intensive care unit (NICU). The screening protocol at each NICU should be based on published recommendation and preferences of screening ophthalmologists and neonatologists. The joint statement of the American Academy of Pediatrics (approved March 1997), the American Association for Pediatric Ophthalmology and Strabismus (approved October 1996) and the American Academy of Ophthalmology (approved November 1996) provided the following guidelines for infants who should be screened for ROP:

A. All infants weighing less than or equal to 1500 grams or less than or equal to 28 weeks gestational age.

B. Infants born weighing more than 1500 grams but who have an unstable course in NICU.

The first examination should be performed prior to hospital discharge, at 4-6 weeks of birth, or between 31-33 weeks of PCA.

Recommendations were made on the basis of combined data from the CRYO-ROP and Light Reduction in ROP (Light-ROP) studies that the first screening be conducted prior to 31 weeks PCA or 4 weeks chronological age which ever was later.

Screening criteria for ROP could be different in low income countries (like sub-Saharan Africa, and rural areas of Asia) where blindness from ROP is virtually unknown due to high mortality. In Indian population, significant number of infants fall outside the screening criteria than the high income group countries, so screening criteria suiting Indian population were proposed as follows:

1. Birth weight of less than or equal to 1700 grams.
2. Gestational age at birth of less than or equal to 34-35 weeks.
3. Exposed to oxygen for more than 30 days.
4. Infants weighing less than 1200 grams at birth and those born at 24-30 weeks gestational age are at particular high risk of not only developing ROP but also developing it earlier, in more aggressive form. Hence, there is a definite need to screen these babies at the earliest.
5. Other factors that can increase the risk of ROP and where the screening should be considered are other premature babies (< 37 weeks and/or < 2000 grams) with:
   • Respiratory distress syndrome
   • Sepsis
   • Multiple blood transfusions
   • Multiple births (twins/triplets)
   • Apnoeic episodes
   • Intraventricular hemorrhage
   • Pediatricians have index of concern for ROP.
TIME FOR SCREENING THE INFANTS AT RISK

Screen all eligible babies at (Table 18-3)

- 31 weeks PCA or 3-4 weeks after birth, whichever is earlier.
- Infants weighing less than 1200 grams at birth and those born at 24-30 weeks gestational age are screened early, usually not later than 2-3 weeks after birth.
- No examination needed in first 2 weeks of birth.
- Next date of examination to be decided by the ophthalmologist based on initial findings.
- Complete one screening session definitely before Day 30 of life.

Ideally, a fixed time should be arranged for screening. This is useful because, NICU staff can anticipate and prepare for the evaluation of admitted babies, and can recall those babies that were discharged without screening. In addition parents of admitted patients are more likely to be available if they are pre-informed. Dilatation can be started by the NICU staff, 15-20 minutes before arrival of the Ophthalmologist. Strict instructions are to be followed by the NICU nurses as regards the dilatation process and this should be demonstrated to the staff. Appropriate written instructions should be presented on the NICU wall for ready reference.

Babies, should be evaluated in an appropriate temperature controlled, clean environment where risk of hypothermia, infections and apnea are minimum. For in-patients in NICU, the screening can be done in temperature-controlled environment of the incubator. The room illumination should be low to avoid glare and annoying reflexes during examination with the indirect ophthalmoscope and viewing lens.

The child should be fed and burped preferably an hour before examination so as to minimize the risk of vomiting after instillation of drops. The pupils are dilated using 0.5-1% tropicamide and 2.5% phenylephrine instilled twice 10 minutes apart, about 15-20 minutes before the due time of evaluation.

Screening for ROP requires indirect ophthalmoscopic (I/O) examination of the retina, including the peripheral retina using a 20 diopter (D) and if available, a 30 D lens. Examination is always started using the 20 D lens as this gives the correct magnification to diagnose the plus stage of disease. Some babies can be examined without any lid retractors by experienced observers, making use of Doll’s eye movements to examine the periphery. However, due to small size of the palpebral fissure, detailed examination may require use of a self-retaining pediatric size wire speculum. A wire vectis or a pediatric depressor is useful to stabilize the globe and visualize the periphery.

SCREENING PROCESS

The baby should be comfortably wrapped and placed flat on the examination surface. An assistant is useful to restrain the baby’s arms and stabilize the head. First, the anterior segment is evaluated using the 20/30 D lens and illumination of I/O for any rubeosis/dilated iris vessels and persistent tunica vasculosa lentis, as well as any congenital ocular anomalies. Next the disc and posterior pole are evaluated for signs of severe ROP, including plus disease or any stage of ROP/avascularity/closed vascular loops and tufts in zone 1. Examination is then continued all around the arcades and extending to the equator in all the quadrants of the eye to detect any ROP/immature/mature retina. Peripheral depression is done at the end of the examination to look for anterior extent of retinal maturation and to evaluate the zone and stage of ROP, if present. All findings should be recorded in appropriate forms, at each visit.

Once the treatable stage of ROP is detected, the parents and neonatologists should be contacted immediately and arrangements for prompt consent and treatment should be made.

Table 18-2 shows key factors in diagnosis of ROP.
Indications for Treatment

The new concept is to catch the ROP affected babies at a young age (Figure 18-4). The indications for treatment of threshold ROP (5 or more contiguous or 8 cumulative clock hours of stage 3+ ROP either in zone I or zone II) were initially proposed by the cryo-ROP study for those stages of the disease that are likely to result in adverse visual outcomes (visual acuity less than 20/200 or worse) in 50% eyes. Visual acuity greater than 20/200 was considered as a successful outcome and appearance of strabismus including that due to macular heterotropia was not considered an adverse outcome. These criteria were initially proposed to prevent any treatment related morbidity based on the motto ‘Do no Harm’. However, in India, Japan, Israel and some of the European countries concerns were raised regarding delayed treatment for some eyes with pre-threshold disease. The ETROP Study proposes newer criteria for early treatment of eyes that have more than 15% risk of adverse outcomes. The treating physicians need to be aware of advances in this field and keep themselves updated about the changing criteria of treatment.

Pre-threshold ROP is further divided into high-risk or type 1 ROP and low-risk or type 2 ROP based on results of Early Treatment for Retinopathy of prematurity (ETROP) study.

Type 1 ROP: Retinal ablation should be considered for any eye with type 1 ROP that includes the following:
1. Zone I, any stage ROP with plus disease.
2. Zone I, stage 3 ROP with or without plus disease.
3. Zone II, stage 2 or 3 ROP with plus disease.

Plus disease is defined in this case as at least 2 quadrants of dilation and tortuosity of the posterior retinal blood vessels. This is a revised definition of plus disease and is in contrast to Cryo-ROP study which required 4 quadrants of dilation and tortuosity. While using the present guidelines for ROP treatment, one also needs to take into account the need for early screening with smaller babies.
TABLE 18-3: Screening time: Important note

<table>
<thead>
<tr>
<th>When to do first examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three visits are very critical to the detection of ROP at an early stage</td>
</tr>
<tr>
<td>1. At 32-34 weeks,</td>
</tr>
<tr>
<td>2. At 35-37 weeks, and</td>
</tr>
<tr>
<td>3. At 39-42 weeks post conceptional age (PCA).</td>
</tr>
<tr>
<td>Follow 30 days rule for first examination.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Done at 32 weeks and thereafter every two weeks. On appearance of ROP weekly screening is done till 40 weeks when maturation of the retinal vessels is deemed to occur and progression of ROP stops.</td>
</tr>
</tbody>
</table>

| Last screening/exit screening: At 45 weeks PCA |

**Practical Guideline for Treatment Criteria**

Our practical simple indicators of treatment are based on clinical trial guidelines.

Start screening for ROP between 20 to 30 days of life, earlier (20 days) for smaller babies (less than 30 weeks gestational age and 1500 grams birth weight). One screening session should be completed before day 30 of life. Delaying the timing of first screening increases the likelihood of seeing advanced disease with consequent reduced success rates (Table 18-3).

Treat all eyes that have either new vessels or Plus disease or both in zone I and all eyes with plus disease in zone II. Mild ROP that has either no new vessels or no plus disease can be followed up closely.

**PREVENTION OF BLINDING ROP**

ROP can be prevented and an efficient screening protocol is a must to achieve this. Certain factors need to be kept in mind towards achieving this are:

- O₂ saturation should be monitored and preferably be kept at 90-93%.
- Use of ketotifen in postnatal period.
- The role of antenatal steroids is controversial. They are believed to reduce the incidence and severity of respiratory distress syndrome and patent ductus arteriosus, etc.
- Maternal risk factors such as anemia, nutritional deficiency and toxemia should be corrected if any.

**Treatment of ROP**

The treatment should be done at the earliest, preferably within 24 hours and not later than 72 hours. The aim of treatment is to ablate the whole of the avascular retina as rapidly and completely as possible with minimum side effects due to the treatment modality itself. Treatment for acute ROP can be done either by laser photoablation or cryotherapy.

**LASER TREATMENT OF ROP**

Laser energy helps to destroy the abnormal, avascular retinal tissue and so eliminates the stimulus for growth of abnormal blood vessels. It also ends the progression of the scar tissue formation and reduces the vascularity and hence the Plus component of ROP. The effect is usually apparent within one week of adequate laser therapy.
Technique of Laser Treatment with Topical Anesthesia

After ensuring the baby is well fed, burped, diapered and wrapped in warm clothing, the hands of the baby are restrained away from their face by either an assistant or restraining binds. Topical anesthesia is instilled 2-3 times. While awaiting the onset of anesthesia, set the laser machine and ensure it is working. At present the acceptable standard of care for ablation in ROP is the Diode red (810 nanometer wavelength) laser indirect ophthalmoscope. Green laser wavelengths (532 nm) can also be effectively used in most cases. However in eyes with poorly dilating pupils secondary to vascular engorgement or new vessels of iris due to severe plus disease, and those with significant tunica vasculosa lentis non-red wavelengths are at a disadvantage. The green laser radiation in these cases is absorbed by the blood vessels and can lead to cataract formation in a few days. In such situations only diode red indirect ophthalmoscope laser or alternate treatment modalities (cryopexy / diopexy) is an advantage.

A sterile pediatric lid speculum is inserted into the conjunctival sac to hold eyelids apart from taking care not to touch or abrade the cornea. An assistant holds the head while the surgeon additionally holds the chin to stabilize the face. Initial settings of power and duration on the laser console, depends on the fundus pigmentation and area to be treated. The ischemic retina must be destroyed (ablated) to preserve the central retina. For average Indian patients, start laser treatment using initial settings of about 300 milliwatts and duration of 150 milliseconds. The repeat mode is kept between 300-400 milliseconds. During treatment, the intensity of burns should be grayish white and burns placed nearly confluent and not more than one-half burn width apart. While it is essential to treat the avascular retina from the ridge/vascular part of retina up to the ora for 360 degrees, it is critical to treat up to the base of the ridge and all around the region of proliferation and not to leave any untreated areas near the posterior edge of the avascular retina (Figure 18-5). A wire vectis or pediatric scleral depressor is used to rotate the globe, stabilize it and also to indent the anterior retina and bring it into the line of the laser rays.

Throughout procedure of laser, an infant pulse oximeter should be connected to baby’s foot or ensure that baby is making clear vocal sounds with no secretions from the throat such as vomit. A
very quiet child should arouse immediate suspicion of apnea/cardiac arrest and would need immediate attention towards resuscitation. At the end of the procedure, wipe the eyes with a clean wet cotton swab to reduce edema of the speculum. Instill a drop of antibiotic; ensure that airways are freely open and the child is breathing well.

**Postoperative Instructions**

It is expected that eyelids have moderate edema and erythema for 3-4 days. Furthermore, there may be mild conjunctival congestion, chemosis and subconjunctival hemorrhage for a few days. NICU staff and parents should be advised of these adnexal effects to avoid any alarm. In case of excessive manipulation during treatment and especially in eyes with poorly dilating pupils, topical steroids are prescribed 3-4 times a day to reduce any inflammation and especially decrease the risk of post-laser posterior synechiae.

When a child is under the care of NICU staff, the baby is handed over to them for feeding and checking vitals. When a child is with parents and treated in the eye hospital, it is important to ensure that child takes its next feed properly before discharging the baby. Usually, the baby is little exhausted and lazy for 10-15 minutes after laser treatment and may not have enough strength to feed immediately. After a short rest, encourage the child to feed by waking up through stimulating their soles of feet. After initially taking feed slowly, most babies return to their previous feeding status.

**WARNING:** In case of any doubt or difficulty in feeding the child, do not force feed as the baby may aspirate and may prove disastrous. If there is difficulty in feeding immediately transfer the baby to a warm environment with oxygen support if needed, inform the pediatrician/NICU to avoid hypoglycemia, hypoxia or apnea. It is good practice to have an anesthetist/pediatrician available until the baby is well fed, has stable vitals and is discharged.

Adhering to these practical tips will go a long way in ensuring a smooth postoperative period and preventing any serious life-threatening problems complication.

If adequate regression has not occurred or focal areas of active new vessels are seen, secondary treatment is done to laser free areas and around the active proliferation.

**CRYOTHERAPY FOR RETINOPATHY OF PREMATURITY**

The indications, preparation of the eye and extent of retinal ablation for cryotherapy are the same as those for performing laser. A pediatrician or an anesthesiologist must be available to monitor the vital signs during and for at least a day after the treatment session. Informed consent should be obtained from the parents with risk and benefits clearly explained. The need for hospitalization and post treatment care should also be emphasized.

Instruments and materials as detailed for laser are needed. Instead of a laser machine, a standard cryotherapy machine utilized in routine retinal detachment or cataract surgery is used. A special probe with a narrow shaft, a curve that fits the small eye and with a protective shaft covering or a tip-only freeze probe should be used. The Indirect Ophthalmoscope used for monitoring Cryo-spots should have a small pupil aperture option, with adequate bright light. One can use either a 28 diopter or a 20 diopter condensing lens.

Cryotherapy can be applied with topical (0.5% proparacaine hydrochloride applied to the cornea every 20 minutes during treatment), subconjunctival (0.5 ml of 1% lidocaine hydrochloride), or general anesthesia. If topical or local anesthesia is chosen, intravenous sedation should be administered.
Procedure

After a pediatric speculum is inserted, it is prudent to identify the extent of the avascular retina, by putting the indentor just anterior to the ridge and measuring and recording the point from the limbus. Cryotherapy under indirect ophthalmoscopic viewing is then started. Initial treatment nasally, is useful as pressure from the cryoprobe softens the globe and facilitates treatment temporally, where the avascular zone is usually more posterior. Contiguous spots of cryotherapy should be applied throughout the avascular retina anterior to the ridge and the extraretinal fibrovascular proliferation. On average it takes 2-8 seconds for the avascular retina to reach the desired end point of retinal whitening. Often, 30 to 50 applications are needed, depending upon the area to be ablated. Care should be taken to avoid prolonged scleral depression, which raises the intraocular pressure and increases the risk of central retinal artery occlusion, corneal edema, hyphema and vitreous hemorrhage.

Treatment can often be completed without making conjunctival incisions, except in some eyes with zone I or posterior zone II disease. A small incision 4 mm posterior to the limbus at the center of the quadrant is adequate to allow the cryoprobe tip to fit. One to four incisions may be made depending on the extent of the disease. These incisions need not be sutured if they are less than 4 mm in length. Vitreous hemorrhage may also occur from florid areas of extraretinal fibrovascular proliferation caused by pressure on the globe. As the therapeutic window for treating ROP is narrow (72 hours), one may not be able to wait for the hemorrhage to settle down since by that time the progression may be irreversible. Under such circumstances, one can resort to performing cryotherapy without direct visualization using the information gathered at the beginning of the treatment.

Postoperative Care

Topical steroid antibiotic drops are given four times a day for 3-4 days. Use of cycloplegics (1% Tropicamide 3-4 times a day) is optional. The parents should be explained about the type of procedure performed, adnexal reaction, and need to re-evaluate for response to treatment. If the infant was intubated then pediatricians need to monitor the baby over the next 1-2 days. This is necessary as apnoeic spells can occur frequently during the immediate postoperative period.

LASER VS CRYOTHERAPY

Laser is the treatment of choice (Figure 18-6) and is as effective as cryotherapy. Advantages of laser photocoagulation are:

- More precise – Zone 1 ROP can only be reached with laser delivery methods
- The complications are less with laser photocoagulation
- Less painful (can be done under with or without sedation)

ROP should be treated within 24-48 hr of detection; rush disease needs to be treated with laser photocoagulation within few hours of detection.

TRANSCONJUNCTIVOSCLERAL DIODE LASER (TCSDL, DIOPEXY) FOR ROP

An alternate to cryotherapy and LIO ablation is to use a transconjunctivoscleral laser diopexy.

Technique

The protocol for preparation of the eye(s) for TCSDL is similar to that used for diode LIO. Laser is done transconjunctivoscleral, using the diode retinopexy probe and monitored using an indirect
ophthalmoscope with +20 D lens. The desired end-point is a greyish-white lesion, with spots placed one-fourth spot width apart. Conjunctival incisions are made depending on posterior extent to be treated. Conjunctival incisions would need more than a simple topical anesthesia that is used for non-incision cases. Follow-up is done every 3-7 days and treatment is repeated in eyes with incomplete regression.

The main indication for the use of TCSDL is for initial management of severe cases of threshold ROP in situations where LIO is difficult or unavailable. Problems related to cryopexy, such as the need for general anesthesia, adnexal reaction, scleral injury, and breakdown of blood-retinal barrier are circumvented. TCSDL combines the advantages of a laser therapy mode with those of a transconjunctival modality when transpupillary therapy is not possible.

**Signs of Regression**

All signs of plus disease should completely regress before stopping repeated treatment sessions. Signs that indicate disease has reached a quiescent phase of acute ROP after retinal ablation include:

- **Pupil dilates well**
- **There is no rubeosis**
- **Media is clear**
• Vascular dilatation and tortuosity are absent
• Feeder vessels to proliferation/hemorrhages are ‘silent’ and not dilated or tortuous
• No increase in traction
• All elevated focal areas have an avascular base with no feeder vessels.

If after initial laser the ROP is still showing activity, additional laser needs to be done in 3-7 days of first session till complete regression occurs. Lens sparing vitrectomy should be considered early enough in case traction/ridge elevation of more than 4 clock hours has developed. Surgery has better outcomes in laser failed cases if done before 41 weeks of post-conceptional age.

Expected Outcomes of Retinal Ablative Treatment

The preliminary evidence that ablation of the peripheral non-vascularised retina of premature infants affected with “threshold” retinopathy of prematurity (ROP) is effective and safe was reported by cryotherapy for retinopathy of prematurity study (Cryo–ROP study). Since the Cryo – ROP study was reported, both argon and diode indirect ophthalmoscope laser system have come in vogue that make treatment of the peripheral avascular retina safer with less attendant stress to the infant. Infants treated with retinal ablation at threshold disease show almost a 20% reduction in unfavorable outcomes, defined as a fold through the macula, partial or total retinal detachment. The issue however is of those infants who in spite of threshold disease have a favorable outcome. Of these infants less than 20% have visual acuity of 20/40 or better. The benefits of cryotherapy for management of threshold ROP, for both structure and visual function was maintained across 15 years of follow-up. However, a gradual increase in unfavorable structural outcome between 1 and 15 years was observed. In control eyes this increase averaged 0.51% per year and in treated eyes the increase averaged 0.35% per year. Comparison of outcomes between 10 and 15 years showed that visual acuity of treated eyes remained virtually stable during this 5-year interval, with an average increase in unfavorable outcomes of only 0.06% per years. While the visual acuity of control eyes showed an average 0.44% per year increase in unfavorable outcomes. In both control and treated eyes, there was an increase in the prevalence of high myopia between 3 and 12 months of age. Between 12 months and 10 years of age, there was nearly no change in distribution of refractive error in control eyes. The higher prevalence of myopia of 8D or more in treated eyes, as compared with control eyes, may be due to the effect of cryotherapy on preservation of retinal structure in eyes that in the absence of cryotherapy, would have progressed to retinal detachment.

Diode laser photocoagulation with indirect ophthalmoscope delivery has become the preferred method for treating threshold ROP today. Laser treated eyes have better structural and functional outcomes compared with eyes treated with cryotherapy. Laser treated eyes have less myopia than cryotherapy after 10 years. The excessive refractive error in the cryotherapy treated eyes is probably related to the effective power of the crystalline lens.

Results from Cryo-ROP examination conducted at 3.5, 5.5 and 10 years follow up indicate that eyes that were saved from blindness by cryotherapy developed visual acuity better than 20/200 but worse than the normal range for that age. These findings were supported at the 15 year follow up examination. The incidence of blindness was reduced from 55.1% in control eyes to 36.3% in treated eyes. The visual acuity between 20/20 and 20/200 was increased from 25.9% in the control group to 48.9% in the treated group. Thirty eyes had visual acuity of 20/20 or better at 15 years examination.

Thus, it is well evident that benefits of ablative therapy (cryotherapy or indirect laser photocoagulation) in threshold ROP persists well into the second decade of life. The need for continued ophthalmologic follow up of children with a history of severe ROP is mandatory.
SURGICAL MANAGEMENT

Although retinal ablation is effective in a majority of cases of threshold ROP, few cases still progress to retinal detachment. Detachment is often seen associated with areas of incomplete peripheral ablation or in eyes with inexorably progressive disease. Fibrous proliferation and contraction of neovascularization along the ridge and onto the overlying vitreous precede tractional retinal detachment. Condensation of vitreous into sheets and strands act as a scaffold for further extension of the fibrovascular tissue. Traction along the retinal surface and contraction of posterior hyaloid face contribute to distortion of the posterior pole architecture. The specific tasks of surgical intervention for ROP related retinal detachments vary depending on the tractional components causing retinal detachment. Lens sparing vitrectomy is the preferred treatment for posterior disease and most forms of tractional progressive stage 4 ROP, where as scleral buckle may be beneficial in rhegmatogenous detachments and those where the main tractional component is the sole tractional vector located near or anterior to the equator.

The goal for extramacular retinal detachment (stage 4A ROP) is an undistorted or minimally distorted posterior pole, total reattachment, and preservation of the lens and central fixation vision. Lens sparing vitrectomy\(^45\) and scleral buckle\(^46\) have been used to manage stage 4A ROP. The disadvantage of scleral buckle for stage 4A ROP are the dramatic anisometric myopia\(^47\) and the second intervention
required for removal of the buckle, so that the eye continues to grow. All tractional forces cannot be alleviated with scleral buckling alone. Lens sparing vitreous surgery can interrupt progression of ROP from stage 4A to stages 4B or 5 by directly addressing transvitreous traction resulting from fibrous proliferation. The functional goal for stage 4B eyes is ambulatory vision. The surgical goal for stage 5 ROP is to reattach as much as retina as possible. Form vision can be preserved following vitrectomy for stage 5 ROP. Figures 18-7 and 18-8 show pre- and postoperative anatomical outcome after Stage 5 ROP. Table 18-4 shows the surgical outcome results of ROP.

Nowadays anatomical and visual gain is possible with surgery even in advanced cases of ROP. Before contemplating surgery, a surgeon must remember the following:

- A good understanding of the patho-anatomy of ROP affected eyes (Figures 18-9A to D)
- USG is necessary delineating the funnel configuration in severely affected eyes
- The neonatologist’s description of the case and support is essential
- Pre-anaesthetic consultation is a must
- Extensive and careful counseling of the parents must be done.
TABLE 18-4: Surgical results of ROP

<table>
<thead>
<tr>
<th>Authors</th>
<th>Stage 4a</th>
<th>Stage 4b</th>
<th>Stage 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV Azad et al</td>
<td>(100%) 5/5 fully attached</td>
<td>(50%) 3/6 posterior pole attached</td>
<td>(38.5%) 15/39 posterior pole attached</td>
</tr>
<tr>
<td>Lakhanpal et al</td>
<td>100%</td>
<td>92.1%</td>
<td>59%</td>
</tr>
<tr>
<td>Hubbard G et al</td>
<td>84%</td>
<td>92%</td>
<td>47%</td>
</tr>
<tr>
<td>Fuchino Y et al</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kono T et al</td>
<td></td>
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<td></td>
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</tbody>
</table>


COUNSELING

Counseling of parents is of utmost importance.
- Sympathetic approach should be maintained
- Anesthetic risks need to be explained
- Poor functional outcome
- Need for regular follow ups should be stressed
- Realistic expectations

New Considerations in ROP

- It needs to be understood that multiple factors cause ROP—the differential affliction of twin/triplets/quadruplets is a good example of this. The genetic background of parents and the nature of prenatal, natal and postnatal injuries are highly relevant (Citations).
- Newer developments in management have taken place with the arrival of anti-VEGF drugs.
- Long term effect of ROP in premature infants needs to be considered and proper visual rehabilitation provided for refractive error, amblyopia, etc.

Conclusions

The critical factor to ensure better outcomes are to screen early, follow-up weekly or more closely, watch out for Plus and/or new vessels and treat such eyes vigorously for full retinal ablation of avascular retina. ROP is a continuous race against time with a very small window of opportunity of 7-10 days where optimum treatment outcomes with least complications can be achieved.

ROP affects a large number of preterm babies in our country who will become blind if the disease is not treated. Around 1.68 million babies are at risk of developing ROP and 7% will eventually become blind without treatment. ROP is not a blinding disease if detected early and treated promptly with laser. Spontaneous regression is the rule in 80-90% cases and only 7-10% of cases develop blinding ROP. ROP does not occur at birth. It is good to follow 30 days rule after birth when first screening should be done. Surgical interventions offer the potential for preservation of vision for eyes with ROP related retinal detachment; especially if it is directed prior to macular distortion. Even in advanced stages surgery is possible and can provide useful vision. In selected cases of stage V useful navigation vision is possible. In future pharmacological stabilization of aberrant angiogenesis may be one approach.
References

Introduction

Rhegmatogenous retinal detachment (RRD) is an uncommon entity in pediatric population. Though uncommon, it is important to identify and treat these children with retinal detachment as early as possible because of few important reasons. First, though the prognosis is not as good as in adult rhegmatogenous retinal detachment, almost 40% of treated children show some degree of visual improvement. This definitely has a profound long term effect on future development of the child in all aspects—physical, mental, social and economical.

Although the incidence is low, there is a high chance of bilateral involvement. In some cases, RRD can be part of a syndrome complex which may have serious systemic involvement. All this makes early diagnosis and prompt management of pediatric RRD cases very important.

Because of inability of children to exactly assess their own vision, difficulty in examination and relatively poor prognosis, identification and management of these young patients presents a formidable challenge to vitreoretinal surgeon. It also demands a great deal of parental determination and dedication.

Epidemiology

Because of low incidence, there are very few reported case series of RRD in children. In general, RRD has an annual incidence of 12.4 cases per 1,00,000 population. RRD in paediatric population (birth to 18 years) has been estimated to be only 3.2% to 5.6% of total RRD patients—it means approximately 0.38 to 0.69 cases per 1,00,000 population and retinal detachment (RD) surgeries performed in children constitute approximately 3.1% of total RD surgeries.

AGE AND SEX DISTRIBUTION

Most childhood RRD present at and around 10 years of age. Boys outnumber girls by approximately 4 times in pediatric RRD population. In a consecutive series of 111 eyes of juvenile RRD in Indian population, Nagpal et al found 77.47% cases belonged to boys. The high incidence of trauma in boys correlates well to overall high incidence of RRD in boys—trauma being one of the commonest etiological factors in childhood RRD.

PECULIAR FEATURES OF PEDIATRIC RRD

It is difficult for children to exactly express the nature and duration of their symptoms. Hence, children with RRD often present late and hence with more advanced disease (Figure 19-1). Because most of them are not very cooperative, examiner has to rely more upon physical findings than history. Also visual assessment in children—both pre- and postoperative is a challenging job. Examination has to be very thorough and yet quick enough, so the child does not lose cooperation. Examination also demands great deal of patience as well as clinical acumen on examiners part. Many a times, surgeon has to consider examination under general anesthesia for complete evaluation and confirmation of diagnosis. Because of frequent need of multiple surgeries and relatively poor prognosis, management of these children demands a great deal of financial and emotional investment from the society as well as the parents.

Etiopathogenesis

Rhegmatogenous retinal detachment is characterized by presence of full thickness retinal break (‘Rhegma’ in Greek means break). The precursors for this are liquefied vitreous and tractional forces
Pediatric Retinal Detachment

FIGURE 19-1: RRD in 8-year-old boy. Thin retina and extensive subretinal gliosis indicates long standing RD

that can produce and maintain a retinal break through which fluid gains access to sub retinal space. The most common predisposing factors for retinal detachment in children include abnormal vitreoretinal adhesions in association with posterior vitreous detachment (PVD), conditions like high myopia and retinoschisis, previous history of ocular (most commonly cataract) surgery, trauma and various vitreoretinopathies like Stickler’s syndrome and Marfan’s syndrome. These conditions predispose an eye for development of RRD due to very high incidence of associated vitreous detachment and retinal breaks.

Weinberg et al found that, each case of pediatric RRD can be categorized into any of the following four broad groups.
1. Structural ocular abnormalities—56%
2. Trauma—63%
3. Previous ophthalmic surgery—51%
4. Preceeding uveitis—13%

They found that every childhood RRD has at least one of the above risk factors while more than 50% cases had 2 or more risk factors.

Fivgas et al has found high myopia (> 4D) and previous ocular surgery (34% incidence for each) as the two most important risk factors of RRD development in children.

In general, there are four most important risk factors which alone or in combination are present in majority cases of RRD in children.
1. High myopia
2. Previous history of ocular surgery
3. Previous history of trauma
4. Congenital or developmental eye anomalies.
Causes of RRD in Children

1. Congenital, hereditary or developmental diseases
   - Choroidal coloboma
   - Incontinentia pigmenti
   - Congenital retinoschisis
   - Norrie’s disease
   - Persistent hyperplastic primary vitreous (PHPV) or persistent fetal vasculature syndrome
   - Connective tissue disorders like Marfan’s syndrome, Ehlers-Danlos syndrome
   - Familial exudative vitreoretinopathy (FEVR)
   - Optic disc pit maculopathy
   - Vitreoretinopathies like Stickler’s syndrome, Wagner’s syndrome
   - Retinopathy of prematurity (ROP)

2. Post-traumatic or post-ocular surgery

3. Post-inflammatory conditions
   - Intermediate or posterior uveitis
   - Toxoplasmosis, toxocariasis
   - CMV retinitis
   - Eales’ disease.

4. Idiopathic: In a recent series of 82 consecutive pediatric RRD cases, Lee et al found that 19% of cases were idiopathic. These cases were neither associated with high myopia, trauma nor with any other predisposing condition. Most peculiar feature in these cases was presence of inferior temporal dialysis in 76% of cases. Bilateral involvement is seen in 20% of patients. RD is usually subclinical with presence of demarcation line and intraretinal cysts suggestive of its long standing nature. PVR is rare as overlying vitreous base impedes access of RPE cells to vitreous cavity. Presence of bilateral non-traumatic retinal dialysis is an indication for examination of other family members.

   Over the past 40 years, primary causes of pediatric RRD (trauma, myopia and associated condition) have not changed although contribution of congenital cataract, ROP, uveitis and glaucoma had reduced, probably due to advances in the management of these conditions.

HIGH MYOPIA AND RRD IN CHILDREN

High myopia is present in about 34% cases of childhood RRD and hence is an important independent risk factor. Risk increases with higher degrees of myopia and is highest when high myopia is associated with aphakia. Early occurrence of posterior vitreous detachment, increased incidence of lattice degeneration, thin retina and probably weak adhesion between RPE and photoreceptors contribute to more frequent occurrence of retinal breaks and RRD in myopic subjects. It has been shown that increase in axial length by 1mm increases the risk of RD by hazard ratio of 1.3. There is also a high chance of bilateral retinal detachment associated with high myopia. These eyes are also very prone to develop retinal tears and detachment after trauma than non-myopic eyes.

Although isolated high myopia is a sole and independent risk factor in pediatric RRD, in almost every case, the myopia is part of broader ophthalmic or systemic abnormalities such as retinopathy of prematurity, Marfan’s syndromes, Ehlers-Danlos syndrome, osteogenesis imperfecta, and vitreoretinopathies like Stickler’s syndrome, Wagner’s syndrome.
PEDiatric Retinal Detachment

**RD IN CHILDREN WITH HISTORY OF TRAUMA**

Trauma is one of the most common causes of childhood RRD. Children aged under 10 years account for about 6.5% of all ocular injuries. More indulgence in sports related activities, lack of experience and common sense may be the contributing factors behind frequent ocular injuries in children. Open as well as closed globe injuries can be complicated by rhegmatogenous retinal detachment in children. Most of the these children are boys (M:F = 4:1). Leading causes of blunt trauma in Indian children are cricket ball injuries and trauma while playing ‘Gulli-Danda’. Blunt trauma is associated with development of retinal tears in 2-5% of cases, which in future can give rise to RRD. In posterior segment penetrating injuries, retinal detachment can occur in 20% of eyes and it is 4.5 times more likely to occur if associated with vitreous haemorrhage.

A retinal tear is generally produced immediately after trauma. But in young patients, due to tamponading effect of formed vitreous, RD usually doesn’t develop immediately. Following trauma, vitreous liquefaction can occur. Fluid then starts sipping in the subretinal space through the break leading to retinal detachment. Average interval between trauma and diagnosis of RRD is 17.3 months in cases of blunt trauma and 14.7 months in case of penetrating trauma. Penetrating injuries and retained intraocular foreign bodies though less common are associated with severe PVR in children. Also, the frequency of PVR varies with type of trauma—its incidence is 43% after perforating injury, 21% after globe rupture, 15% after penetrating injury and 11% after retained intraocular foreign body (IOFB).

**RD WITH HISTORY OF PREVIOUS OCULAR SURGERY**

Almost 1/3 to half the pediatric RRDs have prior history of ocular surgery. Gonzales et al found a very high incidence (61%) of prior history of ocular surgeries in pediatric RRD cases in a recently published retrospective study. Surgery for congenital cataract, ruptured globe repair, pars plana vitrectomy, glaucoma surgeries including Molteno tube implants as well as trabeculectomy and penetrating keratoplasty can be associated with future development of RRD in children.

Cumulative probability of RRD within three years after extracapsular cataract surgery is found to be 0.81%. Rabiah et al found 3.2% overall frequency of retinal detachments after pediatric cataract surgery. The mean interval between cataract surgery and retinal detachment was found to be 6.8 years, which is significantly more as compared to adults. However, a primary posterior capsulotomy or anterior vitrectomy procedure or postcataract surgery Nd: YAG laser posterior capsulotomy may not be associated with increased incidence of RRD in children, unlike in adults.

**Examination Technique in Children**

Best way to examine a child is by using indirect ophthalmoscope with 20/30 D condensing lens. A great amount of patience, talkativeness, tactful approach and a quick but thorough examination are essential for a successful pediatric eye examination.

Few children are exceptionally cooperative and never pose any problem during examination—even fundus examination with scleral indentation is possible. A small group of children are so apprehensive that no matter what measures are taken, they will never let the examiner have a proper look and ultimately examination under anesthesia will be required.

But majority of children will fit into the third group where, with a little perseverance and persuasion, they will allow an almost complete examination.
A few things to be remembered during examination are:

- Observation of child interacting in his/her environment can give important clues regarding visual function.
- Talk a lot with the child. Befriend and start a conversation regarding school, friends, games, etc. before beginning examination.
- Always start with lowest possible intensity of ophthalmoscope light.
- Avoid excess touching/stretching the lids.
- Examine the eye with poor vision first.
- Use of sedatives or wrapping the child in a cloth can sometimes be useful in a moderately apprehensive child.

Ultimately, never hesitate to repeat examination under anesthesia if slightest of doubt persists.

**Presenting Symptoms and Modes of Presentation**

In symptomatic children, poor visual acuity is the most common presenting complaint (62% of cases). Detection during an ophthalmic check-up (28% cases) either as a routine or during follow up period of an ocular procedure or notice of associated features by parents like leucocoria (10% cases), ocular deviation, or smaller sized eye are the other common modes by which a child with RRD can present to the clinician.

Average duration of symptoms is approximately 1 to 2 months, which is slightly longer than seen in adult population of RRD cases (less than 30 days for all ages). In India, presentation of children with RRD is probably even more delayed (165 days in one study) as compared to western population. Because of higher prevalence of bilateral ocular pathology, children with RRD often have poor vision in both eyes. This makes it difficult to exactly pinpoint the duration of symptoms in many cases.

Bilateral occurrence of RRD is also quite common in pediatric age group. Fivgas et al in a retrospective series found 22% incidence of bilateral RRD in children who are diagnosed to have RRD in one eye. Also 89% patients showed at least some form of ocular pathology in both the eyes. This fact again highlights the importance of a careful examination of the other eye in all RRD cases in children. It also justifies the attempt of surgical repair in an apparently hopeless case of RRD, where because of advanced nature of the disease, surgery at first may not seem to be a viable option. But ultimately the same eye; whatever postoperative vision it may have-may turn out to be the only seeing eye.

Whenever a RRD is diagnosed incidentally, the child almost always has normal or near normal vision in the other eye. This emphasizes the need of a routine ophthalmic screening in all children with apparently normal visual function. Annual school screening programs can be of immense help for early detection of these children.

**Past Medical and Family History and Systemic Examination**

Fivgas et al found history of prematurity in 19%, mental retardation in 7% and congenital cytomegalovirus infection in 3.5% of cases of pediatric RRD. Family history of RRD is seen in about 19% of cases, most of which are associated with high myopia. Most of these cases, in which RRD has an association with positive family history and presence of high myopia, turn out to be Stickler’s syndrome.
Pediatric Retinal Detachment

In these children, it is also important to look for systemic features like skeletal deformities, orthopathies, facial dysplasia, deafness, hyperelasticity of skin, CVS anomalies, etc. to rule out associated systemic disorders.

**Characteristics Features of RRD in Children**

Because of tendency of late presentation, pediatric RRD are characterized by a more extensive area of detachment, more common macular involvement and advanced PVR at the time of diagnosis. Macula is detached on presentation in approximately 79% of these cases. Nagpal et al found 97.29% incidence of macular involvement on diagnosis in pediatric RRD in Indian population—most probably because of more delayed presentation (165 days) in Indian children (Table 19-1).

Delayed presentation naturally results in the development and rapid progression of proliferative vitreoretinopathy (PVR) in these children. PVR at presentation in seen in about 20 to 40% of children with RRD.\(^1,4,6,8\)

Late diagnosis, frequent macular involvement and advanced proliferative vitreoretinopathy (PVR) at presentation are the chief reasons, why pediatric RRDs have a poorer prognosis as compared to adult RRDs.

**TYPES OF BREAKS**

The types of break responsible for RRD in children depends upon the etiology. Almost 2/3 of post-traumatic RRD are caused by retinal dialysis. Forty-seven percent of traumatic dialysis are inferotemporal, 28% superonasal, 20% superotemporal and 5% inferonasal.\(^9\)

Higher frequency of inferotemporal dialysis seen clinically in post-traumatic cases is probably due to the peculiar anatomy of the human orbit as the globe is least protected in inferotemporal quadrant.\(^10\)

A round hole with or without lattice degeneration is the most common causative break in RRD associated with high myopia. RD caused by giant retinal tear is seen in about 10% of cases. Cases with giant retinal tear are most commonly associated with high myopia and vitreoretinopathies like Stickler’s syndrome. It is interesting to note that in pediatric RRDs which present without any known etiology, inferotemporal dialysis is the causative lesion in almost 2/3rd of cases.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Mean age (yr)</th>
<th>RD duration (days)</th>
<th>Macula Off (%)</th>
<th>PVR (%)</th>
<th>Bilat. (%)</th>
<th>Breaks (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fivgas(^1)</td>
<td>29</td>
<td>9.6</td>
<td>52</td>
<td>79</td>
<td>45</td>
<td>22</td>
<td>HST-55 Dialysis-21</td>
</tr>
<tr>
<td>Butler(^7)</td>
<td>15</td>
<td>12.4</td>
<td>90</td>
<td>67</td>
<td>—</td>
<td>—</td>
<td>Dialysis-33</td>
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<tr>
<td>Weinberg(^6)</td>
<td>39</td>
<td>10</td>
<td>—</td>
<td>74</td>
<td>31</td>
<td>26</td>
<td>GRT-15</td>
</tr>
<tr>
<td>Yokohama(^4)</td>
<td>55</td>
<td>12</td>
<td>30</td>
<td>—</td>
<td>22</td>
<td>—</td>
<td>Holes-40 Dialysis-27</td>
</tr>
<tr>
<td>Nagpal(^8)</td>
<td>111</td>
<td>13.6</td>
<td>165</td>
<td>97.29</td>
<td>45.9</td>
<td>10.8</td>
<td>Holes-34.23</td>
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<tr>
<td>Lee(^9)</td>
<td>88</td>
<td>14</td>
<td>—</td>
<td>66</td>
<td>—</td>
<td>—</td>
<td>Dialysis-44 GRT-10</td>
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<tr>
<td>Gonzales(^10)</td>
<td>46</td>
<td>9.8</td>
<td>30</td>
<td>83</td>
<td>59</td>
<td>18</td>
<td>HST-59</td>
</tr>
</tbody>
</table>
Management of Pediatric RRD

Surgery is the only treatment option for any case of rhegmatogenous retinal detachment. As in adults, pediatric RRD cases are treated with either scleral buckling alone, pars plana vitrectomy (PPV) alone or combination of PPV with scleral buckling.

SCLERAL BUCKLING IN CHILDREN

Scleral buckling is used as the primary modality of treatment in 60 to 70% cases of childhood retinal detachment. Good anatomical success rate with scleral buckling, technical difficulty in inducing complete PVD in children during vitrectomy and high incidence of post vitrectomy cataract development, make scleral buckling as the 1st choice of treatment for pediatric RRD.

But presence of thin sclera, thin and fragile muscles, small orbit and narrow palpebral fissure can pose difficulties during buckling surgery in children. Pre-existing shallow anterior chamber and forward shift of lens iris diaphragm following scleral buckling may lead to angle closure and rise in intraocular pressure during early postoperative period. Scleral buckling with encircling band induces myopic shift in refraction in these eyes. Amount of myopia induced by encircling band is about –2.75 D in adults. But in children especially in infants, the axial elongation induced by encircling band and forward displacement of lens, can cause severe myopic shift, post encircling procedure. In retinopathy of prematurity, upto 12 D of anisometropia was reported following scleral buckling. This necessitates a second surgery to severe the encircling band in order to not inhibit the eye growth or induce anisometropic amblyopia.

Technique of scleral buckling in children is essentially similar as in adults. Because of higher incidence of PVR at presentation and increased risk of post surgery reproliferations, a more prominent and/or larger buckle is preferable to counteract the tractional forces in children. A combination of segmental buckle with encircling element may be favorable than segmental buckle alone to give good support at the vitreous base and thus lowering the possibility of redetachment and subsequent PVR. To avoid buckle induced growth inhibition and anisometric amblyopia, encircling band should be cut approximately 3-6 months after permanent reattachment is ensured in all children younger than 3 years.

Results of Scleral Buckling in Pediatric RRD

In eyes without PVR, scleral buckling has shown a very high primary reattachment rate (70-100%). Sadeh et al reported 100% reattachment rate using combination of segmental buckle with encircling element. Haring et al in his series of 33 eyes, reported 100% anatomical attachment. 60.6% eyes in his series had 20/40 or better vision. Yokohoma et al showed 95% initial reattachment rate after scleral buckling surgery in pediatric RRD without PVR changes. But reattachment rate in RRD with PVR (grade C or D) treated with scleral buckling was only 33%, emphasizing the need to consider vitreous surgery in eyes presenting with PVR.

VITREOUS SURGERY IN THE MANAGEMENT OF PEDIATRIC RRD

Standard 3-port pars plana vitrectomy is preferred in pediatric RRDs associated with giant retinal tear, very large or posteriorly located break/s, old detachments with severe PVR and in eyes with recurrent RD following scleral buckling.
SURGICAL ANATOMY OF PARS PLANA IN CHILDREN

Understanding the surgical anatomy of the ciliary body especially the pars plana region in children is very important in view of selecting a safe site for sclerotomy placement during vitreous surgery. The knowledge of growth characteristics of pars plana region is essential for understanding the anatomy of an infant eye with a surgical point of view.

The pars plicata of a mature new born is nearly of adult size, while pars plana is relatively narrow. Anteroposterior extension of the pars plana begins in the postnatal period (Table 19-2).

At post natal age of 6 months, the nasal and temporal ciliary body represents 64% and 57% of the adult length respectively. Seventy-six percent of final length of ciliary body at adulthood is reached by 24 months of age. But the ciliary body, parsplana and retina do not attain entire adult proportions before 7 years of age.

**Selection of Safe Sclerotomy Site**

Sclerotomies can safely be placed 3.5 mm behind the limbus in children older than 2 years. In younger children, following guidelines can be used as shown in (Table 19-3). In infants, sclerotomies are made through pars plicata to avoid iatrogenic retinal breaks. But the disadvantage of pars plicata approach is its direct proximity to the crystalline lens leading to increased risk of mechanical damage to the lens during surgical manipulation. A minimum pars plana width of 3mm is required for pars plana surgical approach during vitreous surgery. It is estimated that majority of infants at 6 months do attain a par plana width of 3 mm. Hence, pars plana surgical approach can be considered in infant with 6 months or older age.

**TABLE 19-2: Developmental morphology of the pars plicata and pars plana in the postnatal phase**

<table>
<thead>
<tr>
<th>Age in months</th>
<th>&lt;6</th>
<th>6-12</th>
<th>12-24</th>
<th>24-72</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciliary body (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal</td>
<td>3.06</td>
<td>3.54</td>
<td>3.87</td>
<td>4.28</td>
<td>4.79</td>
</tr>
<tr>
<td>Temporal</td>
<td>3.31</td>
<td>3.85</td>
<td>4.14</td>
<td>4.94</td>
<td>5.76</td>
</tr>
<tr>
<td>Pars Plana (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal</td>
<td>2.23</td>
<td>2.69</td>
<td>2.98</td>
<td>3.25</td>
<td>3.64</td>
</tr>
<tr>
<td>Temporal</td>
<td>2.48</td>
<td>2.96</td>
<td>3.15</td>
<td>3.85</td>
<td>4.32</td>
</tr>
</tbody>
</table>

(Source: Aiello et al, Arch Ophthalmol 1992; 110:802-5)

**TABLE 19-3: Safe sclerotomy location**

<table>
<thead>
<tr>
<th>Age (in months)</th>
<th>&lt;3</th>
<th>&gt;3-6</th>
<th>up to 12</th>
<th>&gt;12-24</th>
<th>&gt;24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sclerotomies from limbus (mm)</td>
<td>1.0-1.5</td>
<td>1.75-2.0</td>
<td>2.5</td>
<td>3.0</td>
<td>3.5</td>
</tr>
</tbody>
</table>


**Viewing Systems for Pediatric Vitreous Surgery**

Wide field viewing systems – both contact and non-contact, are being used for pediatric vitreous surgery. Smaller sized cornea and small eyeball, especially in ROP cases, pose challenges to the operating surgeon. BIOM (binocular indirect ophthalmo microscope) or pediatric Lander lens system are most preferred systems for visualization during pediatric vitreous surgery. Contact lenses provide more free space for surgeon and also allow easy placement of instruments in the eye. A small sized
contact lens for paediatric vitreous surgery has been designed by Peyman et al\textsuperscript{28} with contact diameter of 7 mm, static field of view of 94 degrees and maximum field of view of 129 degrees.

**Vitrectomy: General Principles**

Because of lower systolic blood pressure in children, central retinal artery perfusion can easily be compromised if infusion pressure during vitrectomy is kept high.\textsuperscript{22} Infusion bottle height is approximately kept at 35 cm above eye level which maintains the intraocular pressure of about 25 mm Hg. Use of minimum infusion pressure also reduces the risk of intraoperative corneal edema.

**Lensectomy**

Lensectomy may be required in cases of pediatric RRD associated with anterior PVR, giant retinal tear and in eyes with subluxated or cataractous lens. Lens is usually soft and can easily be removed with vitrector. Remnants of the capsular bag are generally removed bimanually using combination of forceps in one hand for traction and vitrector in other hand for cutting zonules. Use of forceps alone is avoided as aberrant attachments of zonular fibres may create iatrogenic peripheral retinal tears.\textsuperscript{22}

**PVD Induction**

Induction of posterior vitreous detachment is important for successful reattachment of the retina and it is the most challenging part of pediatric vitreous surgery. Use of high suction-directly with vitrector or by a soft tipped cannula generally separates posterior vitreous. In difficult case, direct traction can be applied to the posterior vitreous by directly grasping the vitreous with the forceps close to the disc margin. Intraoperative use of triamcinolone acetonide helps in PVD induction by improving visualization of posterior hyaloid.

Iatrogenic retinal breaks during pediatric vitrectomy should be avoided at all cost. Because of inability of completely dissecting the vitreous from inner retinal surface, iatrogenic retinal break/s in most pediatric cases usually results in recurrence and eventually inoperable retinal detachment.\textsuperscript{29}

**Enzyme-assisted Vitrectomy**

Enzyme-assisted vitrectomy aims at disinserting the posterior hyaloid from the retinal surface in a complete and less traumatic manner and have a potential role to play in the management of pediatric RRD. Plasmin, a non-specific protease, acts on laminin and fibronectin, which form the biological ‘glue’ which sticks the vitreous to the retinal surface. It spares the type 4 collagenase, leaving the internal limiting lamina intact, but causes vitreous liquefaction in a dose dependent manner.\textsuperscript{30, 31} This safe and more complete peeling of posterior hyaloid results in less residual collagen on anterior retinal surface and thus less tractional effect on the underlying neurosensory retina. This property has two potential benefits in pediatric RRD management. First, more complete and safe removal of posterior hyaloid theoretically eliminates preretinal scaffold for cell migration and proliferation thereby results in reduction in postoperative proliferation activity and secondly reduces traction for posterior hyaloid face separation thereby reduces the risk of iatrogenic breaks during PVD induction. These two factors should enhance the overall anatomical success rate in management of these cases. Also enzymatic vitrectomy will allow 23’G’ or even 25’G’ instruments to be used in pediatric vitreous surgery. These smaller instruments will have the advantage of more safety and increased mobility especially in phakic, pediatric eyes.
**Pediatric Retinal Detachment**

**Tamponading Agent**

Silicone oil is preferred over intraocular gases as a tamponading agent in children. Intraocular gases are generally not advisable in children because of problem of inadequate postoperative positioning and difficulty in accurately assess intraocular pressure in children during postoperative period. Also delayed visual rehabilitation may be responsible for amblyopia. Advantages of silicone oil over long-acting gases include earlier visual rehabilitation and less requirement of strict prone positioning after surgery. Scott et al. showed complete retinal attachment in 58% of cases and preservation of preoperative vision in 70% of cases of complex retinal detachments in children treated with PPV and silicone oil. In general, retinal reattachment and improvement in visual acuity can be achieved in the majority of pediatric eyes using vitrectomy and silicone oil as tamponading agent. As in adults, long term effects of silicone oil in children include development of cataract, corneal decompensation and increased intraocular pressure. Early emulsification and perisilicone oil proliferation is more common in children. Hence, considering the long life expectancy, timely removal of silicone oil from pediatric eyes is of utmost importance for maintaining the vision in these eyes.

**Cataract as a Complication of Vitrectomy in Children**

Ninety eight percent of vitrectomized eyes in adults show some cataract (nuclear sclerosis) progression by the end of first year. On the other hand, almost 67% of pediatric lenses are found to be clear after lens sparing vitrectomy. In children, post-vitrectomy cataracts are often posterior subcapsular in nature and more commonly associated with use of intraocular gases.

**RD Associated with Congenital or Developmental Ocular Disorders**

**CHOROIDAL COLOBOMA**

Coloboma of fundus is a congenital defect caused by improper closure of embryonic fissure. It is seen in about 0.14% of general population. Incidence of retinal detachment is about 40% in these patients and usually manifests in second decade of life. Histologically, near the margin of the coloboma, retina splits into 2 layers. Inner layer continues as an Intercalary membrane on the coloboma, while outer layer turns back, disorganizes and fuses with retinal pigment epithelium. The junction of these 2 layers or where the split occurs is called Locus Minoris Resistentiae (LMR) or place of least resistance.

Break/s responsible for RRD in eyes with choroidal coloboma can be at three locations. Breaks can occur at LMR, in the intercalary membrane or in peripheral retina. Management of retinal detachment unrelated with coloboma (RD with peripheral break/s where detachment does not extend in colobomatous area) is similar to that occurring in the non colobomatous eyes. But when coloboma is directly responsible for retinal detachment, the management approach differs. External buckling in coloboma related RD is difficult because of, difficulty in identifying the breaks in the intercalary membrane, difficulty in creating chorioretinal adhesion around the breaks due to absence of choroid and RPE and posterior location of breaks. Hence the preferred technique is vitrectomy with internal tamponade using silicone oil. Vitrectomy allows better identification and hence management of these breaks with greater certainty. The best approach is to isolate the coloboma from rest of the retina by treating the pigmented fundus just beyond the edge of coloboma with laser. Diode laser is preferred over argon laser due to less chance of damage to nerve fiber layer as a result of relatively deeper penetration. Alternatively attempts have been made to directly close
the breaks in intercalary membrane using cyanoacrylate glue. Silicone oil is the preferred tamponading agent in these eyes for long-term effect (Figure 19-2).

Primary attachment rate with silicone oil as tamponade is found to be 86.7% as compared to only 46% seen in gas filled eyes. Final attachment rate at 1 year is about 80% while about 70% of treated cases show some improvement in visual function.

**CONGENITAL X-LINKED RETINOSCHISIS**

Congenital X-linked retinoschisis is a bilateral condition occurring in males and characterized by stellate maculopathy and peripheral retinoschisis. Peripheral retinoschisis is present in about 50% of the cases and is associated with more severe vision threatening complications like vitreous hemorrhage (40%) and retinal detachment (22%). Usually the patients are younger than 10 years of age. The other causes of visual loss could be hemorrhage in large schisis cavity with or without vitreous hemorrhage, rapid progression of schisis threatening macula or obstruction of the macula by overhanging inner wall of a schisis cavity, combined schisis with tractional or rhegmatogenous RD. Retinal detachment may develop in these eyes when break/s develop in both outer and inner layers. Retinal detachment in retinoschisis can be difficult to recognize as subretinal fluid is often shallow and overshadowed by overlying nerve fibre layer separation.

Surgical approach is scleral buckling for detachment without PVR and when outer layer breaks are anterior to equator. Remaining cases are managed by vitrectomy, excision of inner schisis wall, diathermy of avulsed vessels, fluid gas exchange and internal tamponade with long acting gases or silicone oil. Inner schisis wall should be removed during vitrectomy because there is no other effective way in children to remove the posterior cortical vitreous overlying the schisis. Studies have shown almost 90% final attachment rate, while visual acuity improvement is seen in about 60% of treated cases.

**REGRESSED RETINOPATHY OF PREMATURITY**

Retinal detachments associated with regressed ROP are broadly classified into early (within 1 year) and late (after 1 year). Incidence of early retinal detachment following advanced ROP has been significantly reduced due to better screening techniques and effective ablative management. For
those cases which develop early retinal detachment in regressed ROP, outcome of surgery is unfortunately very disappointing. Prognosis is more favourable in eyes that have not progressed to stage 5 ROP.\textsuperscript{41} Lens sparing vitrectomy techniques are advocated for pathology limited to posterior pole (zone 1 and posterior zone 2 disease) while 360 degrees encircling band may be employed for peripheral tractional detachments.

Late retinal detachments do occur infrequently in these children. Characteristic retinal and vitreous pathological changes place these patients at increased risk of retinal detachment throughout their lives. Late retinal detachments are most commonly rhegmatogenous, but may also be tractional or a combination of both. Two broad demographic age groups have been observed in these late detachments. Between age 4 and 8 years, combined rhegmatogenous—tractional detachment is seen more commonly in boys. Mostly there is associated history of trauma. The second group with rhegmatogenous retinal detachment present in early adolescence.\textsuperscript{42, 43} Usually there is localized vitreous detachment associated with round holes or horse shoe tears. Though the exact cause is uncertain, retinal breaks in eyes with regressed ROP can be secondary to ongoing changes of ROP or due to abnormal vitreoretinal interface changes caused by ROP.\textsuperscript{43} Machemer et al\textsuperscript{44} postulated that chronic exudation from vascular abnormalities may stimulate glial proliferation in vitreous. Associated high myopia and frequent lattice like lesions also place these eyes at a higher risk for RD.

Depending on location of the breaks and amount of vitreous traction, the treatment options could be scleral buckling or vitrectomy or both.\textsuperscript{43} However, all these eyes invariably need pars plana vitrectomy to achieve long-term attachment of retina. Silicone oil is the preferred tamponading agent in these eyes.\textsuperscript{45}

**HEREDITARY VITREORETINOPATHIES: STICKLER’S SYNDROME**

Hereditary vitreoretinopathies are characterized by an abnormal vitreous gel and associated retinal changes. Stickler’s syndrome is an autosomal dominant disorder with characteristic ophthalmic and systemic features like deafness, arthritis and orofacial abnormalities. Abnormal vitreous is the pathognomonic feature associated with progressive high myopia (75-85%). Vitreous shows optical emptiness, liquefaction, bands and syneresis. Retinal detachment is a significant risk (10-48%) occurring in first decade of life.\textsuperscript{46, 47} RD is usually bilateral and spontaneous. Retinal detachment may be caused by giant retinal tear or multiple breaks. In view of large, multiple tears pars plana vitrectomy is preferred choice in these eyes.

It is very important to screen the family members of a patient suspected to have Stickler’s syndrome.

**CONNECTIVE TISSUE DISORDERS: MARFAN’S SYNDROME**

Marfan’s syndrome is an inherited disease caused by defective fibrillin gene. In addition to multisystemic abnormalities, ectopia lentis and myopia are the most common ocular features, both of which predispose patients to retinal detachment. Retinal detachment is the most serious ocular complication, seen in 8-38% (up to 75.5%) of patients with Marfan’s syndrome and is bilateral in almost 70% of cases. RD is usually total in 75 % eyes and macular involvement is seen in nearly 90% eyes. Male are predominantly affected probably due to higher incidence of trauma.

The management of these detachments is difficult, as there are often multiple small atrophic breaks seen in different meridians, extensive lattice degeneration, thin sclera and the surgical view
may be marred by ectopia lentis and poorly dilating pupils. Retinal breaks are commonly located along temporal periphery. (50% or more). Giant retinal tears are reported in 11% eyes. Uncomplicated detachments with clear media, centrally placed lens and peripheral break/s are managed with scleral buckling while complicated detachments need pars plana vitrectomy with internal tamponade, mostly silicone oil. Eyes undergoing pars plana vitrectomy invariably need lensectomy as the lens is usually subluxated in superotemporal quadrant. In general, anatomical success rate is in the range of 80 to 90% (combined scleral buckling and vitrectomy).

**OUTCOME OF SURGERY IN PEDIATRIC RRD**

Delay in diagnosis, higher incidence of PVR, need for multiple surgeries and associated congenital anomalies affect overall outcome in these eyes. The anatomical and functional results are summarized in Table 19-4.

<table>
<thead>
<tr>
<th>Investigator</th>
<th>n</th>
<th>Surgery type (%)</th>
<th>Mean Surg. per eye</th>
<th>Final success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fivgas</td>
<td>29</td>
<td>SB/Vit</td>
<td>28/72</td>
<td>2.2</td>
</tr>
<tr>
<td>Butler</td>
<td>15</td>
<td>SB</td>
<td>80</td>
<td>1.46</td>
</tr>
<tr>
<td>Weinberg</td>
<td>39</td>
<td>SB/Vit</td>
<td>41/13(SB+PPV-46)</td>
<td>1.6</td>
</tr>
<tr>
<td>Yokohama</td>
<td>55</td>
<td>SB</td>
<td>76</td>
<td>87</td>
</tr>
<tr>
<td>Nagpal</td>
<td>111</td>
<td>SB</td>
<td>61.26/38.73</td>
<td>1.29</td>
</tr>
<tr>
<td>Sadeh</td>
<td>16</td>
<td>SB</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Gonzales</td>
<td>46</td>
<td>SB</td>
<td>74</td>
<td>78</td>
</tr>
<tr>
<td>Horle</td>
<td>30</td>
<td>SB</td>
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<td>70</td>
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<tr>
<td>Moisseiev</td>
<td>28</td>
<td>SB</td>
<td>100</td>
<td>32</td>
</tr>
<tr>
<td>Haring</td>
<td>33</td>
<td>SB</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Scleral buckling is the preferred procedure and vitrectomy was reserved for more complicated cases and in eyes with failed scleral buckle. Single surgery attachment rate is found to be around 60 to 80% while final attachment rate is around 80 to 90% in pediatric RRD. Gonzales, et al reported 78% anatomical attachment rate. The best anatomical results are noted in RDs with atrophic holes or dialysis (almost 100%) followed by tractional tears (74%) and giant retinal tears (67%). Younger age, worse initial vision, more extensive detachment, large and posterior tears and presence of PVR are associated with poor anatomical outcome.

Though not very encouraging, at least some degree of visual improvement is expected in about 60 to 70% of the cases. Haring et al reported 20/40 or better vision in 60.6% eyes following scleral buckling. Binocular vision could be achieved in 52.4% patients. Final visual acuity correlates well with presenting vision and is adversely affected by duration of the RD and presence of PVR. Visual rehabilitation is an integral part of the management following surgery in these eyes as amblyopia is a potential cause for visual impairment. There is life long risk of recurrent RD, glaucoma and cataract indicating need for frequent prolonged follow-up.
Summary

The incidence of RRD is low in pediatric population. Ocular trauma/surgery and congenital structural abnormalities are the commonest etiological factors in this age group. There is higher incidence of bilateral involvement. Anatomical outcome is generally good following scleral buckling or vitrectomy.

Although visual improvement is modest, the value of surgery must be considered in context with the expected natural history of these eyes as, if left untreated, most will ultimately result in phthisis with irreversible vision loss. Delay in diagnosis, more frequent macular involvement, early and frequent development of PVR, preexisting congenital anomalies, development of amblyopia and lack of health care facilities are some of the chief reasons which limit the potential of visual recovery in these children.

In view of higher frequency of vision threatening abnormalities in the fellow eye, these patients need regular follow-up throughout their life. Once detected, prompt prophylactic treatment of asymptomatic lesions should be considered.

School vision screening tests, education of high risk patients and their parents regarding the threat of detachment and symptoms of the detachment can help in early diagnosis and treatment to improve overall final outcome. Finally improved surgical techniques may also help to reduce the incidence of pediatric RRD.

References

Textbook of Vitreoretinal Diseases and Surgery

Introduction

Retinoblastoma is the most common intraocular tumor in children. Many tumors possibly arise in infancy or childhood but do not present until later in life like melanocytoma and choroidal osteoma. The other common intraocular tumors in children include juvenile xanthogranuloma, medulloepithelioma, circumscribed choroidal hemangioma, choroidal osteoma, congenital hypertrophy of the retinal pigment epithelium, combined hamartoma of the retina and retinal pigment epithelium and tumors associated with the phacomatoses—von Hippel Lindau syndrome, tuberous sclerosis, neurofibromatosis and Wyburn Mason syndrome.

Epidemiology

Retinoblastoma is the most common intraocular malignant tumor in children with a reported incidence of 1 in 15000 to 1 in 18000 live births.¹ The tumor is bilateral in 25% to 35% cases.² Until recently, enucleation was considered the standard treatment modality for children affected by this tumor. Early diagnosis and recent advances in management like use of chemotherapy and protocol based management strategy have improved the prognosis of this potentially fatal tumor.

Clinical Presentation of Retinoblastoma (Figures 20-1A to G)

Leukocoria is the most common clinical presentation seen in about 56% of patients.³ Other less common presentations include squint, hypopyon, hyphema, vitreous hemorrhage. More advanced cases may present with tumor necrosis and sterile orbital inflammation or with extraocular extension and proptosis.⁴ Extraocular extension is most likely to occur at the sites of the scleral emissary veins. Atypical clinical manifestations include hypopyon with anterior segment invasion or spontaneous phthisis bulbi.⁵ Metastasis can occur in long standing and neglected cases and is most commonly seen in brain, skull, distant bones and lymph nodes.

The clinical appearance of the fundus lesion varies with type of tumor growth. Three patterns of tumor growth are usually recognized.⁴

1. Endophytic tumor: Here the tumor grows as a yellow-white mass lesion from the retinal surface towards the vitreous cavity and can eventually give rise to vitreous seeds. Retinal vessels are not seen on the surface of the tumor and there is no associated retinal detachment.

2. Exophytic tumor grows under the retinal surface giving rise to retinal detachment.

3. Diffuse infiltrating tumor involves the retinal surface as a placoid thickening. This is usually seen in older children and can present with secondary glaucoma.

In a child presenting with leukokoria, other causes like persistent hyperplastic primary vitreous, Coats’ disease, ocular toxocariasis, endogenous endophthalmitis should be excluded before embarking on the definitive treatment of retinoblastoma.

A dilated fundus evaluation with an indirect ophthalmoscope is useful to diagnose retinoblastoma in 90% cases. An examination under anesthesia is required in every case and should include measurement of corneal dimensions, intraocular pressure, iris and anterior chamber examination for any neovascularization and anterior chamber seeding. Subtle proptosis of the affected eye could be an indicator of extraocular tumor extension and should be looked for.⁴ It is important to evaluate the fundus thoroughly with indentation of the periphery to detect any peripheral tumor.³ Ultrasound
**FIGURE 20-1A:** Leucokoria is the most common presentation of retinoblastoma, which is seen in the left eye of this 2 year old child. In addition there is esotropia.

**FIGURE 20-1B:** Large exophytic tumor involving more than 75% of the vitreous volume with total retinal detachment.

**FIGURE 20-1C:** An endophytic tumor is seen with the presence of overlying vitreous seeds.
FIGURE 20-1D: Retinoblastoma may present with involvement of the anterior segment. This 4-year-old child presented with pseudohypopyon in the right eye.

FIGURE 20-1E: Rarer presentations include spontaneous phthisis bulbi following tumor necrosis.

FIGURE 20-1F: This 5-year-old child had hyphema following trivial trauma. Hyphema drainage was performed. The child presented after 4 months with extraocular extension of retinoblastoma which manifested as conjunctival masses.
FIGURE 20-1G: Orbital retinoblastoma may occur following extraocular extension of primary retinoblastoma. This may present as a fungating mass. This 5-year-old child had leucocoria since the age of 2 years.

B-scan can be used to measure the tumor dimensions and is especially useful in cases with media opacity like hyphema or vitreous hemorrhage. B scan appearance of intralesional hyper-reflectivity suggesting calcification within the tumor is characteristic of retinoblastoma (Figure 20-2). Computed tomography and magnetic resonance imaging is required if any extraocular extension or intracranial tumor spread is suspected (Figure 20-3). Also, in cases with diagnostic dilemma, CT scan can detect the typical intraocular calcification of retinoblastoma. Any associated pinealoblastoma or trilateral retinoblastoma can be detected by CT scan or MRI (Figure 20-4).

Classification of Retinoblastoma

Reese Ellsworth has been the most widely used system of classification of retinoblastoma for many years. This classification was originally devised to predict the prognosis following external beam radiotherapy. In recent years, the appropriateness of this classification has been questioned as it is not useful to prognosticate chemoreduction, the current favored treatment for management of retinoblastoma. The new International Classification of Intraocular Retinoblastoma is a sequential tumor grading which correlates better with the treatment outcome (Table 20-1).

Management

Management of retinoblastoma requires a multimodality approach involving an ocular oncologist, pediatric oncologist, radiation oncologist; geneticist and ocular oncopathologist. The primary goal
FIGURE 20-2: Ultrasound B-scan of the left eye of a child with retinoblastoma with the presence of an intraocular mass and high reflective spots within suggestive of intraocular calcification. On the A-scan there is presence of corresponding high spikes.

TABLE 20-1: International classification of intraocular retinoblastoma

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A:</strong></td>
<td>Small tumor (&lt; 3 mm) outside macula.</td>
</tr>
<tr>
<td><strong>Group B:</strong></td>
<td>Tumor &gt; 3 mm or any macular tumor or any tumor with subretinal fluid.</td>
</tr>
<tr>
<td><strong>Group C:</strong></td>
<td>Localised subretinal or vitreous seeds.</td>
</tr>
<tr>
<td><strong>Group D:</strong></td>
<td>Diffuse subretinal or vitreous seeds</td>
</tr>
<tr>
<td><strong>Group E:</strong></td>
<td>Tumor touching the lens, neovascular glaucoma, tumor anterior to anterior vitreous face involving ciliary body or anterior segment, diffuse infiltrating retinoblastoma, opaque media from hemorrhage, tumor necrosis with aseptic orbital cellulitis, phthisis bulbi.</td>
</tr>
</tbody>
</table>

The management of retinoblastoma is to safeguard the life of the child. Salvage of the eye and vision are the secondary and tertiary goals respectively. Management is based on the stage of the disease at presentation—intraocular retinoblastoma, retinoblastoma with high-risk factors, orbital retinoblastoma and metastatic retinoblastoma.
INTRAOCULAR RETINOBLASTOMA

Management options for intraocular retinoblastoma can be in the form of focal or local therapy and systemic chemotherapy. Focal therapy includes cryotherapy, transpupillary thermotherapy, laser photocoagulation and plaque brachytherapy. Local therapy can be either external beam radiotherapy or enucleation.

**Cryotherapy**

Cryotherapy is most useful for small peripheral tumors measuring up to 4 mm in diameter and 2 mm in thickness.\(^2\)\(^4\) Triple freeze thaw cryotherapy is usually applied at 4-6 week intervals until complete tumor regression. Cryotherapy administered before chemotherapy can have a synergistic effect by increasing the delivery of chemotherapeutic agents across the blood retinal barrier.\(^4\) Complications of cryotherapy includes serous retinal detachment, retinal tear and rhegmatogenous retinal detachment.

**Laser Photocoagulation**

The delivery of laser has improved with the use of the indirect ophthalmoscope laser photocoagulation system. The tumor is surrounded by 2 rows of laser burns to cordon off the blood supply to the tumor and never treated directly.\(^2\)\(^4\) There is a 30% recurrence rate with this modality. Complications include transient serous retinal detachment, retinal vascular occlusion, retinal traction and preretinal fibrosis.

**Transpupillary Thermotherapy**

The mechanism of thermotherapy is different from classic laser photocoagulation in that the temperature rise is lower than that of photocoagulation.\(^9\) The thermal effect of the sub photocoagulation laser leads to the apoptosis of the tumor cells. The tumor is treated directly sparing
the retinal blood vessels unlike in laser photocoagulation where the feeder vessels are treated. The scar produced is almost equal to the size of the tumor itself and there is minimal collateral damage to the surrounding retina. Thermotherapy is commonly applied through the indirect ophthalmoscope, operating microscope or the transcleral route. This is used for relatively small retinoblastomas without associated vitreous or subretinal seeds. This treatment provides satisfactory control for tumors measuring up to 4 mm in basal diameter and 2 mm in thickness. Tumor regression can be achieved in 86% of cases with multiple cycles of thermotherapy. The common complications are focal iris atrophy, focal paraxial lens opacity, retinal traction and serous retinal detachment. Thermotherapy can also be used synergistically with chemoreduction as heat amplifies the cytotoxic effect of platinum analogues.10

**Plaque Brachytherapy**

Plaque brachytherapy involves the placement of a radioactive implant on the sclera over the base of the tumor to irradiate the tumor transclerally.11 Commonly used materials include Ruthenium106 and Iodine125.

Plaque brachytherapy is now sparingly used as one of the primary treatment modalities for retinoblastoma. Tumor recurrence rate of 12% at one year follow-up has been reported when plaque is used as the primary treatment.12 It is used in situations where chemotherapy is contraindicated or in cases of recurrence or no response to chemoreduction or external beam radiotherapy. It can be done for tumors with basal dimension up to 16 mm and height up to 8 mm and located more than 3 mm from optic nerve or macula. Plaque brachytherapy delivers focal radiation to the tumor with minimal collateral damage; hence there are fewer chances of radiation optic neuropathy and retinopathy.13 Unlike with external beam radiotherapy, it minimizes the problems of bony orbital growth retardation and the risk of second malignant neoplasm.

Plaque brachytherapy requires precise localization of the tumor and measurement of its basal dimensions. The tumor thickness is measured by ultrasonography. This data is used for dosimetry on a three-dimensional computerized tumor modeling system. The plaque design is chosen depending on the basal tumor dimensions, its location, and configuration. The dose to the tumor apex ranges from 4000-5000 cGy. The radiation exposure time thus calculated guides the time of plaque implantation and removal. The surgery is performed under radiation safety precautions. The plaque is sutured to the sclera after confirming tumor centration with a dummy plaque and left in situ for the duration of exposure, generally ranging from 36 to 72 hours. The patient is hospitalized with radiation safety precautions for the duration of exposure. The results of plaque brachytherapy are gratifying. Shields et al reported in their series that 90% of the eyes destined for enucleation could be salvaged with plaque brachytherapy.11

The common complications are radiation optic neuropathy and radiation retinopathy. Special designs of plaques have reduced the incidence of radiation-induced complications especially to the optic nerve.4

**External Beam Radiotherapy (EBRT)**

External beam radiotherapy is no longer the first line management of retinoblastoma. Its use has fallen out of favor in view of the potential complications associated with it and reports demonstrating its definite potential to give rise to second nonocular neoplasms in germline retinoblastoma survivors.13,14 It is used in cases where there is no response to chemoreduction or where chemotherapy
is contraindicated. It is also used as an adjuvant therapy in cases of orbital retinoblastoma after local tumor control with chemoreduction and enucleation or exenteration. It is also used following enucleation in patients with involvement of the optic nerve transection, scleral infiltration and orbital extension.\(^4\) With EBRT, Reese Ellsworth stage I tumors have nearly 100% globe salvage rate while Reese Ellsworth stage V tumors have only about 30% chance of globe salvage (Table 20-2).\(^{15,16}\)

The major problems with EBRT are the stunting of the orbital growth, dry eye, cataract, radiation retinopathy and optic neuropathy. EBRT can induce second malignant neoplasms especially in patients with the hereditary form of retinoblastoma. There is a 30% chance of developing another malignancy by the age of 30 years in such patients.\(^{14}\) The risk of developing second malignant neoplasm is higher in children less than 12 months of age.\(^{14}\)

**Chemotherapy**

The introduction of newer chemotherapy protocols has revolutionized the management of retinoblastoma and has dramatically improved the prognosis for life; eye and vision salvage.\(^{17}\) Chemotherapy can be systemic or local. Systemic chemotherapy can be neoadjuvant (chemoreduction), adjuvant for treatment of metastasis, and palliative.\(^{4}\) Local periocular chemotherapy is under trial. Chemotherapy has to be administered under the guidance of an experienced pediatric oncologist with careful monitoring of blood cell counts and systemic health status. Chemoreduction essentially means going back in time, where the large tumor volume is reduced to an extent that it can be treated with focal therapy. Hence, chemoreduction is used in combination with sequential aggressive local therapy (SALT) and is now used extensively as the first line management of retinoblastoma.\(^{18-20}\) This combination of treatment modalities provides for an eye salvage rate of nearly 100% in Reese Ellsworth groups 1 to 4.\(^{21}\) Results are poor, however, in advanced retinoblastoma. About 50% of Reese Ellsworth group 5 tumors ultimately need EBRT and/or enucleation.

Chemoreduction involves standard six cycles of neoadjuvant chemotherapy to reduce the tumor size to facilitate use of local therapy. We use a combination of vincristine, etoposide and carboplatin for 6 cycles (Table 20-3). Chemoreduction is most successful in eyes without associated vitreous and subretinal seeds. In cases with diffuse vitreous seeds, periocular injection of carboplatin as deep posterior subtenon injection may be required in addition for effective tumor control. Periocular carboplatin can penetrate the sclera and achieve effective intravitreal concentration.\(^{22,23}\) This management modality is currently under trial.

Reese Ellsworth group 5 tumors, recurrent tumors and metastasis are currently treated with a higher dose of chemotherapeutic agents. High-dose chemotherapy has been recently applied in the management of orbital extension of retinoblastoma.

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**TABLE 20-2:** Eye salvage rates with external beam radiotherapy and chemoreduction

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<thead>
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<th></th>
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<tr>
<td>I</td>
<td>91%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>II</td>
<td>83%</td>
<td>84%</td>
<td>100%</td>
</tr>
<tr>
<td>III</td>
<td>82%</td>
<td>82%</td>
<td>100%</td>
</tr>
<tr>
<td>IV</td>
<td>62%</td>
<td>43%</td>
<td>100%</td>
</tr>
<tr>
<td>V</td>
<td>29%</td>
<td>666%</td>
<td>78%</td>
</tr>
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</table>
Enucleation

Until recently enucleation was the standard management of advanced unilateral retinoblastoma and the advanced eye of bilateral retinoblastoma. This radical modality has been relegated to the second or third line of management with recent refinements in globe and vision salvaging management options. Enucleation is presently indicated as the primary management modality in eyes with International Classification of intraocular Retinoblastoma Group E eyes, that is, eyes with neovascularization of the iris, secondary glaucoma, anterior chamber tumor invasion, and tumors occupying >75% of the vitreous volume. Tumors associated with hyphema or vitreous hemorrhage where the tumor characteristics can not be visualized are also indications for primary enucleation. It is also indicated in those who fail focal therapy, chemotherapy or external beam radiotherapy.

The surgical technique of enucleation has to be meticulous and it is important to take adequate precautions not to accidentally perforate the eye. The rectus muscles have to be hooked carefully as the sclera is thin at the site of the muscle insertions. Gentle traction with the recti muscle traction sutures helps in prolapsing the globe out of the orbit and in getting a long optic nerve stump. The optic nerve stump should be at least 10 mm long, 15 mm being optimal. It would be easier to cut the optic nerve with a blunt tip tenotomy scissors. If the nerve is cut from the medial approach, a straight tenotomy scissors is useful as the medial orbital wall is straight. The lateral orbital wall being angulated at 45 degrees entails the use of a semi-curved scissor to obtain a long stump of optic nerve. The optic nerve should be cut a little above the apex so as to preserve the structures passing through the superior orbital fissure, which would help in retaining motility of the prosthesis and prevent post operative ptosis. The enucleated eye should be routinely inspected to look for any extraocular extension and optic nerve thickening.

Patients with tumor necrosis and sterile orbital inflammation present a special challenge in enucleation. Imaging should be done routinely for them to rule out any extraocular extension. In cases with no extraocular extension, a short course of systemic and topical steroid given before the surgery helps to control the inflammation and decreases the chance of intraoperative bleeding. Enucleation is also more difficult in these patients because of the scarring of the orbital tissues following inflammation.

Orbital implants are not contraindicated in retinoblastoma and are routinely used. The common materials used to make implants are PMMA, silicon, hydroxy apatite and porous polyethylene. Porous implants are commonly used today because of their unique property of orbital integration, thus providing good centration and better prosthesis motility. Integrated implants, however, are better avoided in situations where post-operative radiotherapy might be required (suspected

<table>
<thead>
<tr>
<th>TABLE 20-3: Chemoreduction regimen and doses for intraocular retinoblastoma</th>
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<tbody>
<tr>
<td><strong>Day 1:</strong> Vincristine + Etoposide + Carboplatin</td>
</tr>
<tr>
<td><strong>Day 2:</strong> Etoposide</td>
</tr>
<tr>
<td><strong>Standard dose (3 weekly, 6 cycles):</strong></td>
</tr>
<tr>
<td>• Vincristine 1.5 mg/m$^2$ (0.05 mg/kg for children ≤ 36 months of age and maximum dose ≤ 2 mg)</td>
</tr>
<tr>
<td>• Etoposide 150 mg/m$^2$ (5 mg/kg for children ≤ 36 months of age)</td>
</tr>
<tr>
<td>• Carboplatin 560 mg/m$^2$ (18.6 mg/kg for children ≤ 36 months of age)</td>
</tr>
<tr>
<td><strong>High-dose (3 weekly, 6-12 cycles):</strong></td>
</tr>
<tr>
<td>• Vincristine 0.025 mg/kg</td>
</tr>
<tr>
<td>• Etoposide 12 mg/kg</td>
</tr>
<tr>
<td>• Carboplatin 28 mg/kg</td>
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</table>
infiltration of the optic nerve transection or extraocular extension), which would be detrimental to implant vascularization.

**Post-enucleation Adjuvant Chemotherapy**

Histopathological examination of the enucleated eyeball is done in all cases, specifically looking for certain high-risk factors. Recent studies have identified certain high-risk factors on histopathology which can reliably predict metastasis (Table 20-4). Systemic metastasis remains the major cause of mortality in patients with retinoblastoma. Hence, patients with high-risk factors require adjuvant chemotherapy to minimize systemic metastasis. Honavar et al have observed a 4% incidence of metastasis in patients with high-risk factors who have received adjuvant chemotherapy, versus 24% incidence in patients who have not received adjuvant chemotherapy. Bone marrow biopsy and cerebrospinal fluid analysis are routinely done in patients with high-risk histopathological factors and intrathecal methotrexate is instituted if the cerebrospinal fluid shows tumor cells.

Adjuvant chemotherapy is also indicated in cases with inadvertent globe perforation during surgery or where intraocular surgery has been done in eyes with unsuspected retinoblastoma.

<table>
<thead>
<tr>
<th>TABLE 20-4: Histopathologic high-risk factors predictive of metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anterior chamber seeding (Figure 20-5A)</td>
</tr>
<tr>
<td>• Iris infiltration</td>
</tr>
<tr>
<td>• Ciliary body infiltration</td>
</tr>
<tr>
<td>• Massive choroidal infiltration (Figure 20-5B)</td>
</tr>
<tr>
<td>• Invasion of the optic nerve lamina cribrosa</td>
</tr>
<tr>
<td>• Retrolaminar optic nerve invasion (Figure 20-5C)</td>
</tr>
<tr>
<td>• Invasion of optic nerve transection</td>
</tr>
<tr>
<td>• Scleral infiltration</td>
</tr>
<tr>
<td>• Extrascleral extension (Figure 20-5D)</td>
</tr>
</tbody>
</table>

**FIGURE 20-5A:** Anterior chamber and iris invasion (H & E stain; 40x)
MANAGEMENT OF ORBITAL RETINOBLASTOMA

Orbital retinoblastoma can be primary (orbital extension of an intraocular tumor at initial presentation), secondary (orbital recurrence following uncomplicated enucleation), accidental (inadvertent globe perforation or intraocular surgery in eyes with unsuspected retinoblastoma), overt (extraocular or optic nerve extension recognized during surgery) and microscopic (extraocular or optic nerve invasion detected on histopathology).4

All cases of suspected orbital retinoblastoma require CT scan or MRI imaging to confirm orbital extension and to look for any associated intracranial extension. A through clinical evaluation should be done in all cases, specifically looking for any regional lymph nodes. A metastatic workup should
also be done in all cases including chest X-ray, ultrasound abdomen, bone marrow biopsy, cerebrospinal fluid cytology and a whole body PET or CT scan if possible.

Management of orbital retinoblastoma requires a combined treatment approach to take care of the local disease, microscopic metastasis and to prevent relapse as well. Our standard management protocol consists of high dose chemoreduction for 3-6 cycles followed by enucleation or exenteration depending on the extent of the residual tumor. Post operative external beam radiotherapy is given for all these patients followed by high dose chemotherapy till 12 cycles.

**METASTATIC RETINOBLASTOMA**

Metastasis is the major cause of retinoblastoma related mortality especially in the developing countries. The major sites of metastases are regional lymph nodes, central nervous system and bone marrow. High dose chemotherapy along with hematopoietic stem cell rescue has shown encouraging results with 67% three year disease free survival. Hematological side effects, diarrhea, ototoxicity and cardiotoxicity are the major side effects. The prognosis however seems to remain poor in patients with central nervous system involvement.

**FOLLOW-UP SCHEDULE**

The usual protocol is to schedule the first examination 3-6 weeks after the initial therapy. In cases where chemoreduction therapy has been administered, the examination should be done every 3 weeks with each cycle of chemotherapy. Patients under focal therapy are evaluated and treated every 4-8 weeks until complete tumor regression. Following tumor regression, subsequent examination should be 3 monthly for the first year, 6 monthly for three years or until the child attains 6 years of age, and yearly thereafter.
GENETIC COUNSELING

Genetics of retinoblastoma is complex and the genetic counseling is often challenging. However, current understanding of the molecular mechanism of the disease suggests that a parent with bilateral retinoblastoma has 45% chance of having an affected child, 85% of whom will have bilateral disease and 15% will be unilateral. Since all the children of parents with unilateral disease carry the germ line mutation, 45% of their children will also develop retinoblastoma. In patients with no family history of retinoblastoma, if the affected child has unilateral retinoblastoma, 1% of the siblings are at risk and 8% of the offspring may develop retinoblastoma. In cases of bilateral retinoblastoma with no positive family history, 6% of the siblings and 40% of the offspring have a chance of developing retinoblastoma.

Recent Advances

The recent work on genetics of retinoblastoma is focused on identification of new mutations and preimplantation genetic testing for families who have children affected with germinal retinoblastoma. Identification of more mutations will help in designing a screening test panel for individuals at risk.

Direct intra-arterial chemotherapy with melphalan has been tried recently in Phase I/II studies in patients with Reese-Ellsworth V eyes and has shown promising results in terms of globe salvage. Further studies are required in this direction to establish the feasibility and efficacy of this procedure.

In summary, the current trend is to provide an individualized (Table 20-5) multispecialty management for patients with retinoblastoma. The recent advances in the management of retinoblastoma have yielded gratifying outcome in terms of preservation of life, salvage of the eye, and optimal residual vision.

<table>
<thead>
<tr>
<th>TABLE 20-5: Current suggested protocol</th>
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</thead>
<tbody>
<tr>
<td><strong>A. Intraocular tumor, Reese-Ellsworth Groups 1 to 4, Unilateral or Bilateral</strong></td>
</tr>
<tr>
<td>1. Focal therapy alone for smaller tumors if the standard tumor size indications are satisfied.</td>
</tr>
<tr>
<td>2. Standard 6 cycle Chemoreduction and sequential aggressive focal therapy for larger tumors and all tumors located in the macular area.</td>
</tr>
<tr>
<td>3. Consider focal therapy for small residual tumor, and plaque brachytherapy/EBRT for large residual tumor if bilateral, and enucleation if unilateral.</td>
</tr>
<tr>
<td><strong>B. Intraocular tumor, Reese-Ellsworth Groups 5A and 5B, Unilateral</strong></td>
</tr>
<tr>
<td>Primary enucleation</td>
</tr>
<tr>
<td><strong>C. Intraocular tumor, Reese-Ellsworth Groups 5A and 5B, Bilateral</strong></td>
</tr>
<tr>
<td>1. High dose chemotherapy and sequential aggressive focal therapy</td>
</tr>
<tr>
<td>2. Consider focal therapy for small residual tumor, and plaque brachytherapy/EBRT for large residual tumor.</td>
</tr>
<tr>
<td><strong>D. Advanced intraocular tumor, unilateral or bilateral, with neovascularization of iris, anterior segment seeds, iris infiltration, necrotic retinoblastoma with orbital inflammation, media opacity precluding tumor visualization, and eyes with no visual potential.</strong></td>
</tr>
<tr>
<td>Primary enucleation</td>
</tr>
<tr>
<td><strong>E. Extraocular tumor</strong></td>
</tr>
<tr>
<td>1. Baseline CT scan / MRI, bone marrow and cerebrospinal fluid cytology</td>
</tr>
<tr>
<td>2. Intrathecal methotrexate if cerebrospinal fluid is positive for tumor cells</td>
</tr>
<tr>
<td>3. High dose Chemotherapy for 6 cycles, followed by enucleation or exenteration, external beam radiotherapy, and continued chemotherapy for 12 cycles</td>
</tr>
<tr>
<td><strong>F. High-risk factors on histopathology</strong></td>
</tr>
<tr>
<td>1. Standard 6 cycle adjuvant chemotherapy</td>
</tr>
<tr>
<td>2. High dose adjuvant chemotherapy and orbital external beam radiotherapy in patients with scleral infiltration, extraocular extension, and optic nerve extension to transection.</td>
</tr>
</tbody>
</table>
Pediatric Intraocular Tumors—I

References

Chapter 21

Pediatric Intraocular Tumors–II
Medulloepithelioma

The first description of this tumor was by Verhoeff who described this tumor as a teratoneuroma in 1904. This rare embryonal tumor originates from the medullary epithelium on the inner layer of the developing optic cup. This tumor is classified into 2 types—teratoid and nonteratoid forms. The nonteratoid form also called as a diktyoma is constituted by medullary epithelial cells. The teratoid form of the tumor contains cartilage, skeletal muscle and brainlike tissue (Figures 21-1 and 21-2). Either of these forms can be benign or malignant. The malignant form has been reported to be more common ranging from 66 to 90%. In the absence of local extraocular extension, distant metastases are rarely seen.
Histopathology reveals the presence of cells arranged in cords with cystic spaces in the lesion (Figure 21-3). These cells resemble the medullary epithelium, the optic cup, pigmented and non pigmented ciliary epithelium, vitreous and neuroglia. The non teratoid variety is also called a diktyoma based on the net-like arrangement of the cells. In the teratoid variety, the primitive medullary neuroepithelium can differentiate into various heterotopic tissues like cartilage, skeletal muscle and brainlike tissues.

The tumor commonly affects children, the mean age of affliction being 4 years. The tumor commonly presents clinically as decreased vision and pain. Sometimes there may be leucocoria or an anterior chamber mass. A ciliary body mass is more likely to occur or rarely a tumor of the optic nerve and retina. Sometimes there may be a lens coloboma in the quadrant of the tumor. This tumor is locally invasive and causes destruction of the surrounding tissues. Secondary cataract, subluxation of lens, cyclitic membrane formation, uveitis, retinal detachment and glaucoma can occur. Whitish opacities may be found in the tumor, these being foci of cartilage and is seen in the teratoid form of medulloepithelioma. The presence of cysts in the tumor is highly suggestive of medulloepithelioma.

Diagnosis is primarily based on clinical features. B-scan shows presence of cysts in the lesion. A-scan may show areas of moderate reflectivity in the tumor. Fluorescein angiography may demonstrate numerous leaking vessels in the tumour. Magnetic resonance imaging reveals hyperintensity on T1-weighted images and hypointensity on T2-weighted images.

Differential diagnosis includes persistent hyperplastic primary vitreous, pars planitis or vascular malformations and tumours like retinoblastoma, melanoma, melanocytoma, neuroblastoma or teratoma.

Management is by primary enucleation. Local resection for anteriorly located tumors has been proposed, but the friable nature and frequent recurrence makes local resection unfavorable. In cases with extraocular extension, exenteration is required. Chemotherapy and radiation are not effective in the management of this tumor.

Prognosis for life is good except when extraocular extension is present.
Choroidal Hemangioma

Choroidal hemangioma is the most common vascular tumor of the choroid. This benign tumor is classified into two types—circumscribed and diffuse. The circumscribed form is commoner than the diffuse form. Witschel and Font reported that 63% were circumscribed and 37% diffuse.9

Histopathology reveals the presence of microscopically congested vessels and absence of cellular proliferation in the blood vessel walls.10 The tumor has sharply demarcated margins. This tumor is supposed to be a congenital hamartomatous tumor. Arteriovenous shunts develop during embryogenesis and disappear during normal development and have been implicated in the pathogenesis of this tumor.

The circumscribed variety usually presents in adulthood, in contrast to the diffuse variety which presents in childhood. These tumors usually present with blurring of vision, metamorphopsia due to serous fluid or hyperopia due to retinal elevation by the tumor.11 These are typically non pigmented elevated masses with an orange red color. Most of them are unilateral and solitary. Commonly located posterior to the equator as an orange-red mass, the posterior margin of the majority of these lesions is located within two disc diameters of the optic disc or fovea.12 Most of these lesions are less than 19 mm in diameter and have a mean elevation of 3 mm.12 Visual deterioration commonly results from exudative retinal detachment, hyperopia due to the tumor, macular edema, retinal degeneration, loss of photoreceptors, chorioretinal adhesions and cystoid degeneration.

Diagnosis in most cases is clinical. Ultrasound B scan shows acoustic solidity without choroidal excavation and high internal reflectivity within the tumor on A scan images. Fluorescein angiography in the early arterial phase shows hyperfluorescence of the large irregular choroidal vessels within the tumour, in the early venous phase shows progressive leakage from the large choroidal vessels and the late angiogram shows staining as a result of collection of fluorescein in the cystic spaces in the overlying sensory retina.13 Indocyanine green angiography shows accumulation of dye early with subsequent washout later.14 Magnetic resonance imaging shows the tumor to be hyperintense to the vitreous on T1 weighted and isointense to the vitreous on T2 weighted images.

Differential diagnosis includes amelanotic melanoma, choroidal osteoma, choroidal metastasis, retinoblastoma and posterior scleritis.

Most tumors do not progress and do not require treatment. Vision threatening lesions especially those associated with subretinal fluid need treatment. Laser photocoagulation was noted to be effective in 62 to 100% of cases.15 Resorption of subretinal fluid occurs with readhesion of the neurosensory retina and retinal pigment epithelium. Different forms of radiation have also been used including external beam radiation, plaque radiotherapy and proton beam radiation.16,17 Early treatment with plaque radiotherapy has been noted to be beneficial.16 Photodynamic therapy has been noted to be safe for tumor located at the fovea.18,19 Transpupillary thermotherapy has been noted to reduce the occurrence of subretinal fluid.20

About 50% of patients have a final visual acuity of 20/200 or worse.11 The prognosis for life is excellent. Amblyopia results due to the hyperopia induced by the tumor.11 Early treatment helps in resolution of subretinal fluid and induced hyperopia.

Congenital Hypertrophy of the Retinal Pigment Epithelium

Congenital hypertrophy of the retinal pigment epithelium (CHRPE) was first described by Buettner in 1975.21 Presumed to be congenital, this tumor is generally asymptomatic and discovered during routine ophthalmoscopy.
There are two forms of the lesion – solitary and multifocal. The solitary or isolated form is seen in the normal population. The solitary or isolated form is seen as deeply pigmented, flat lesion with sharply demarcated margins; some lesions have a surrounding halo. These have been noted even in newborns. Most patients have normal vision and normal anterior segments. Sometimes the lesion is completely nonpigmented and appears as a flat yellow-white well circumscribed defect at the level of the RPE and is known as a ‘polar bear’ spot. Most commonly unilateral, this may be bilateral in 1-2% of cases.22 Approximately 70% of these lesions are located in the temporal quadrant.22 These lesions are stationary and do not demonstrate progressive growth. The multifocal variety can assume 2 forms—one form is unilateral with lesions resembling animal footprints. These lesions are typically seen in one sector of the fundus and are referred to as “bear tracks”. These appear as well demarcated, flat grey to black lesions, with the larger lesions being more peripheral. The other variety is bilateral and the lesions are randomly distributed in the fundus. This form is associated with familial adenomatous polyposis (FAP).23

Gardner’s syndrome consists of a triad of familial adenomatous polyposis of the intestine, skeletal hamartomas and other soft tissue tumors.24 A close relationship exists between familial adenomatous polyposis, Gardner’s syndrome and CHRPE.25 Hundred percent of untreated affected individuals with familial adenomatous polyposis develop carcinoma of the colon or rectum before the age of 50 years. FAP is genetically inherited, autosomal dominant with more than 100 polyps of the colon and rectum. It affects approximately 1 in 10000 individuals and accounts for 1% of all colon cancers.26 There is also an increased incidence of this form of CHRPE in offspring of patients with familial adenomatous polyposis. The ocular lesions in FAP have been reported to be bilateral in 86% of cases.26 The presence of more than four fundus lesions and bilateral lesions has been considered a strong indicator of Gardner’s syndrome. The gene responsible for FAP has been mapped to chromosome 5.28 This is a tumor suppressor gene and plays a role in tumor formation in the gastrointestinal tract, soft tissue and bone. In addition it may lead to defects in RPE melanogenesis and foveal RPE lesions.27,28

Histopathology reveals the presence of a focal area of hypertrophied RPE cells with densely packed round pigment granules and areas of photoreceptor degeneration. In some areas the pigment granules are very sparse and correspond to the lacunae.29 Electron microscopy shows the absence of autofluorescent lipofuscin granules in CHRPE lesions, indicating lack of catabolic functions of these RPE cells.30

The clinical features are characteristic and CHRPE can be diagnosed on fundus examination in most cases. Fluorescein angiography shows hypofluorescence due to the deeply pigmented nature of the lesion. The lacunae in the lesion act as window defects and demonstrate early and late hyperfluorescence. Visual field testing demonstrates a scotoma corresponding to the lesion which occurs due to the loss of photoreceptors. Ultrasonography is of little value as the lesions are flat.

Differential diagnosis of a solitary lesion includes choroidal nevus and choroidal melanoma. Chorioretinal scars, secondary hyperplasia of the RPE, sickle cell disease (sunburst lesions), sector retinitis pigmentosa and pigmented retinopathies should be considered in the differential diagnosis. Multiple bilateral CHRPE lesions indicate a suspicion of underlying polyposis syndrome.

Treatment is not indicated for either solitary or multifocal CHRPE lesions. Periodic observation is needed. Development of nodular lesions from CHRPE has been reported possibly representing reactive RPE proliferation or an acquired adenoma.31 There has been just one case of adenocarcinoma reported to develop from CHRPE.32
The prognosis for life and vision is excellent in solitary lesions. In cases associated with Gardner’s syndrome the systemic prognosis depends on the risk of malignant transformation of the intestinal polyps.

**Combined Hamartoma of the Retina and Retinal Pigment Epithelium**

Combined hamartoma of the retina and retinal pigment epithelium is a rare lesion. A hamartoma is a benign proliferation of cells native to the affected area. The first description of this lesion was by Gass in 1973. Many cases are diagnosed in children and infants and this lends support to the hypothesis that this is a congenital lesion. Combined hamartoma involves the sensory retina, retinal pigment epithelium, the retinal vasculature and the overlying vitreous.

Histopathology reveals thickening of the sensory retina and optic nerve and replacement of these by glial cells, vascular tissue and sheets of pigment epithelial cells. Hyperplastic RPE cells migrate into the retina. The retinal surface is folded due to retinal gliosis and is associated with tortuous retinal vessels. Association of combined hamartoma with neurofibromatosis, tuberous sclerosis, incontinentia pigmenti, optic disc drusen, disc colobomas, Gorlin syndrome and sickle cell anemia has been reported, indicating a possible developmental etiology.

The most frequent presentation of combined hamartoma is with painless loss of vision; other presenting features include metamorphopsia, floaters, strabismus. Many cases are diagnosed in children and infants, indicating a possible congenital origin. Clinical presentation varies depending on a juxtapapillary location or peripheral location. The juxtapapillary lesions are more common in males who develop painless, blurred vision. A typical gray white mass with pigmentation and vessels is seen adjacent to or overlying the disc. The larger retinal vessels are stretched and tortuous and obscured by fibroglial tissue at the vitreoretinal interface. The peripheral lesion appears as an elevated ridge concentric to the optic disc margin and produces dragging of the retinal vessels towards the lesion. Combined hamartoma may also remain undetected and be seen as an incidental finding during fundus examination. Usually unilateral, combined hamartoma may rarely be bilateral when associated with neurofibromatosis. This is a stationary lesion, though increase in size has been reported. Secondary complications can arise predominantly due to vitreoretinal traction and include retinal holes, retinoschisis, vitreous and retinal hemorrhage and choroidal neovascularization.

Diagnosis is mainly based on the clinical appearance. Fluorescein angiography is useful in evaluating ocular hamartoma. Arterial phase shows hypofluorescence, venous phase shows distorted retinal vessels around the margins of the lesion, the central position remaining hypofluorescent. The late phase shows diffuse staining of the mass.

Optical coherence tomography shows an elevated hyperreflective mass with hyporeflective shadowing of the underlying tissues and cystoid macular edema.

Differential diagnosis includes epiretinal membrane; pigmentation and elevation are more in favour of a hamartoma. Other lesions which may be considered include choroidal melanoma, retinoblastoma and toxocariasis.

In the absence of any definite treatment, therapy has been directed to treatment of amblyopia. Pars plana vitrectomy and membrane peeling have not demonstrated any improvement in the visual acuity.

Prognosis for life is good with no reports of malignant transformation. However lesions close to the disc and macula can reduce the vision to less than 20/200 due to foveal traction.
Phakomatoses

The phakomatoses (systemic hamartoses) are a group of syndromes with variable clinical manifestations involving the ocular region, skin, central nervous system and viscera. van der Hoeve in 1932 used the term “phakoma” to indicate a birth mark. Most of the phakomatoses have an autosomal dominant mode of inheritance often with incomplete penetrance. However in Sturge Weber syndrome and Wyburn Mason syndrome heredity does not play a role. The tumors that occur in these syndromes are generally benign.

TUBEROUS SCLEROSIS

In 1880, Bourneville described this rare syndrome characterized by a triad of features- adenoma sebaceum, epilepsy and cognitive developmental deficits. The incidence has been estimated to be 1 in 15,000 live births. The national Tubercous Sclerosis association has laid down diagnostic criteria based on the presence of one or more of the following features: adenoma sebaceum, ungular fibroma, cortical tubers, subendymal nodules, retinal astrocytic hamartoma, cardiac rhabdomyoma, ashleaf skin patches and infantile spasms.

This is an autosomal dominant condition with incomplete penetrance. The TSC2 gene produces the protein tuberin, the TSC1 gene produces hamartin. Both these proteins are tumor suppressors and act in synergy to regulate cell growth and differentiation.

Histopathology reveals the presence of spindle shaped fibrous astrocytes arising from the nerve fiber layer of the retina. Larger lesions may have areas of calcific degeneration and contain cystic spaces with serous fluid or blood.

The most common ocular feature in tuberous sclerosis is a retinal astrocytic hamartoma. This benign lesion can also occur in patients with neurofibromatosis and rarely in the normal population. Ocular lesions have been noticed in the first few weeks of life. In most cases this tumor is congenital and non progressive. Some have demonstrated slow growth with vitreous seeding and vitreous hemorrhage. Clinically there are three forms. The first type is more common in children and is seen as a flat, smooth translucent lesion. The second type seen in older patients is nodular, elevated and calcified. These are seen to be whitish in color with a clusterlike appearance. The third type exhibits features of both and evolves over time into a mulberry like cluster. Secondary changes include vitreous hemorrhage, vitreous seeding and vitreous traction at the tumor surface.

Other ocular manifestations that have been described include fundus depigmentation, subconjunctival nodules, eyelid angiofibroma, ocular coloboma and hamartomas of the iris and ciliary epithelium. Nonocular features include facial angiofibroma, ungular fibroma, benign lesions of the CNS (cortical tubers and cerebral astrocytoma) and hamartomas of the liver, heart, kidneys and lungs. Skin lesions include ashleaf spots, which are hypopigmented macules, which are sometimes present since birth. Shagreen patches are thickened, redundant skin present over the lumbosacral region, trunk, extremities and face. Adenoma sebaceum (facial angiofibroma) is seen as multiple, yellow red papules which are slightly elevated and rubbery. These lesions mimic acne however they occur in the prepubertal years and assume a butterfly distribution on the face and involve the upper lid. Subependymal and cortical hamartomas can occur and are typically calcified. Seizures and developmental delay are commonly associated with this syndrome.

Diagnosis is clinical based on the constellation of features. Fluorescein angiography reveals hypofluorescence in the early phases and staining in the late phase. On ultrasonography, a mass of
medium reflectivity is seen on the A-scan and focal calcifications are seen on the B-scan. Neuroimaging is useful to demonstrate the subependymal nodules of tuberous sclerosis.

The differential diagnosis includes retinoblastoma, amelanotic choroidal melanoma, Coats’ disease, myelinated nerve fibers and choroiditis.

In most cases no treatment is needed. Most cases need treatment for seizures, skin lesions and therapy for the associated developmental deficits. The prognosis for vision is good, unless the lesion involves the fovea. Systemic morbidity is due to occurrence of seizures and hydrocephalus or due to lesions in the kidneys, heart and lungs.

**NEUROFIBROMATOSIS**

This heritable neurocutaneous syndrome was described by von Recklinghausen in his classic monograph in 1882.46 There are 2 types, neurofibromatosis (NF) 1 and 2. NF-1 has peripheral and cutaneous lesions and astrocytic hamartomas in the retina. NF-2 has central lesions especially acoustic neuromas and can be associated with posterior subcapsular cataract. NF-1 affects about 1 in 4000 and NF-2 1 in 50,000 individuals in the general population.

NF-1 and NF-2 are autosomal dominant with nearly 80% penetrance. About 50% of cases of NF-1 are sporadic. The genetic abnormality in NF-1 has been localized to chromosome 17 and for NF-2 to chromosome 22.47 The NF-1 gene codes for protein neurofibromin which regulates cellular proliferation and tumor suppression.47

NF-1 affects many organs including the eye, skin and CNS. This is a disorder of the neuroectodermal cells. The tumors originate from the neural crest cells, the sensory neurons, Schwann cells and melanocytes. The retinal tumor associated with NF-1 includes retinal astrocytic hamartoma, retinal capillary hemangioma and combined hamartoma of the retina and RPE.48

The retinal astrocytic hamartomas in NF-1 are benign and located in close proximity to the optic disc. These appear as white mulberry type clusters. Complications that may occur include neovascular glaucoma and retinal detachment.48 Retinal capillary hemangiomas and combined hamartomas of the retina and RPE have also been described. Optic nerve glioma can cause significant vision loss and proptosis and affects young children with severe visual loss or proptosis.48 Hypopigmented iris lesions “Lisch nodules” are seen on dark irides, these may be darker in light irides. These represent glial- melanocytic hamartomas. These increase in number with age and are universal in all adults with NF-1. In about one third of patients, flat variably pigmented choroidal masses are seen.49 NF-1 may manifest with glaucoma due to trabecular meshwork abnormalities or angle closure. This is usually ipsilateral to the eyelid involved by plexiform neurofibroma.

The most common cutaneous finding includes café-au-lait spots or flat hypopigmented macules which increase in number and size with age. Subcutaneous neurofibromas present as nodular lesions and again increase with age. Plexiform neurofibroma presents with an S-shaped ptosis. Pheochromocytomas, CNS tumors and visceral tumours like gastrointestinal neurofibromas are also associated with NF-1.

NF-2 manifests with acoustic neuromas, neurofibroma, meningioma, glioma and/or schwannoma. The most common eye finding is cortical or posterior subcapsular cataract.

Diagnosis is clinical in most instances and complete ocular examination is essential to evaluate optic nerve function, iris, disc appearance, choroid and intraocular pressure. Fluorescein angiography of a retinal astrocytoma reveals hypofluorescence in the early phase followed by late staining. B-scan ultrasonography reveals focal calcification in the lesions. Routine MRI scanning is not essential though it may be helpful in evaluating the extent of optic nerve and optic chiasm gliomas.
**VON HIPPEL-LINDAU SYNDROME (VHL)**

This autosomal dominant syndrome is characterized by angiomas of the retina, cerebellum, brain stem and angiomas of the kidney, liver and pancreas. The incidence of VHL has been estimated to be 1 in 36,000 births. About 20 percent of the cases have a positive family history.

The lesions found in the retina in VHL are vascular masses composed of retinal capillaries with abnormal fenestrations. Interstitial cells separate the capillary channels. These lesions can grow into the vitreous or outward towards the choroid. These are hemangioblastomas identical to those found in the CNS.

Tumor formation in VHL disease follows Knudson’s two hit hypothesis. The VHL gene is a tumor suppressor gene mapped to chromosome 3p25 and down regulates the production of vascular endothelial growth factor. This autosomal dominant disease has variable penetrance. Analysis of the mutations can reveal the genetic abnormality in 75% of cases.

Clinical presentation is with decreased visual acuity or the tumor may be discovered incidentally. Presence of subretinal fluid or retinal detachment may lead to a visual field defect. The lesion is seen as a round red orange mass. Dilated and tortuous feeding and draining vessels traveling between the lesion and optic nerve is present. The most common location is the temporal retinal periphery, optic disc and rarely at the posterior pole. Presence of bilateral, multiple retinal masses is indicative of VHL syndrome. Two thirds of patients with VHL disease have retinal hemangioblastoma. Secondary changes which may occur include retinal detachment, retinal traction, secondary glaucoma, cataract, vitreous hemorrhage and disc and retinal neovascularization. Systemic associations include cerebellar hemangioblastoma in 25% of cases. Cysts in the pancreas, kidney, liver, adrenal glands and epididymis may be present. Renal cell carcinoma occurs in 22% of cases and pheochromocytoma in 10% of cases.

Diagnosis is established by the presence of peripheral lesions with dilated feeding and draining vessels. Fluorescein angiography in the early phase shows rapid filling, the mid phase shows staining and the late frames show leakage of the dye from the tumor into the vitreous. A detailed family history needs to be elicited. MRI scan of the head and spine and a CT scan of the abdomen should be performed. Differential diagnosis includes Coats’ disease, familial exudative vitreoretinopathy, retinoblastoma, sickle cell retinopathy and retinal cavernous hemangioma.

Management of small asymptomatic lesions is by observation. More posterior lesions can be treated by laser photocoagulation, photodynamic therapy or transpupillary thermotherapy. Larger and anterior lesions can be treated by cryotherapy. In the presence of retinal detachment, scleral bucking or vitrectomy may be needed. VEGF inhibitors have also been found to be effective in reducing associated cystoid macular edema. Long-term observation and follow-up is essential to detect any new tumors or growth of lesions.

This tumor is associated with a poor prognosis. The severity of vision loss is more when the lesions present early in life. Presence of nonocular malignancies like renal cell carcinoma in cases with VHL disease indicates a worse prognosis. The most common causes of death in VHL are cerebellar hemangioblastoma and renal cell carcinoma.

**STURGE-WEBER SYNDROME**

The first description of this syndrome was by Sturge in 1879, he described a syndrome composed of facial hemangioma, ipsilateral bupthalmos and contralateral seizures. In 1884, Milles noted the association of choroidal hemangioma with this syndrome. Weber described the clinical manifestations in greater detail and this entity was known as Sturge-Weber syndrome (SWS).
SWS possibly occurs due to a defect in the neural crest cell migration and differentiation. Increased production of angiogenic factors may play a role in the pathogenesis of this disease. There are no known environmental or genetic factors associated with this syndrome.

The ocular features can manifest in the eyelid, conjunctiva, glaucoma, choroid and retina. Involvement of the eyelid is usually unilateral. Characteristically these cutaneous lesions or nevus flammeus are seen as sharply demarcated portwine colored lesions involving the scalp, forehead, eyelids and lower face. Classically these lesions involve the distribution of the fifth cranial nerve. These lesions thicken with time and there can be associated hypertrophy of underlying bone and soft tissues. Vascular malformations may be present in the conjunctival and episcleral blood vessels. These occur ipsilateral to the facial hemangioma. Glaucoma is possibly the most common and serious ocular manifestation of SWS. The glaucoma occurs on the side of the facial hemangioma. The chances of glaucoma are more if the nevus flammeus involves the upper eyelid. Elevation of intraocular pressure occurs secondary to increased episcleral venous pressure or a developmental defect of the angle. Glaucoma can also occur secondary to neovascularization of the iris and angle leading to extensive peripheral anterior synechiae. Fundus examination of patients with choroidal hemangioma reveals a diffuse red or orange thickening of the choroid, this thickening being maximum at the posterior pole. A bright red pupillary reflex is present in the involved eye and this has been called as the “tomato catsup” fundus. Retinal vessels may be dilated and tortuous. In addition there may be exudative retinal detachment with cystoid degeneration of the macula. Total retinal detachment with secondary cataract and leukokoria may be observed.

The typical CNS lesion is a diffuse leptomeningeal hemangioma that is ipsilateral to the facial hemangioma. This lesion is more pronounced in the occipital region. The adjacent cerebral cortex may show secondary calcification which is seen as a radioopaque double line, the “railroad track” sign. Cerebral atrophy may be present ipsilateral to the skin lesions. This can lead to seizures, cognitive developmental deficits, hemiplegia and focal neurologic deficits.

Diagnosis is based on the clinical features. B-scan ultrasonography can demonstrate marked choroidal thickening, with overlying retinal detachment while A-scan demonstrates high internal reflectivity. Fluorescein angiography reveals early filling of the tumor with late leakage. CT demonstrates abnormal choroidal thickening with enhancement of the globe, while MRI demonstrates distinctive high signal on T1 weighted images.

Children with diffuse choroidal hemangioma may demonstrate hyperopia, exudative retinal detachment and glaucoma. Amblyopia therapy may be needed. The skin lesions can be treated with laser to improve cosmesis. Visual prognosis is good in cases of Sturge-Weber syndrome associated with glaucoma. Exudative retinal detachment associated with SWS has been treated with laser photocoagulation. External beam radiotherapy has been used with successful results. The nodular component of the diffuse choroidal hemangioma has been treated with plaque brachytherapy with successful outcome.

**WYBURN-MASON SYNDROME**

The initial description of this syndrome was by Wyburn-Mason in 1943. This is characterized by arteriovenous malformations of the retina (called as racemose hemangioma) and the CNS. AV malformations can occur in any part of the body including the skin, nasopharynx, orbit, lung and spine. Similar to Sturge-Weber syndrome, this does not exhibit a hereditary pattern.
Pediatric Intraocular Tumors–II

Histopathology reveals the presence of vessel wall thickening and presence of dilated vascular channels occupying the entire thickness of the retina. Cystoid changes may be observed with loss of ganglion cell bodies and axons.

The most common presentation is with reduced visual acuity. The lesions have been divided into 3 groups. Group I comprises patients where there is interposition of an abnormal capillary plexus between a major communicating artery and vein. Group II patients demonstrate direct arteriovenous communication without the interposition of capillary elements. Group III patients demonstrate many anastomosing channels of large calibre. They are also likely to have perivascular sheathing, exudation and pigmentary changes. The visual acuity is likely to be poor. In addition they are likely to have CNS lesions. Usually there is no progression of the lesion with time. AV malformations in the CNS are more likely to occur ipsilateral to the retinal lesions. Visual field defects may be present. Complications that are likely to occur include intraocular hemorrhage, secondary neovascular glaucoma, macular hole and vitreous hemorrhage. Exudation and retinal detachment are unusual. CNS lesions can manifest with cranial nerve palsies and headaches.

Diagnosis is usually clinical. Fluorescein angiography demonstrates rapid filling of the vascular lesions. Differential diagnoses include retinal telangiectasias and collaterals.

Treatment is generally not required and the efficacy of laser photocoagulation or cryotherapy has not been established. Prognosis is generally good both for vision and for life. In patients with severe manifestations, the associated CNS malformations can lead to cerebral hemorrhage.

Juvenile Xanthogranuloma

Juvenile xanthogranuloma (JXG) is a benign tumor of young children which commonly affects the skin and presents as multiple orange papules occurring in crops and regressing spontaneously. In most cases the eyes are not involved, however rarely the iris, ciliary body, choroid and optic disc may be involved. Involvement is unilateral in most cases. More than 80% of the cases occur in the first year of life.

Zimmerman identified five presenting clinical patterns of intraocular involvement in infants and young children with JXG in his case series of 53 patients, which include an asymptomatic localized or diffuse iris tumor, unilateral glaucoma, spontaneous hyphema, red eye with signs of uveitis, and congenital or acquired iris heterochromia. Iris involvement is typically seen as a tumorous nodule or diffuse stromal thickening. Spontaneous bleed with occurrence of a hyphema is possibly the most common presentation. Secondary glaucoma can occur due to tumor infiltration of the anterior chamber angle or from obstruction of aqueous outflow by blood in the anterior chamber. Elevation of intraocular pressure can lead to buphthalmos. Heterochromia iridis can occur due to infiltration of the iris by blood and may be segmental (Figures 21-4 and 21-5).

Histopathology reveals a cellular mass with normal appearing histiocytes along with occasional inflammatory cells including lymphocytes, eosinophils, and Touton type multinucleated giant cells. Typically, JXG lesions are distinguished by the lack of staining for S-100 protein. These also show positivity for macrophage markers, such as CD68 and HAM 56, but lack in Birbeck granules on electron microscopy.

Diagnosis in most cases is by the clinical features of an iris or ciliary body mass with typical cutaneous lesions. Fine needle aspiration biopsy of the anterior chamber mass with careful cytologic analysis can help establish the diagnosis. Diagnosis has also been established following enucleation.
This tumor responds well to topical or subconjunctival corticosteroids and systemic steroids. Other treatment modalities include local excision, irradiation and combined irradiation with corticosteroids. The prognosis for life is excellent in most cases, while in cases with mild ocular involvement the visual prognosis is good. In cases with secondary glaucoma, the visual prognosis is poor.

**Melanocytoma**

This heavily pigmented tumor lies partly or completely within the optic nerve head or uveal tract. This has been described as a specific variant of nevus and is composed of large, round, deeply
pigmented melanocytes with benign cytologic features (Figures 21-6 and 21-7). This tumor is present since birth but is usually detected at a mean age of 50 years. Most patients are usually asymptomatic, however if the tumor is fairly large, they may experience blurred vision. Progressive but reversible loss of visual acuity can occur secondary to necrosis of the tumor or obstruction of adjacent blood vessels. Clinically this appears as an elevated black or brown lesion located eccentrically over the edge of the optic disc. The inferior portion of the disc is involved in two-thirds of the cases. In some cases a choroidal nevus appears to be abutting the melanocytoma, this is part of the tumor but appears less distinct as it lies beneath the RPE. The differential diagnoses include juxtapapillary choroidal melanoma, choroidal nevus, hyperplasia of RPE and combined hamartoma of the retina and RPE. Histologically there are two types of cells in melanocytomas, type I are large, deeply pigmented round with large melanosomes (Figure 21-8) and type II are smaller, less pigmented spindle cells with smaller melanosomes. Type II cells are more metabolically active and possibly undergo malignant transformation rarely.
Diagnosis is based on the ophthalmoscopic features. Continuous growth and visual loss may be suggestive of malignant transformation. Fluorescein angiography demonstrates hypofluorescence. Visual field evaluation demonstrates enlargement of the blind spot, nerve fiber bundle defects and nasal step. Prognosis for vision is good. This tumor is benign, though few cases have undergone malignant transformation (Figures 21-9 and 21-10).

**Malignant Melanoma**

Malignant melanoma is the most common intraocular tumor in adults, however uveal melanoma is rare in children. The incidence has been reported to be 1.1% in patients younger than 20 years of age.
Ocular melanocytosis is nine times more common in young patients with uveal melanoma than in the general population with uveal melanoma. Annual follow-up is recommended for all patients with ocular melanocytosis. In addition to ocular melanocytosis there could be presence of dysplastic nevi syndrome or cutaneous melanoma. Nearly 50% of the lesions can present on the iris. The five year survival for these patients is better than for adults, though the fifteen-year survival is the same as in adults.75

References

58. Weber FP. Right-sided hemihypertrophy resulting from right sided congenital spastic hemiplegia with a morbid condition of left side of the brain revealed by radiogram. J Neurol Psycho-pathol (Lond) 1922;37:301-11.
Ocular Manifestations of HIV/AIDS
Introduction

Acquired immunodeficiency syndrome (AIDS) has emerged as pandemic affecting large parts of the world with around more than 40 million people afflicted by this infection. Globally, since the first AIDS case was detected in USA in 1981, the AIDS epidemic continues its expansion across the globe with approximately 16000 new infections a day. India has rapidly become the country with the second highest population of human immunodeficiency virus (HIV) positive individuals numbering 4 million by the end of 2001. Since the report of the first case of HIV in 1987, AIDS epidemic has become the most serious Public health problem in India in recent times.

Since 1981 the pandemic has spread from developed to underdeveloped countries, high risk groups to general population, urban to rural population, more young people in the productive age group are affected. The epidemic will pose a challenge to all practitioners of medicine including ophthalmologists. HIV is a public health problem, a pandemic that threatens the very existence of much of the globe. Progress has been probably far greater in this field than any other area of medicine in recent years, and the lessons learned from HIV research have broad application to other fields of medicine. Up to 50-75% of patients have at least one ocular manifestation in their lifetime. Recognizing these manifestations at an early stage, performing appropriate laboratory investigations and early effective treatment will help in reducing the morbidity and mortality of AIDS.

Ocular Manifestations of HIV/AIDS

HIV disease progresses from asymptomatic HIV infection to severe immunologic dysfunction in patients with AIDS. Eventually, the patient’s failing immunity leads to the opportunistic infections and malignancies characteristic of AIDS. In addition, direct effects of HIV, particularly on the central nervous system (CNS) may become apparent.

Ocular lesions associated with AIDS were first described by Gary N Holland in 1981. Ocular disorders are among the common manifestations of AIDS.

The lifetime cumulative rate of at least one abnormal ocular lesion ranges from 52-100% in a HIV positive person. Up to 57% of patients will show some abnormal ocular lesion within one year of positive diagnosis of HIV infections.

Disorders fall into four major categories: (i) lesions related to microvascular disease, (ii) opportunistic ocular infections, (iii) neoplasms and (iv) neuro-ophthalmic abnormalities (Table 22-1). The more severe ophthalmic disorders associated with AIDS add greatly to the morbidity of the syndrome. Visual morbidity can be severe, and blindness has been suggested as a leading cause of suicide in those with AIDS.

Infectious Ocular Manifestations

ANTEERIOR SEGMENT MANIFESTATIONS

Numerous pathogens, many with unusual clinical presentations, can infect the anterior segment, ocular surface and adnexae in the setting of HIV-associated disorders. Some of the entities differ a lot in their clinical presentation in HIV patients compared to non-HIV population. Lesions such as conjunctival and adnexal Kaposi’s sarcoma, microsporidial and nocardial keratitis are peculiar in
### TABLE 22-1: Classification of ocular complications of AIDS

<table>
<thead>
<tr>
<th>HIV microvasculopathy</th>
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</thead>
<tbody>
<tr>
<td><strong>Conjunctival</strong>—Dilated capillaries, comma shaped tortuosity, microaneurysms</td>
</tr>
<tr>
<td><strong>Retinal</strong>—Cotton wool spots, retinal hemorrhages, microaneurysms, Roth spots, ischemic maculopathy</td>
</tr>
<tr>
<td><strong>Optic nerve</strong>—Ischemic optic atrophy</td>
</tr>
<tr>
<td><strong>Opportunistic retinal and choroidal pathogens</strong></td>
</tr>
<tr>
<td>Cytomegalovirus, <em>Cryptococcus neoformans</em>, <em>Toxoplasma gondii</em>, <em>Pneumocystis carinii</em>, herpes simplex, varicella zoster</td>
</tr>
<tr>
<td><strong>Opportunistic ocular adnexal / external pathogens</strong></td>
</tr>
<tr>
<td>Herpes simplex, varicella zoster, cytomegalovirus, <em>Microsporidia</em>, <em>Nocardia</em>, <em>Candida</em>, <em>Rhizopus</em>, <em>Mucor</em>, <em>Molluscum contagiosum</em>, <em>Chlamydia trachomatis</em> (L2, LGV)</td>
</tr>
<tr>
<td><strong>Neuro-ophthalmic signs of intracranial disease</strong></td>
</tr>
<tr>
<td>Cranial nerve palsies, papilledema, visual field defects, optic atrophy, pupillary abnormalities</td>
</tr>
<tr>
<td><strong>Neoplasms</strong></td>
</tr>
<tr>
<td>Kaposi’s sarcoma, conjunctival intraepithelial neoplasia, squamous cell carcinoma, primary CNS and ocular lymphoma</td>
</tr>
<tr>
<td><strong>Other complications</strong></td>
</tr>
<tr>
<td>Retinal vasculitis, vascular occlusions, immune recovery vitritis, choroidal effusion, orbital pseudotumors</td>
</tr>
<tr>
<td><strong>Drug reactions</strong></td>
</tr>
<tr>
<td>Steven Johnson’s syndrome, retrobulbar neuritis, optic neuritis, hypotony, glaucoma, iridocyclitis</td>
</tr>
</tbody>
</table>

HIV patients. Patients are surviving longer due to highly active antiretroviral therapy (HAART) and this may lead to an increased prevalence of anterior segment and external ocular disorders. In addition, the evaluation and management of disorders such as blepharitis and dry eye, which were previously overshadowed by more severe, blinding disorders, may demand increased attention, as the general health of this population improves.8

### HERPES ZOSTER OPHTHALMICUS (HZO)

Herpes zoster ophthalmicus (HZO), caused by the varicella-zoster virus (VZV), is typically a disease of the elderly. If present in any young person, HIV infection should be suspected. HZO may be the first manifestation of HIV infection and appears to predict increased risk for the development of AIDS in those already infected with HIV.9 In the HIV-infected patient, the course is often more severe and prolonged,10 with active virus being cultured from corneal scrapings weeks after the onset of HZO. Chronic VZV epithelial keratitis can be difficult to treat. This can sometimes progress to bacterial and fungal corneal super infection and cause complications. HZO should be treated with systemic acyclovir (10 mg/kg every 8 hr IV or 600 to 800 mg by mouth 5 times/day), and the patient should be followed closely for evidence of disseminated infection. Topical steroids may be warranted for uveitis, but systemic steroids should be avoided to prevent further suppression of the immune system.

### HERPES SIMPLEX VIRUS (HSV)

Herpes simplex virus (HSV) keratitis (Figure 22-1) occurs in HIV-infected patients,11 although its incidence may not be increased compared with those not infected with HIV. HSV keratitis in persons with AIDS appears to exhibit a prolonged course, and multiple recurrences are common.11 Young et al observed that HSV in AIDS patients tends to be somewhat atypical. There is a predilection for marginal as opposed to central epithelial keratitis. More resistant to therapy, with median healing time after initiation of topical antivirals alone being 3 weeks compared with less than 2 weeks in
immunocompetent patients. Peripheral location of the geographic or dendritic ulcers may contribute to the delayed healing time. A retrospective cohort study confirmed some, but not all, of the observations made by Young and associates.¹²

Patients whose corneas are compromised by viral infections, trichiasis, or other insults may develop severe secondary bacterial infections. Treatment is with topical antivirals. The course and presentation of HSV keratitis in HIV infected individuals is no different than in the general population, except for an increased risk of recurrence and a relative lack of stromal inflammation.⁸

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum is caused by a DNA virus of the Poxviridae group that produces pearly white, centrally umbilicated skin papules 3 to 5 mm in diameter. The lid margin is involved; a follicular conjunctivitis or keratitis may be seen. In normal hosts, the infection is self-limited, fewer than 10 lesions being present on the face and eyelids. Resolution can sometimes occur within 3 to 12 months of immune reconstitution, although excision, curettage or focal cryotherapy is curative. Immune reconstitution does not necessarily prevent recurrence of molluscum contagiosum, but if new lesions develop, they most likely will be less severe, as seen in immunocompetent individuals.⁸ In the patient with AIDS, lesions have rapid onset, are more numerous, and are larger than in normal hosts and tend to be more resistant to standard therapies.¹³ Although HIV-infected individuals often suffer from multiple molluscum contagiosum lesions of the eyelids, the ocular surface sequelae that plague affected immunocompetent individuals frequently do not develop, most likely due to an inability to mount an inflammatory reaction.⁸

KAPOSI’S SARCOMA

Conjunctival involvement occurs in approximately 10-20% of AIDS patients with Kaposi’s sarcoma.⁸ Conjunctival Kaposi’s sarcoma appears as a bright red subconjunctival mass. Small lesions may be mistaken for simple subconjunctival hemorrhages. Kaposi’s sarcoma usually develops in the inferior
cul de sac, although involvement of bulbar and palpebral conjunctiva may occur. Tumors can be easily overlooked unless the lower lid is pulled down during examination. Kaposi’s sarcoma of the eyelid and conjunctiva is very rare in Indian subcontinent due to very low seroprevalance of Human herpesvirus 8 (HHV-8) in India.14

HIV MICROVASCULOPATHY
Microvasculopathy is the most common ocular manifestation of AIDS.15 It affects between 40% and 60% of HIV-positive patients and is recognized in 89% autopsy specimens. Signs of the microvasculopathy can be seen in 89% to 100% of patients with AIDS.15 The severity of these changes has been correlated with elevated fibrinogen levels and increased red blood cell aggregation, factors that influence the dynamics of blood flow.16,17

Cotton-wool spots (Figure 22-2) are the most common retinal manifestations of AIDS. Individual lesions develop and regress without visible sequelae over a 4-6 week period. All cotton-wool spots may regress before the appearance of new lesions, resulting in a normal-appearing fundus for varying periods of time. Serial examinations therefore may be necessary to identify their presence. Cotton-wool spots are asymptomatic. The diagnostic and prognostic significance of cotton-wool spots is not known. They may be more common in patients with multiple systemic opportunistic infections, but they are not sites of retinal infection and do not appear to be associated with any specific systemic disease. Forty-five percent of HIV-positive patients with CD4+ cell count less than 50 cells/μl will have clinically evident microvasculopathy in contrast to only 16% who have CD4+ cell counts greater than 50 cells/μl.18 Ischemic optic neuropathy has been seen rarely in patients with AIDS; this disorder may be due to similar vascular changes in the optic nerve.

Intraocular Infections
Intraocular Infections are the most devastating of the ocular manifestations of AIDS. A variety of ocular pathogens have been reported, but the frequency of ocular infections for any given agent is lower than that for nonocular infections.
CYTOMEGALOVIRUS (CMV) RETINITIS

Cytomegalovirus (CMV) retinitis\textsuperscript{3-8, 15} is the commonest ocular infection in AIDS patients. Based on a number of clinical and autopsy reports, the prevalence of CMV retinopathy in patients with AIDS is probably about 25\%. Risk rises as CD4+ counts fall to less than 200/cumm. CMV retinitis is the leading cause of visual loss in patients with AIDS, affecting 20-35\%.\textsuperscript{15} It is the AIDS defining diagnosis in 10\%\textsuperscript{15}. Vitreous floaters are the most common symptom.\textsuperscript{15, 19} CMV infection results in full-thickness retinal necrosis. It is characterized clinically by areas of dry, granular, white retinal opacification (corresponding to edema and necrosis) with variable amounts of hemorrhage and vasculitis (Figure 22-3). Early lesions usually arise adjacent to the major vascular arcades of the posterior pole (Figure 22-4). The lesions also

\textbf{FIGURE 22-3:} CMV retinitis presents as full-thickness retinal necrosis characterized clinically by areas of dry, granular, white retinal opacification and hemorrhage

\textbf{FIGURE 22-4:} Early CMV lesions arise adjacent to the major vascular arcades of the posterior pole
may occur first in the peripheral retina; therefore thorough examination of the fundus by indirect ophthalmoscopy is important in the management of AIDS patients.

Active retinitis has three general patterns. The commonest classic lesion is the hemorrhagic,\textsuperscript{18} Large areas of retinal hemorrhage on a background of whitened, necrotic retina “crumbled cheese and ketchup” or “pizza pie appearance” (Figure 22-5).

Another description is a Brush fire appearance which is seen as a yellow-white margin of slowly advancing retinitis at the border of atrophic retina. Granular retinal necrosis is found in the periphery which manifests as focal white granular lesions without associated hemorrhage. Necrotic stage - end result of all patterns of active retinitis is the progression to necrosis. Retinal tears or holes can develop in these areas. There is relatively little inflammatory reaction to CMV infection of the retina. The overlying vitreous remains remarkably clear. With extensive hemorrhage, the appearance may simulate a central retinal vein occlusion or branch vein occlusion. Primary CMV involvement of the optic nerve results in a yellow-white disc with small hemorrhages. CMV retinopathy is relentlessly progressive; spontaneous resolution has not been observed. Individual foci coalesce and spread to involve the entire retina over a period of several months. CMV retinitis severely impairs the quality of remaining life in AIDS patients, 40 percent of those affected losing central vision in both eyes by the time of death. The introduction of highly active antiretroviral therapy (HAART) has markedly reduced the incidence of cytomegalovirus (CMV) retinitis, but has not eliminated new cases altogether.\textsuperscript{20}

**Treatment**

Treatment strategies for CMV retinitis have evolved over the past decade. Current issues of importance include choice of initial anti-CMV drugs; time at which anti-CMV drug treatment is discontinued in patients who achieve immune recovery; strategies for monitoring patients at risk for disease reactivation; and management of complications (retinal detachment, immune recovery uveitis). Table 22-2 summarizes ganciclovir for the treatment of CMV retinitis.
TABLE 22-2: Ganciclovir in CMV retinitis

| Adult Dose | IV induction: 5-7.5 mg/kg/d for 2-3 wk  
| Oral maintenance dose: 1000 mg tid |
| Pediatric Dose | 5 mg/kg once qd |
|    | Decrease dose for severe renal failure, neutropenia, or thrombocytopenia |
|    | A dose dependent increase in neutropenia exists |
|    | Reactivation of retinitis while on maintenance dose will require reinduction |
| Adverse effects. | Myelosuppressive; neutropenia (40%), Thrombocytopenia (18%); Anemia; Infertility; Rash |
|    | Monitor CBC/platelets q2d during induction, then weekly |

Intravitreal implant is an effective long-term alternative but a costly option. Patients treated with ganciclovir often initially feel better as CMV activity in the brain, lungs, liver, kidneys, gastrointestinal tract, and adrenal glands is also inhibited. A physician or infectious disease specialist should coordinate medical care. Ophthalmic assessment is required on a regular basis, with frequency dependent on existence of CMV retinitis and on CD4 count.

Intravitreal injections of ganciclovir (catheterless therapy) have been successful in inhibiting CMV retinitis. A dose of 2000-5000 mcg of ganciclovir in 0.01ml sterile water is given through the pars plana with a 27- or 30-gauge needle 1 to 2 times/wk. Potential problems include endophthalmitis, retinal detachment, and vitreous hemorrhage. On initiating HAART, patients with CMV retinitis may enjoy significant recovery in CD4+ counts and sustained retinitis quiescence without specific anti-CMV therapy. Intravitreal ganciclovir injections seem well suited to offer effective CMV control during temporary periods of decreased CD4+ counts while awaiting HAART-mediated immune system reconstitution. This therapy has become a standard treatment in most centers because of cost considerations. Acyclovir is not effective in treating established CMV retinitis. Other treatment options for CMV infections of the eye are intravenous and/or intravitreal Foscarnet and Cidofovir. Intravitreal Fomvirsen a novel antisense medication is also a lesser known alternative that has fewer roles in extraocular CMV infection. Intravitreous Fomvirsen is well tolerated with an acceptable safety profile. Common adverse ocular were anterior chamber inflammation and increased intraocular pressure.

Vitreoretinal Surgery in CMV Retinitis
Vitreoretinal Surgery in CMV retinitis associated retinal detachment is indicated in 5-50% of patients with CMV retinitis. The risk factors are peripheral retinal involvement greater than 25% area, the presence of active retinitis, older age; lower CD4 cell counts and presence of multiple small holes in several areas of the retina are often responsible for the retinal detachment. These occur at the junction of healthy and necrotic retina. Multiple or single holes, as well as micro holes, were observed in areas of retinal necrosis leading to complex retinal detachments. Strong vitreoretinal adherences in young AIDS patients, associated with chronic inflammation, are important elements in the pathophysiology of retinal detachment in AIDS patients. Primary repair with vitrectomy, air-fluid exchange, endolaser, and silicone oil endotamponade has improved surgical outcome.

CMV retinitis is an indolent infection spreading slowly over the course of many weeks or months to eventually involve the entire retina. Without treatment, vision is usually lost because of optic nerve involvement, spread of the lesions into the macula with macular necrosis, or retinal detachment.
Ocular Manifestations of HIV/AIDS

Rarely, visual acuity may be impaired because of media opacification from dense vitreous inflammatory debris. The presence of CMV retinitis generally implies that the patient is severely immuno-compromised. The initial and maintenance treatment of CMV retinitis must be individualized based on the characteristics of the lesions, including location and extent, specific patient factors, and characteristics of available therapies among others. Management of relapse or refractory retinitis must be likewise individualized. Ophthalmologic screening for patients at high risk for retinitis or who have a prior diagnosis of extraretinal disease is recommended.

**TOXOPLASMIC RETINOCHOROIDITIS IN AIDS**

Toxoplasmic retinochoroiditis is the second commonest intraocular infection affecting 1-2% of AIDS patients.\(^{25}\) It is usually newly acquired primary infection from dissemination to the retina from latent extraocular sites. Toxoplasmic retinochoroiditis may be the presenting sign of toxoplasmic infection and should alert one to look for evidence of CNS involvement. Greater than 50% of patients with AIDS with toxoplasmic retinitis have associated encephalitis. All cases should undergo CNS imaging with contrast of the brain to seek evidence of toxoplasmic encephalitis. Lesions are multifocal extensive and aggressive, with or without severe vitritis.\(^{26, 27}\) Patients can have a maximal anterior segment granulomatous or non-granulomatous inflammation. Optic neuritis, scleritis and orbital cellulitis may also be seen. Diagnosis needs to be confirmed by various techniques, including polymerase chain reaction (PCR) of aqueous and vitreous, serum and intraocular antibody determination.\(^{28}\)

Aggressive treatment is required and for a long time. Treatment is with oral sulphadiazine 1gm TID and pyrimethamine in the dose of 75-150 mg loading dose followed by 25-75 mg for 6-12 weeks along with a tapering schedule of oral steroids. Sulpha allergic patients can be given oral clindamycin 300 mg QID along with azithromycin 250-500 mg per day for 6-8 weeks. Other alternatives are spiramycin, atovaquone, cotrimoxazole, clarithromycin and doxycycline. Untreated large toxoplasmic retinochoroidal lesions rapidly undergo fibrosis and cause tractional retinal detachments (Figure 22-6) that are difficult to treat.

![FIGURE 22-6: Retinal gliosis due to healed toxoplasma retinochoroiditis in a 35-year-old HIV positive male](image-url)
OCULAR TUBERCULOSIS (TB) IN AIDS

Ocular TB in AIDS is relatively rare and can occur even at CD4+ cell counts greater than 200 cells/ 
microlitre. Babu RB et al\(^9\) have reported various presentations of ocular TB that included 
choroidal granulomas, subretina abscess worsening to panophthalmitis, conjunctival tuberculosis, and 
panophthalmitis. 1.95% cases of AIDS had ocular tuberculosis in their series. It is important to diagnose 
treat ocular tuberculosis in AIDS patients as immune recovery tuberculosis can destroy eye 
when HAART is instituted. Diagnosis is by clinical appearance and presence of pulmonary or 
extrapulmonary tuberculosis, along with demonstration of mycobacterium tuberculosis MPB-64 
genome by PCR study of ocular specimens. Treatment is a complete 9-12 months course of anti-
tuberculous therapy (ATT). HAART should be instituted 2-3 months after instituting ATT.

OCULAR SYPHILIS IN AIDS

Syphilis increases the risk of a coinfection of HIV to 5 to 7 times that of the general population.\(^30\) All 
patients presenting with syphilis should be offered HIV testing and all HIV-positive patients should 
be regularly screened for syphilis.\(^31\) Syphilis agent may enhance the transmission of the other, probably 
through increased incidence of genital ulcers. Syphilis serology may be negative when patients 
present with inflamed eyes and co-infection with syphilis and HIV.

The testing titers are also higher than those observed in immunointact patients, and syphilis 
tends to progress much more rapidly to the tertiary stage in these patients. The eyes and visual 
system can be affected in many different ways by syphilis but none of the signs are pathognemonic. 
All structures of the eye may be affected but the commonest manifestation is uveitis (intraocular 
inflammation).\(^32\) Uveitis can occur at all stages of syphilis including primary infection\(^33\) and may 
spontaneously resolve but the relapse rate is high without treatment.

Patients with posterior uveitis may have vitritis, focal retinitis, chorioretinitis periphlebitis, retinal 
aemorrhages, papillitis, and exudative retinal detachments. Many other signs of intraocular 
involvement may be seen including optic neuritis, neuroretinitis, arterial and venous occlusion. Most 
patients recover well with penicillin treatment but visual loss can occur from macular edema and retinal 
ischemia from the endarteritis.\(^34\) However, not all ocular syphilis can be cured with neurosyphilis 
regimens and many more will relapse with less intense regimens.\(^35\) Penicillin in megadose (Aqueous 
Crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 h or 
continuous infusion, for 10–14 days) remains the antibiotic of first choice. Alternatives are Doxycycline 
200 mg BD for 28 days or Amoxycillin 2 g TDS plus probenecid 500 mg QDS for 14 days.\(^37\)

Other Rarer Intraocular Infections

PNEUMOCYTIS CARINII CHOROIDITIS

Pneumocystis carinii pneumonia (PCP) is one of the most common opportunistic infections seen in 
patients with AIDS. It is also the most common cause of death in these patients. Macher and coworkers 
reported the first reliable evidence of Pneumocystis infection of the choroid.\(^38\) Subsequently there 
were a few more reports.\(^39-41\) Diagnosis of choroidal involvement is extremely important, since the 
presence of Pneumocystis choroiditis is evidence of life-threatening systemic infection. Treatment 
should be instituted and may include oral trimethoprim-sulfamethoxazole or IV pentamidine. The 
choroidal lesions will usually respond to therapy. Other infections known to occur are cryptococcal 
choroiditis, fungal retinitis and chorioretinitis and atypical mycobacterial infections.
NECROTIZING HERPETIC RETINOPATHIES

Acute Retinal Necrosis (ARN) and Progressive Outer Retinal Necrosis (PORN)
It is a devastating retinal infection caused by the herpesviruses especially herpes simplex and varicella zoster. This is characterized by a variable degree of full thickness, discrete or confluent retinal necrosis, arteriolitis and phlebitis, retinal haemorrhages and vitreous inflammation. Reaction in the anterior segment varies from mild to severe. ARN, consisting of severe vitritis and a necrotizing retinitis, has been well documented in nonimmunocompromised patients.

The clinical presentation of ARN in AIDS patients may vary and may not demonstrate the severe, extensive inflammation classically seen in ARN patients. The lesions may be unilateral or bilateral. The retinitis may affect the outer retinal layers, sparing the inner layers until very late in the disease process. The natural course is for rapid progression and destruction of the outer retina. Some patients have extensive areas of retinal necrosis, retinal detachment, and proliferative vitreoretinopathy. Differential diagnosis includes CMV, syphilis, Pneumocystis infection, toxoplasmosis, and fungal choroiditis.

Diagnosis is confirmed by demonstration of virus by PCR techniques.

Although ganciclovir and Foscarnet are more toxic than acyclovir, they are effective against herpes viruses as well as CMV. If the retinitis has failed to respond to acyclovir in one eye, one may wish to consider the use of ganciclovir or Foscarnet. During resolution however multiple necrotic retinal holes (Figure 22-7) develop leading on to a rhegmatogenous retinal detachment and proliferative vitreoretinopathy. Despite surgery results for these complex detachments remain poor. Table 22-3 shows differentiating features of three types of viral retinitis in AIDS.

Progressive Outer Retinal Necrosis (PORN) Syndrome
The progressive outer retinal necrosis (PORN) syndrome is a recently described clinical variant of necrotizing herpetic retinopathy in patients with the acquired immunodeficiency syndrome (AIDS). It is caused by varicella-zoster virus infection of the retina. Its course and clinical features distinguish it from the acute retinal necrosis syndrome and CMV retinopathy. Early disease is characterized by...
TABLE 22-3: Differentiating features of three types of viral retinitis in AIDS

<table>
<thead>
<tr>
<th></th>
<th>Acute retinal necrosis syndrome (ARN)</th>
<th>Progressive outer retinal necrosis (PORN)</th>
<th>Cytomegalovirus retinitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune status</strong></td>
<td>Healthy / rarely Immunosuppressed</td>
<td>Immunosuppressed</td>
<td>Immunosuppressed</td>
</tr>
<tr>
<td><strong>Laterality</strong></td>
<td>Bilateral 30-80%</td>
<td>Bilateral 71%</td>
<td>Bilateral 30-50%</td>
</tr>
<tr>
<td><strong>Visual loss</strong></td>
<td>Initially mild later gross</td>
<td>Early loss of vision</td>
<td>Variable depending on the site of involvement</td>
</tr>
<tr>
<td><strong>Anterior segment</strong></td>
<td>Mild to moderate anterior uveitis</td>
<td>Mild non granulomatous uveitis</td>
<td>Mild non granulomatous uveitis</td>
</tr>
<tr>
<td><strong>IOP</strong></td>
<td>Raised</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Vitreous reaction</strong></td>
<td>Significant vitritis</td>
<td>Minimum/no vitritis</td>
<td>Minimum/no vitritis</td>
</tr>
<tr>
<td><strong>Retinal involvement</strong></td>
<td>Full thickness</td>
<td>Deep retinal involvement without granular border</td>
<td>Full thickness involvement with granular border</td>
</tr>
<tr>
<td><strong>Pattern of involvement</strong></td>
<td>Multi focal ,predominantly peripheral</td>
<td>Multifocal early macular involvement</td>
<td>Usually unifocal, fovea relatively spared</td>
</tr>
<tr>
<td><strong>Classic appearance</strong></td>
<td>Late Swiss cheese</td>
<td>Cracked mud</td>
<td>Cottage cheese with cats up or pizza pie</td>
</tr>
<tr>
<td><strong>Vasculitis</strong></td>
<td>Common</td>
<td>Uncommon</td>
<td>Seen but not common</td>
</tr>
<tr>
<td><strong>Retinal hemorrhages</strong></td>
<td>Common</td>
<td>Uncommon</td>
<td>Common in active lesion</td>
</tr>
<tr>
<td><strong>Retinal detachment</strong></td>
<td>Common</td>
<td>Common</td>
<td>Less common</td>
</tr>
<tr>
<td><strong>Optic nerve involvement</strong></td>
<td>Common</td>
<td>Uncommon</td>
<td>Seen but less common</td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td>Rapid</td>
<td>Rapid</td>
<td>Slow</td>
</tr>
</tbody>
</table>

Adapted from: Ocular lesions associated with AIDS in India, practical guidelines for diagnosis and management, Dr. Jyotirmay Biswas Sankara Nethralaya, Chennai

Multifocal deep retinal opacification. Lesions rapidly coalesce and progress to total retinal necrosis over a short period of time. Despite aggressive therapy with intravenous antiviral drugs, prognosis is poor; disease progression and/or recurrence is common, and the majority of patients develop no light perception vision. Total retinal detachments are common. Prophylaxis against retinal detachment using laser retinopexy has not been useful in most cases. PORN syndrome is an uncommon, but devastating complication of AIDS.

**Neuro-ophthalmic Complications of Intracranial Disease**

Neuro-ophthalmic problems, including optic neuropathies, motility disturbances, and visual field defects, are an important and common part of the AIDS spectrum. However, diverse and challenging to the clinician, they may be the initial presentation of HIV infection. While opportunistic infections and neoplasms comprise the major source of neuro-ophthalmic problems, HIV itself may also be cause of neuropathy due to various mechanisms. Coexisting infections and neoplastic processes in the eye and brain create a diagnostic challenge for the clinician. Although tuberculous meningitis is the most common neuro-infection, with the advent of the Acquired Immunodeficiency Syndrome (AIDS) pandemic, more and more cases of fungal meningitis especially due to cryptococcal infection are seen in clinical practice. Cryptococcal meningitis has emerged as a leading cause of infectious...
Ocular Manifestations of HIV/AIDS

morbidity and mortality in patients with AIDS. Papilledema due to cryptococcal meningitis is the commonest neuroophthalmic lesion noted in AIDS patients. Other manifestations include cranial nerve palsies, optic neuritis, optic atrophy and pupillary abnormalities.

Central nervous system opportunistic infections (OIs) lesions like toxoplasmic encephalitis, lymphoma, progressive multifocal leucoencephalopathy (PML) and fungal granulomas can also produce peculiar neuroophthalmic features in AIDS patients. These entities may present with ophthalmic symptoms and, the diagnosis of these entities is made with noninvasive methods. Imaging studies, especially magnetic resonance imaging, are very useful for the diagnosis of tuberculous meningitis, toxoplasmic encephalitis and PML.

Once HAART is initiated, some patients can develop a clinical worsening of some CNS OIs with or without atypical neuroimaging manifestations. This paradoxical worsening is known as the immune reconstitution inflammatory syndrome (IRIS) and it results from reconstitution of the immune system’s ability to recognize pathogens/antigens in patients with prior OIs and low CD4+ T-cell counts. In this context, IRIS can be seen in patients with CNS cryptococcosis, tuberculosis, or PML. On the other hand, HAART-induced immune reconstitution can improve the prognosis of some untreatable diseases such as PML, and can allow maintenance therapy of some CNS-OI to be safely discontinued in patients with high and sustained CD4+ T-cell response. Therefore it is important to monitor these patients for worsening or improvement of ocular complication during HAART.

Newer Entities

IMMUNE RECOVERY UVEITIS SYNDROME

Immune recovery uveitis (IRU) is an intraocular inflammatory disorder originally described in individuals with human immunodeficiency virus (HIV) and inactive cytomegalovirus retinitis following highly active antiretroviral therapy. Immune recovery uveitis (IRU) is characterized by vitritis and posterior segment complications thereof, most commonly cystoid macular edema (CME) and/or epiretinal membrane formation. Preretinal neovascularization, papillitis, proliferative vitreoretinopathy, and anterior segment inflammation, sometimes with iris synechiae and cataract, have been reported in a smaller number of cases. Symptoms typically include floaters and/or moderate to severe vision loss. Risk factors include larger retinal involvement due to CMV retinitis and intravitreal use of Cidofovir. Eyes with IRU respond favorably to antiinflammatory therapy in the form of oral topical or periocular steroids under close supervision without reactivation of retinitis. CMV retinitis is usually inactive in cases of IRU due to an improvement in immunity. IRU can occur in eyes with active CMV retinitis, particularly at the onset of the inflammation. More aggressive anti-CMV drug therapy, especially during the initial period of immune recovery, seems to be associated with a reduced risk of IRU, presumably because of a decreased antigen load.

From a practical standpoint, patients who were never on HAART found to have CMV retinitis should be treated aggressively with anti-CMV drugs, and treatment should be continued through the period during which immune recovery is achieved, before considering discontinuation of treatment.

NEOPLASMS IN HIV

Squamous Cell Carcinoma

Squamous cell carcinoma occurs at an earlier age in HIV-infected individuals, and is often more aggressive, than in immunocompetent individuals. Squamous cell carcinoma has been linked to
infection with the human papilloma virus (HPV), which may explain its increased prevalence in immunosuppressed individuals with HIV disease. Smaller lesions can be excised followed with cryotherapy invasive lesions necessitate enucleation or exenteration. More recently, topical medications, including mitomycin-C, 5-fluorouracil, and interferon, have been used successfully for treatment of various types of ocular surface squamous neoplasia.

Non-Hodgkin Lymphoma (NHL)

NHL is the second most common opportunistic neoplasm in HIV-infected individuals. Since the introduction of HAART, there has been a substantial reduction in the incidence of NHL in HIV-infected individuals and some studies suggest there is no difference in the incidence of NHL in non-HIV and HIV patients. Lymphoma can occur in the eyelids, conjunctiva and orbits, where it can cause painful proptosis. Primary ocular lymphoma in immunocompetent individuals often presents with unilateral or bilateral decreased vision, vitritis, and retinal or choroidal infiltrates. In HIV-infected individuals, NHL should be suspected in patients of any age who have prominent vitreous humor cells, with or without subretinal material. Intraocular lymphoma usually occurs when CD4+ T-lymphocyte counts are less than 50 cells/ml.

Intraocular lymphoma can also cause anterior chamber cellular reactions. Lesions suspicious for lymphoma should be biopsied, and systemic evaluation for non-ocular sites of disease should be undertaken. Treatment consists of radiation or chemotherapy.

Our Experience with Ocular Complications of AIDS at Minto Eye Hospital

The most common ophthalmic lesions seen causing morbidity was CMV retinitis and herpes zoster ophthalmicus. A total of 184 cases of AIDS patients were seen between 2000-2003. HIV retinopathy was another commonest posterior segment lesion seen in 18 (10.28%) cases. 13 (72.22%) were males and 5 (27.77%) cases were females. Unilateral in 8 (50.00%) and bilateral in 7 (38.88%), one case (5.55%) presented with ischemic optic neuropathy. CMV retinitis was seen in 18 cases (10.28% overall) (25.35% among those with ocular findings, i.e. 71 cases) seen in 34 eyes of 18 patients, predominantly seen in 16 (88.8%) males cases and 2 (11.22%) female cases. In 4 (22.22%) CMV retinitis was the AIDS defining diagnosis. 1 (50%) female case presented with CMV retinitis as first presentation of HIV disease. Bilateral in 16 (88.8%), 9 (50%) cases presented with end stage disease. 4 cases died within 4-9 weeks of diagnosis. 9 (50%) cases were lost to follow up. Average age of cases was 34.77 years overall and 30 years in females (2 cases). No children manifested with CMV retinitis. 12 (66.66%) cases had classic pizza pie fundus appearance, 2 (11.11%) cases frosted branch angiitis appearance was seen, CMV papillitis was seen in 1 case, and mixed presentation was seen in 3 cases. Average CD4+ counts among 11 cases in which CD4+ counts were done were 87.53 cells/microliter. 5 cases died due to various systemic disorders during the period of follow up. CD4+ counts done in 5 cases gave an average count of 214.5 cells/microliter cases. Average age at presentation among with HIV retinopathy was 28.13 years. Acute retinal necrosis was seen in 4 (2.28%) cases, all were males, 100% unilateral, Cutaneous zoster history was seen in 3 cases. 2 cases had herpes zoster ophthalmicus. 1 case of intravenous drug abuse was associated with ARN. One case died shortly after diagnosis due to
systemic illnesses. In 1 case ARN was aids defining diagnosis. One case of immune recovery vitritis was seen in a 28 year old case with improvement in CD4+ counts from 22 cells/ cumm to 384 cells/ cumm 3 months after starting HAART.

Forty-nine cases had anterior segment lesions, herpes zoster ophthalmicus 18 (10.28%) cases was the commonest anterior segment disease. Male : female ratio was 14:4, no children had HZO. Average age at presentation of HZO was 33.33 years. HZO was the first presentation of HIV in 6 (33.33%) cases. Cornea was involved in 5 cases during acute stage. Complete recovery with standard treatment was seen in 10 cases. Two cases had recurrent epithelial defects/ sterile corneal ulceration. Two cases developed HZO keratouveitis. Corneal ulceration with opacity and vascularization occurred ultimately in 5 cases. 2 cases developed acute retinal necrosis within 1-1½ years of herpes zoster ophthalmicus. Steven Johnson syndrome with conjunctival involvement as a result of drug reaction to nevirapine and sulphonamides was seen in 2 cases (1.14%). Other lesions included Molluscum contagiosum seen in one female patient, herpes simplex keratitis and blepharitis was seen in 2(1.14%) cases each.

Neuro-ophthalmic lesions were seen in the study included optic atrophy 5(2.85%) cases due to cryptococcal and tuberculous meningitis in 3 cases and drug toxicity due to anti-tubercular drugs. Papilledema due to cryptococcal meningitis was seen in 4 cases. Extraocular muscle palsy 6th nerve paralysis due to meningitis was seen in one case. Facial palsy due to suspected Progressive multifocal leukoencephalopathy (PML) was seen in one case.

CORRELATION WITH CD4+ CELL COUNTS

CD4+ counts were determined in 38 cases and CD4+ counts ranged from 24 to 370 median CD4+ count was 128.21 cells/microlitre. Out of the 38 cases had ocular lesions related to HIV, in whom CD4+ counts were done 13 cases had CMV Retinitis showed very low CD4+ cell counts with an average CD4+ cell count of 87.53 cells/microlitre. Follow-up examination was done in 60 cases. The duration of follow-up ranged between 12 to 18 months. 20 patients died during the period of follow up because of multiple systemic infections of these patients had CMV retinitis.

VISUAL ACUITY

The visual acuity at initial presentation was in the range of 6/6-6/12 in 122 (n=175, 69.71%) cases. Main causes for deterioration in vision among the patients were CMV retinitis (4 cases), optic atrophy (2 cases), corneal ulcer (1 case), herpetic eye disease (HZO, HSV, ARN) (4 cases) and drug toxicity of optic nerve (1 case).

Conclusion

HIV-related eye disease will remain an important problem for many decades to come, but a variety of factors will make its study more difficult in the future. Regular follow up of patients especially those with lower CD4 cell counts would enable early diagnosis and treatment of most sight threatening complications of HIV/AIDS. Immune recovery phenomenon is a new challenge that an ophthalmologist has to face and appropriate diagnosis and management with anti-inflammatory treatment is imperative after ruling out infective etiologies since most of these patients would have lost vision due to CMV.
References

Introduction

Central serous chorioretinopathy (CSC) was first described by von Graefe in 1866 as central recurrent retinitis. Gass in 1967 named it Idiopathic central serous chorioretinopathy. Klein and Maumenee were the first to postulate that the source of subretinal fluid was from the choriocapillaris. Central angiospastic chorioretinopathy is another term applied to this condition.

CSC is essentially an idiopathic condition. It is a circumscribed serous detachment of the neurosensory retina which occurs over an area of leakage from choriocapillaris through the retinal pigment epithelium (RPE). The leakage beneath the retina results from disturbed fluid equilibrium causing its elevation and producing macular detachment with subsequent distortion of vision.

There are two main types of CSC, based on nature of RPE leak. The more common type termed acute, typical or classic CSC is seen in younger patients with focal leaks from RPE, mild to moderate visual loss and a benign self limiting course. A second uncommon type with widespread alterations of RPE pigmentation in posterior pole is termed chronic or diffuse retinal pigment epitheliopathy (DRPE).

DRPE is associated with older age, chronic (more than 6 months), detachment of posterior pole, poorly defined RPE leakage, multiple pigment epithelial detachment (PED’s) and poor visual prognosis owing to cystoid macular edema, foveolar atrophy, subretinal fibrosis and less commonly CNV. CSC usually occurs between ages 25 and 50 years and affects men more often than women (6:1). Patients above 50 have bilateral disease with male: female 2:1. CSC is common in Asians, Hispanics and Latinos than in Caucasians. Blacks appear to be least affected. It is seen in hyperopics and not in myopes due to pre-existing chorioretinal atrophy.

Stress has been implicated as a causative factor as also certain personality types like type A personality (competitive drive, sense of urgency, aggressive nature and hostile temperament), hypochondria, hysteria and conversional neurosis. Steroids whether systemic, topical or inhaled are associated with CSC. It may also be seen in pregnant women, especially in the last trimester. Other systemic associations include organ transplantation, endogenous hypercortilism (Cushing’s disease), systemic hypertension, systemic lupus erythematosus (SLE), gastrointestinal reflux disease and use of sildenafil citrate.

Pathophysiology

It is not yet clearly understood. The previous hypothesis of abnormal ion transport across RPE and focal choroidal vasculopathy has given way to the concept of multifocal choroidal hyperpermeability subsequently leading to secondary dysfunction of the RPE as shown by ICGA. Abnormal pumping functions at the level of RPE have been implicated, although the primary pathology may involve the choriocapillaris.

In other words, the intrachoroidal edema or leakage exerts pressure on pigment epithelium causing it to blister up into focal or multifocal elevations known as serous detachments. The blister disrupts or develops a mechanical opening usually at junction between its elevated and attached areas, permitting fluid leakage through pigment epithelium beneath the neurosensory retina which is avascular although neovascularization, may evolve as a secondary complication.
Central Serous Chorioretinopathy

A study by Michael Tittl et al showed that there was increased foveal pulsatile choroidal blood flow (CBF) and an abnormal distribution of fundus pulsation amplitude in areas close to the leak in patients with active CSC. CBF in eyes with CSC was 45% lower than in fellow eyes. The decreased CBF might be correlated with small localised hypofluorescent areas which may indicate non-perfused areas of choriocapillaries that are frequently seen during ICGA.

Yet another study has shown that there is an abnormal subfoveal CBF regulation in patients with relapsing CSC compared with age matched non smoking healthy volunteers during isometric exercise. At 85% increase in ocular perfusion pressure, subfoveal CBF was approximately twice as high in patients with CSC compared with healthy control group.

Multifocal electroretinogram (mfERG) has demonstrated bilateral diffuse retinal dysfunction even when CSC involves only one eye. Multifocal ERG may prove useful as a clinical marker for susceptibility to serous detachment. As per a study by Aimee V , Chappelow et al, after recovery of CSC, mfERG A wave and B wave amplitudes increased markedly where the detachment resolved and moderately elsewhere in the posterior pole of both eyes. They remained either subnormal relative to controls. mfERG B wave latencies improved from prolonged to mid normal value in both eyes. These findings support the theory that subretinal fluid retention in CSC is secondary to diffuse pathologic changes in choroid and RPE.

Elevated circulating cortisol and epinephrine which affect the autoregulation of choroidal circulation have been seen in persons with type A personality, systemic hypertension and obstructive sleep apnoea. The incidence of CSC in persons with Cushing’s syndrome is 5%. Tewari et al demonstrated that patients with CSC showed impaired autoresponse with significantly decreased parasympathetic activity and increased sympathetic activity. Carvalho-Recchia et al showed in a series that 52% of patients with CSC had used exogenous steroids within 1 month of presentation as compared with 18% of control subjects.

Helicobacter pylori infection may represent a risk factor in CSC, though no studies apart from, Cotticelli et al have substantiated the same. The presence of bacteria is well co-related with visual acuity and other retinal findings following an attack.

Keratoconus and CSC are two uncommon diseases, possibly due to dysfunction of epithelium and its basement membrane which can occur together in some individuals.

Symptoms and Signs

A patient with CSC may present with sudden onset blurred or distorted vision (6/9 – 6/12 or 6/60) which is usually improved by a small hyperopic correction. Metamorphopsia, micropsia, persistent after images, altered color vision and grey purple color vision may be some of the other presenting signs. Occasionally patients who have detachments of retina are asymptomatic because the bubble of fluid does not involve the center of macula or foveal region.

The ophthalmoscopic signs include serous detachment of the RPE, extramacular RPE atrophic tracts, multiple bullous serous retinal and RPE detachments and RPE atrophic changes. The neurosensory detachment may be very subtle, requiring contact lens examination (slit lamp biomicroscopy) for detection. The other signs include delayed retinal recovery time following photostress, loss of color saturation and loss of contrast sensitivity.

The subretinal deposition of a yellowish material in a reticulated leopard spot pattern under neurosensory retina due to neurosensory detachment was found in eyes with chronic CSC (Figures 23-1 to 23.4) All patients were older men being treated with steroids.
FIGURE 23-1: Showing ink blot leakage pattern on fundus fluorescein angiography (FA) (Courtesy: Dr Nazimul Hussain, Al Zahra Pvt Hospital, UAE)

FIGURE 23-2: Shows smoke stack leakage pattern on FA (Courtesy: Dr Nazimul Hussain, Al Zahra Pvt Hospital, UAE)
An experienced clinician can often diagnose idiopathic CSC based solely upon history and chief complaints in a young anxious patient who presents with unilateral metamorphopsia of recent onset. The classic fundus appearance is best seen with binocular indirect ophthalmoscopy, subtle cases requiring FFA for definitive diagnosis.

**Imaging Studies**

**FLUORESCEIN ANGIOGRAPHY**

One or several hyperfluorescent leakages are seen at the RPE level. The characteristic angiographic patterns include:
**Expansile Dot Pattern (80–90%)**
This is the most common pattern seen as a small focal hyperfluorescent leak through the RPE in the early phase which increases in size and intensity as the angiogram progresses. It is the hallmark angiographic feature of the disorder in its classic form. Late phase pooling is seen.

**Smokestack Pattern (10-20%)**
This starts as a central hyperfluorescent dot that then spreads vertically and laterally resembling a plume of smoke. This pattern is related to the convection currents and pressure gradient between the protein concentration of subretinal fluid and the fluorescein dye entering the detachment.

**Diffuse Pattern**
Occurs due to one or more leaks outside the posterior pole. This pattern of fluorescein leakage many times does not have any obvious leakage points and is seen in patients having large areas of serous detachment.

**INDOCYANINE GREEN ANGIOGRAPHY**
It shows areas of hyperfluorescence due to filling delay in the early phase, dilated choroidal veins in the transit phase and focal choroidal hyperfluorescent patches due to leakage in the late phase. ICGA can help to differentiate between the atypical diffuse CSC in older patients from occult choroidal neovascularisation in exudative age related macular degeneration and idiopathic polypoidal choroidal vasculopathy.

In 500 cases of CSC, 50% had associated PED, 30% were bilateral and 10 cases had chronic exudative CSC. FFA showed inkblot pattern in 70%, while smoke stack pattern was seen in 10%.

90% patients showed resolution within 1 month with treatment which consisted of anxiolytics, focal laser (10-20%) and PDT (2 cases).

**OPTICAL COHERENCE TOMOGRAPHY (OCT)**
It is an excellent non-invasive method for diagnosing and following the resolution of subretinal fluid in CSC. Subtle fluid accumulation beneath the sensory retina and the RPE not evident on FFA and clinical examination can be picked up by OCT.

The OCT opthalmoscope provides complementary morphological information on patients with CSC. The presence of more diffuse RPE changes levels further support to the concept that CSC is a diffuse rather than localised RPE anomaly.\(^\text{16}\)

The topography mode program of OCT can be used to measure the height of retinal detachment (RD). By multiplying the size of area of the RD and the average height of RD, the volume of subretinal fluid can be determined.\(^\text{17}\)

FD-OCT (Fourier-Domain-OCT) has shown elongation of photoreceptor outer segments and decreased thickness of outer nuclear layer in CSC.\(^\text{18}\)

**Chronic CSC**
It is a kind of diffuse retinal pigment epitheliopathy which occurs in older people when the neurosensory detachment involves the central macula for at least 6 months. The FFA in these patients
Central Serous Chorioretinopathy

is characterised by granular hyperfluorescence corresponding to window defects and blockage caused by RPE atrophy and clumping in one or more areas of subtle continued leakage. Many a times there is a permanent reduction of visual acuity in these patients.

Bullous CSC

This rare form of CSC, described first by Gass in 1973 is seen in patients receiving high dose of systemic steroids like organ transplant patients. Large amount of subretinal fluid which extends upto the inferior periphery may cause a bullous type of retinal detachment. Associated multiple large PED’s, subretinal fibrin and large areas of RPE rips may be present.

Subretinal Deposits

CSC of any type can have subretinal lipid deposits which are multiple yellow, hard edged or subretinal fibrin which are gray white translucent sheets. These changes are probably secondary to the turbidity of subretinal fluid.

Differential Diagnosis

1. Choroidal neovascular membrane (from ARMD, pathological myopia, choroidal rupture, presumed ocular histoplasmosis syndrome)
2. Vogt-Koyanagi-Harada syndrome
3. Optic disc pit with serous macular detachment
4. Posterior scleritis
5. Multifocal choroiditis
6. Metastatic cancer
7. Vascular disorders
8. Eales’ disease
9. Uveal effusion syndrome
10. Segmental RP
11. Retinoschisis
12. Lymphoma.

Natural Course and Management

Most cases of CSC (80-90%) undergo spontaneous resolution of subretinal fluid within 3-4 months along with recovery of visual acuity which may take up to 1 year. Mild metamorphopsia, faint scotomata, abnormalities in contrast sensitivity and mild color vision deficits however may frequently persist.

Some eyes (5%) suffer permanently diminished visual acuity resulting from foveal atrophy, cystoid macular degeneration, CNVM, subretinal fibrosis, extensive RPE degeneration. These patients often have recurrent or chronic serous retinal detachments resulting in progressive RPE atrophy and permanent visual loss to 6/60 or worse. The final clinical picture represents diffuse retinal pigment epitheliopathy. The risk of choroidal neovascularization from previous CSC is small but has increasing frequency in older patients diagnosed with it. Patients with classic CSC (focal leaks) have a 40-50% risk of recurrence in the same eye.
Treatment involves urging patients to modify their behavioral patterns and take a more relaxed approach to life. Recent studies have supported the use of oral indomethacin to hasten the recovery time.

Apart from observation for spontaneous resolution of CSC, the medical treatment includes alprazolam, dietary modification, antihistaminics, nonsteroidal anti-inflammatory drugs (NSAID’s) and beta blockers.

Topical diclofenac (Voltaren), ketorolac (Acular LS) and bromfenac (Xibrom), all belong to NSAID’s which function by inhibiting enzyme COX which blocks the synthesis of prostaglandins. Inflammation functions to make the blood retinal barrier more permeable. Principle COX-2 pathway is inhibited by these NSAID’s making them excellent alternative to laser therapy.¹⁹

Systemic corticosteroids are contraindicated as they result in worsening of CSC from exacerbations of serous detachments already present. Tatham and Macfarlane described a case series of patients who were treated with propanolol for CSC.²⁰

Ketoconazole, an adrenocorticoid antagonist at oral dose of 600mg/day for 4 wks lowered the endogenous cortisol in patients with CSC. Median lesion height and greatest linear dimension (as on FFA and OCT) were stable at 4 weeks and decreased at 8 weeks.²¹

Intravitreal bevacizumab (avastin) has resulted in visual and anatomic improvements in CNV attributable to CSC.²²

**Surgical Care**

Laser photocoagulation should be considered under the following circumstances:
1. Unresolving CSC of 4 months or more duration.
2. Recurrence in an eye with visual deficit from previous CSC.
3. Presence of visual deficits in opposite eye from previous episodes of CSC.
4. Occupational of other patient need requiring prompt recovery of vision.

When considering the potential risks versus the potential benefits of laser treatment, the greatest rationale for treatment is the possibility of progressive loss of vision from detachment of macula from prolonged detachment. Laser light is focused onto retina selectively over the area of leakage and a small area of normal RPE surrounding the leakage.²³ Laser effectively burns the leak area shut. The intensity of burn should be sufficient enough to just blanch the RPE with a spot size of 100-200 microns and exposure time of 0.1 sec and power of 80 mW to start with and titrated with increments of 30 mW until the blanching effect is observed at the level of RPE.

Laser treatment may be considered for patients with a leak located more than 375 micrometers from fovea. In cases where the leak is very near the macula photocoagulation may leave a blind spot. Resolution of detachment predictably occurs more expeditiously following treatment of leak with laser. Although it shortens the course of disease and decreases the course of CSC, it does not appear to improve the final visual prognosis. Diffuse multiple leaks can be treated with grid laser over the area of granular hyperfluorescence (in cases of chronic CSC). Complications from photocoagulation include accidental burn of fovea and the risk of development of choroidal neovascular membrane after treatment.

A study was conducted to evaluate the efficacy of diode laser (810nm) photocoagulation in CSC patients and compare it with effects of argon green laser (514nm)-[parameters; 100 micrometers, 100-200 ms and power just enough to produce minimal greying]. It concluded that diode laser is a
better alternative to argon laser in terms of faster visual rehabilitation and better contrast sensitivity. Also diode laser has well recognised economic and ergonomic advantages of being less costly, more efficient, portable and easy to maintain. 24

**TRANSPUPILLARY THERMOTHERAPY**

Transpupillary thermotherapy (TTT) using 810 nm laser (200 Mw, for 1 min, 3 mm over the leak) has also been used with moderate success. TTT has been suggested as a lower risk alternative to laser photocoagulation in cases where the leak is in the central macula. 25

According to a study, TTT resulted in resolution of CSC with subfoveal angiographic leaks, with significant improvement in visual outcome in comparison to the natural history of persistent CSC. The study included 40 eyes with CSC between 4 and 12 months duration of which 25 eyes opted for TTT for subfoveal leaks and 15 eyes were followed without treatment. Within 3 months, TTT resulted in resolution of serous detachment in 24 eyes in single session while one eye required repeat treatment. 8 control eyes demonstrated persistent CSC at last follow up. VA improved in 23 treated eyes and 5 control eyes. 26

**PHOTODYNAMIC THERAPY (PDT)**

It is a painless OPD procedure. A special photodynamic dye (verteporfin) is injected in an arm vein. Fifteen minutes later a cold laser light is aimed at choroidal neo-vascularization which selectively absorbs the dye. The laser light activates the dye causing the production of a very active form of singlet O₂ that seals the leak. Patients can go home immediately following PDT but must avoid direct sunlight for two days following treatment to avoid skin burns from the dye.

Yannuzzi et al described the use ICGA, to first identify areas of choroidal hyperpermeability that were then targeted with PDT. 27 Lai et al described the use of half dose verteporfin in the treatment of CSC. They proposed 3 mg/m\(^2\) of verteporfin infused over 8 minutes, followed 2 mins later with ICG/FFA guided laser. This resulted in complete resolution of the neurosensory detachment and/or pigment epithelial detachment by 1 month in 85% of the eyes treated. 28

A study was conducted to evaluate the changes in choroidal vasculature in CSC after ICGA guided PDT with verteporfin. All eyes with persistent or chronic CSC that had fluorescein leakage at fovea received a single session of PDT with verteporfin (6 mg/m\(^2\)) followed by application of 50 J/cm\(^2\) at 689 nm. 6 eyes from 6 patients with mean follow-up of 12.7 months were analysed. Narrowing of original dilated choroidal vessels and decrease in extravascular leakage could be demonstrated in 100% eyes. After 3 months mean diameter decreased from 546 microns to 371 microns (p = 0.028). Five patients had improvement in visual symptom and BCVA. Fluorescein leakage stopped at 1 month in 5 eyes and 3 months in 6 eyes. One eye developed CNV at 3 months follow-up. 29

PDT with verteporfin resulted in beneficial outcome in treatment of subfoveal CNV secondary to CSC without serious adverse effects. Marked visual improvement occurred. 30 Report has shown PDT can cause resolution of macular detachment in diffuse retinal pigment epitheliopathy. 31 PDT seems to be effective for treating CNV complicating PDT performed for CSC. 32

Stress reducing activities like exercise, meditation or yoga can be recommended.

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