Causes of visual loss in patients with uveitis.

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For Nicole, with love.

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Beyond all human assistance, the almighty God has led my steps throughout and given me the strength and courage needed to complete this work. To him be praise and honour.

Declaration

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, all material which is not my own has been properly acknowledged.

Paul MB Kabasele

"The eye is the lamp of the body. If your eyes are good, your whole body will be full of light. But if your eyes are bad, your whole body will be full of darkness." The Bible.

Abstract

The last major study of causes of vision loss in 600 eyes with uveitis was published over 10 years ago and there have been many advances in treatment over this time. In this thesis I undertook a study of 1594 patients (2593 eyes) with uveitis currently attending the clinic, 75% of whom were aged between 24 and 63 years. The type of uveitis, sight threatening complications that developed and treatment were followed from presentation to final follow up. At presentation, 16% of eyes had BCVA ≤ 6/18 (e.g. 6/18-6/36) and 14% of affected eyes had BCVA 6/60 or worse. At one year follow-up, we found 11% of eyes with vision loss to 6/18-6/36 and 8% of eyes with severe visual loss or blindness. In the group of eyes followed up for 10 years or more, 19% developed severe visual loss or blindness and 16% developed vision loss to 6/18-6/36. Chronic macular damage was the main cause of visual loss, accounting for both for visual impairment and for severe visual loss, accounting for 41% and 36% respectively. Cystoid macular oedema accounted for 29% in visual impairment and 19% in severe visual loss or blindness. When classified by uveitis types, CMO was the main cause of vision loss in intermediate uveitis (38%), glaucoma was the leading cause in anterior uveitis (32%), and chronic macular damage accounted for 46.3% in panuveitis and 58.8% in posterior uveitis.

Additionally, I looked at the outcome and subsequent impact on vision of ocular surgery for cataract, glaucoma and vitreo-retinal procedures. Visual prognosis after cataract surgery was favourable in anterior and intermediate uveitis. Eyes which underwent glaucoma surgery had vision stabilised or slightly improved over time. The mean log MAR BCVA prior to glaucoma surgery was 0.53+/- 60, and 0.31+/- 49 at final follow-up visit. (P= 0.012). There was no statistically significant improvement in visual acuity in eyes which had undergone vitreo-retinal procedures. The mean logMAR BCVA were 1.1+/-0.82 and 0.87+/-0.80 respectively pre-operative and at last post- op visit. (P=0.28)

The 3rd main results chapter looks at patients presenting with retinal vasculitis who had ischemia and the long term outcome for these eyes. Of the 106 eyes which developed ischemia, 24% had vision loss to 6/18-6/36 at presentation, 23% of these had BCVA 6/60 or worse. Chronic macular damage was the main cause of visual impairment and accounted for 36%, macular ischemia accounted for 67% of severe visual loss or blindness. I found that in most eyes with ischemia, visual loss developed early in the first 5 years and do not worsen with time.

Conference presentations.

1. Paul MB Kabasele, SR Taylor, SL Lightman. Causes of visual loss in uveitis. *Royal College of Ophthalmologists, Liverpool 2010; World Ophthalmology Congress, Berlin 2010; Association for Research in Vision and Ophthalmology, Florida 2011.*

2. Paul MB Kabasele, SR Taylor, SL Lightman. Incidence of uveitis due to Behçet's disease and complications. *14th International Conference on Behçet's disease. London 2009.*

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List of abbreviations.

AU: Anterior uveitis.
AAU: Acute anterior uveitis.

ACAID: Anterior chamber associated immune deviation.

ACE: Angiotensin converting enzyme.

AION: Anterior ischemic optic neuropathy.

AMPPE: Acute multifocal placoid pigment epitheliopathy.

APCs: Antigen- presenting cells.

AS: Ankylosing spondylitis.

ASAT: Aspartate aminotransferase.

ALAT: Alanine aminotransferase.

BAB: Blood-aqueous barrier.

BCVA: Best corrected visual acuity.

BK: Band keratopathy.

BRB: Blood-retina barrier.

BRVO: Branch retinal vein occlusion

BSCR: Birdshot chorioretinopathy.

CAU: Chronic anterior uveitis.

CMO: Cystoid macular oedema.

CMR: Cellophane macular reflex.

CNVM: Choroidal neovascular membrane.

COS: Cone outer segment.

CRP: C-reactive protein.

C-ANCA: Cytoplasmic antineutrophil cytoplasmic antibodies.

CNVM: Choroidal neovascular membrane.

CRAO: Central retinal artery occlusion.

CRVO: Central retinal vein occlusion.

CSR: Central serous retinopathy.

DFN: Dalen- Fuchs nodules.

ECC: Extracapsular cataract extraction

ERG: Electroretinogram.

ERM: Epiretinal membrane.

ESR: Erythrocyte sedimentation rate.

FAF: Fundus auto fluorescence.

FFA: Fluorescein fundus angiography.

FHC: Fuchs' heterochromic iridocyclitis.

GWC: Goldmann-Witmer coefficient.

GVHD: Graft vs Host disease.

HLA: Human leukocyte antigen.

HO-1: Heme oxygenase-1.

ICCE: Intracapsular cataract extraction.

IFN: Interferon

IL: Interleukin.

ILM: Internal limiting membrane.

iNOs: Inducible nitric oxides.

IOL: Intraocular lens.

IOP: Intraocular pressure.

IPM: Interphotoreceptor matrix.

IS: Inner Segment.

IU: Intermediate uveitis.

JIA: Juvenile idiopathic arthritis.

KPs: Keratic precipitates.

LFP: Laser Flare photometry.

Log MAR: logarithm of minimum angle resolution.

LYVE: Lymphatic vessels endothelium.

MCP: Monocyte chemoattractant protein

MEWDS: Multiple evanescent white dots syndromes.

MFC: Multifocal Choroidopathy.

MIF: Macrophage migration inhibitor factor.

MIP: Macrophage inflammatory protein.

MPH: Macular pseudohole.

MS: Multiple sclerosis.

NGAL: Neutrophil gelatinase-B associated lipocalin.

NFL: Nerve fibre layer.

NK: Natural killer.

NO: Nitric oxide.

NPE: Non-pigmented ciliary epithelium.

NVD: Neovascularisation disc.

NVE: Neovascularisation elsewhere.

OCT: Optical coherence tomography.

OHT: Ocular hypertension.

OS: Outer segment.

OT: Ocular toxoplasmosis.

oxLDL: Oxidized-low-density lipoprotein.

P-ANCA: Perinuclear antineutrophil cytoplasmic antibodies.

PAMPs: Pathogen-associated molecular patterns

Panu: Panuveitis.

PAS: Peripheral anterior synechiae.

PBMC: Peripheral blood monocyte cells.

PCNSL: Primary CNS lymphoma.

PCR: Polymerase chain reaction.

PE: Pigmented ciliary epithelial layer.

PIC: Punctate Inner Choroidopathy.

PMNs: Polymorphonuclear cells.

PSCLO: Posterior subcapsular lens opacification.

Pu: Posterior uveitis.

RANTES: Regulated on action normal t-Expressed and secreted.

RD: Retinal detachment.

RFNL: Retinal fibre nerve layer.

ROS: Rod outer segment.

RPE: Retinal pigment epithelium.

RPPP: Retinal pigment epithelial protective protein.

SACE: Serum angiotensin Converting-Enzyme.

SC: Serpiginous choroidopathy.

SCE: Stiles-Crawford effect.

SD-OCT: Spectral domain optical coherence tomography.

SIJ: Sacroiliac joint.

SLE: Systemic lupus erythematous.

SO: Sympathetic ophthlamia.

SOD: Superoxide dismutase.

SpA: Spondyloarthritis.

SUN: Standardization of uveitis nomenclature.

TB: Tuberculosis.

TCRs: T-Cell receptors.

TD-OCT: Time domain optical coherence tomography.

TIGR: Trabecular meshwork-inducible glucocorticoid response.

TINU: Tubulointerstitial nephritis syndrome.

TLRs: Toll-like receptors.

TM: Trabecular meshwork.

TNF: Tumour necrosis factor.

UBM: Ultrasound biomicroscopy.

VA: Visual acuity.

VEGF: Vascular endothelial growth factor.

VMT: Vitreomacular traction syndrome.

VKH: Vogt-Koyanagi-Harada syndrome.

WDs: White dots syndromes.

Chapter 1: Introduction

1.1 Anatomy of the eye

The eyeball is not a simple sphere but can be viewed as the result of fusing a small portion of a small, strongly curved sphere with a large portion of a large, not so strongly curved sphere (Figure 1.1). The small piece, occupying about one-sixth of the whole, has a radius of 8 mm (0.3 inch); it is transparent and is called the cornea; the remainder, the scleral segment, is opaque and has a radius of 12 mm (0.5 inch). The ring where the two areas join is called the limbus. Thus, on looking directly into the eye from in front one sees the white sclera surrounding the cornea; because the latter is transparent one sees, instead of the cornea, a ring of tissue lying within the eye, the iris. The iris is the structure that determines the colour of the eye. The centre of this ring is called the pupil [1]. The dimensions of the eye are reasonably constant, varying among normal individuals by only a millimetre or two; the sagittal (vertical) diameter is about 24 mm (about one inch) and is usually less than the transverse diameter. At birth the sagittal diameter is about 16 to 17 mm (about 0.65 inch); it increases rapidly to about 22.5 to 23 mm (about 0.89 inch) by the age of three years; between three and 13 the globe attains its full size. The eye is made up of three coats, which enclose the optically clear aqueous humour, lens, and vitreous body (Fig.1.1). The outermost coat consists of the cornea and the sclera; the middle coat (the uvea) contains the main blood supply to the eye and consists, from the back forward, of the choroid, the ciliary body, and the iris. The innermost layer is the retina, lying on the choroid and receiving most of its nourishment from the vessels within the choroid, the remainder of its nourishment being derived from the retinal vessels that lie on its surface[1].

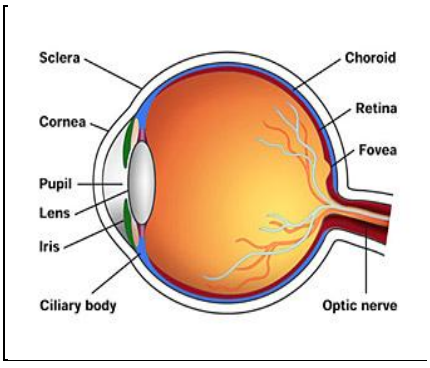


Figure 1.1 Anatomy of the eye.

The ciliary body and iris have a very thin covering, the ciliary epithelium and posterior epithelium of the iris, which is continuous with the retina.

Within the cavities formed by this triple-layered coat there are the crystalline lens, suspended by fine transparent fibres-the suspensory ligament or zonule of Zinn-from the ciliary body; the aqueous humour, a clear fluid filling the spaces between the cornea and the lens and iris; and the vitreous body, a clear jelly filling the much larger cavity enclosed by the sclera, the ciliary body, and the lens. The anterior chamber of the eye is defined as the space between the cornea and the forward surfaces of the iris and lens, while the posterior chamber is the much smaller space between the rear surface of the iris and the ciliary body, zonule, and lens; the two chambers both contain aqueous humour and are in connection through the pupil.

1.1.1 *The uvea.*

The uvea is the vascular tissue surrounding the eye, lying between the corneoscleral shell externally and the retina internally (Fig.1.1). It consists of three basic parts: the Iris, the ciliary body and the choroid [2]. The functions of the uvea include pupillary reactions, the formation of aqueous fluid and the supply of nutrition to the eye. It also plays an important role in the immunological defence mechanisms of the eye [3].

The iris is made up of three layers. A compact arrangement of fibroblasts, melanocytes, and collagen constitute the anterior and most superficial layer which terminates at the iris root peripherally, except where spokelike extensions continue to Schwalbe's line. The stroma (middle layer) consists of pigmented and nonpigmented cells in a loose extracellular matrix of collagen and mucoplysaccharides. It also contains a rich supply of blood vessels and nerves as well as the iris sphincter muscle. The dilator muscle made of smooth muscle fibres and the pigment epithelium composed of two layers apposed to each other apex to apex constitute the posterior layers of the iris [4].

The ciliary body extends from the iris anteriorly to the ora serrata posteriorly and is divided into two parts: The anterior portion (pars plicata or corona ciliaris) made of 70-80 meridional process that secrete aqueous and the posterior portion (pars plana or orbiculus ciliaris) measuring 3.5-4mm in length. The ciliary body contains two epithelial layers: the nonpigmented epithelium (NPE) which is the continuation of the neurosensory retina anteriorly, and the pigmented epithelium (PE) which is an extension of the retinal pigment epithelium. The NPE in the pars plana region is thought to be responsible of the acid mucopolyssaccharide component of vitreous, while it is responsible for the

secretion of aqueous in the anterior portion [5]. The capillaries within the ciliary process are fenestrated. Thus the primary component of the blood-aqueous barrier is the zonula occludens at the apical aspect of the NPE [6].

The choroid has a blood flow that is comparable only to that of the kidney. Therefore systemic influences can be assumed to rapidly affect this portion of the eye. Hence, the large blood flow and its anatomy act as a sort of trap for many blood-borne problems, most notably metastatic fungal disorders. Indeed most fungal lesions begin as a choroiditis [7]. It has the capacity to function as a repository for immunoreactive cells, in the extreme taking on the anatomic structure of a lymph node (lymphoid hyperplasia). Therefore this organ can be the centre for profound immune responses. The high concentration of mast cells in the choroid may be one mechanism by which immunoreactive cells could spread to other parts of the eye. The mast cell's release of immunoreactive factors could help T-cells egress and ingress from this compartment[8].

1.1.2 *The Retina*

The retina is the tissue layer that converts light into visual signals transmitted to the brain. This process is carried out by two major types of photoreceptors, rods and cones that are distinguished by their shape, type of photopigment, retinal distribution, and pattern of synaptic connections [9] (Fig.1.2). Photoreceptors consist of four major compartments: a photosensitive outer segment containing highly packed disc membranes and the proteins required to initiate a response to light, an inner segment (IS) where proteins and lipids are synthesised and energy produced, a nuclear region, and a synaptic terminal that sends information to the second order neurons in the retina [10]. The different architectures of photoreceptors' outer segments (OS) represent a major distinctive feature of these two cell types. Rods with their longer OS composed of individualised discs unconnected to the ciliary plasma membrane contrast starkly with cones. The latter features shorter OS that arise initially as invaginations with subsequent formation of a series of discs (or invaginations), which are continuously connected to the membrane of the cilium that extends over the length of the OS. Lack of rim formation is the reason for this open formation of cone discs.[11] A striking difference between rod and cone circuitry is the degree of convergence. Each rod bipolar cell is contacted by a number of rods, and many rod bipolar cells contact a given amacrine cell (Fig.1.2). In contrast, the cone system is much less convergent. Thus, each retinal ganglion cell that dominates central vision receives input from only one cone bipolar cell, which in turn, is contacted by only a single cone. More convergence makes the rod system better detector of light, because small signals from many rods are pooled to generate a large response in the bipolar cell. However, such convergence also reduces the spatial resolution of the rod system. The one-to-one relationship of cones to bipolar and ganglion cells is just what is required to maximize visual acuity [9]. Proper functioning of photoreceptor cells requires a delicate balance of proteins, lipids, and metabolites, which, if disturbed, can lead to retinal degeneration. To prevent the toxic effects of accumulated photo-oxidative products, photoreceptor cells undergo a daily renewal process wherein ~10% of their volume is shed and subsequently phagocyted by adjacent RPE. To maintain a relatively constant length, the photoreceptor OS basally regenerates roughly the same volume of cellular material each day [12].

The ganglion cell layer is constituted of at least three major classes of neurons. The smallest midget ganglion cells comprise approximately 80% of these neurons, and the larger parasol ganglion cells approximately 10%. The axons of the ganglion cells constitute the nerve fibre layer (NFL). Exiting the eye at the optic disc, these axons form the optic nerve (the second cranial nerve) and synapse in the

midbrain. The whitish appearance of the optic nerve head is due to the myelin sheath that covers these axons as they leave the eye[13]. Within the central area, ganglion cell densities reach 32,000-38,000 cells/mm^2 in a horizontally oriented elliptical ring 0.4-2.0 mm from the foveal centre. In peripheral retina, densities in nasal retina exceed those at corresponding eccentricities in temporal retina by more than 300%; superior exceeds inferior by 60%[14].

The RPE is a monolayer of cells that perform many functions vital for retinal preservation [15-17]. The apical membrane of the RPE lies adjacent to the OS of photoreceptor cells, whereas basolateral membrane contacts the Bruch's membrane [18]. The retina is exposed to high levels of light throughout the day, which, if unabated could lead to damaging photo-oxidative reactions and ultimately to retinal degeneration. The RPE has evolved several strategies to prevent these noxious effects. Light filtration by the RPE pigments functions as a preventive mechanism against photo-oxidation, high levels of antioxidants expedite either enzymatic or non-enzymatic removal of resulting chemically reactive species, and RPE cells also can repair considerable damage to DNA, proteins , and lipids. In addition to its role as a protective barrier, the RPE transports nutrients and ions between the retina and the choriocapillaris. The RPE conveys new retinoids from the bloodstream and is absolutely required for the regeneration of 11-cis-retinal in a process referred to as "visual cycle" [19, 20]. Lipofuscin is an autofluorescent cellular waste product that cannot be degraded or removed from cells. Lipofuscin in the retina, formed from the condensation of two molecules of all-transretinal and one molecule of phosphatidylethanolamine, is believed to accumulate because of incomplete digestion of OS in the RPE [21, 22]. Once in the RPE, lipofuscin is converted to the photo-inducible free-radical generator A2E, a pyridinium bisretinoid toxic to RPE cells. Because RPE cells are post mitotic, they cannot dilute A2E by simple cellular division, so progressive build-up of A2E occurs within the cell. Indeed, one damaging effect of A2E is inhibition of phagolysosomal degradation of OS by the RPE [23, 24]. Additionally, oxidized low-density lipoproteins (oxLDL) inhibit the breakdown of OS in the RPE by delaying the maturation of RPE phagosomes [25, 26]. OS renewal is a tightly regulated process, with the RPE challenged daily by a new batch of phagocytised OS. Breakdown in the ability of this cell layer to efficiently degrade these products would eventually lead to a build-up of undigested lipids and proteins within the RPE, resulting in further production of compounds like A2E. Such excessive accumulation of photo-oxidized products in the RPE is believed to be an underlying cause of degenerative retinal diseases such as age-related macular degeneration. However, an alternative hypothesis is that all-trans-retinal is a toxin, whereas A2E represents a product of de-toxification [27]. It has been estimated that each RPE cell phagocytes hundreds of thousands of OS discs over a human lifetime. Retinal health requires important interactions between photoreceptors cells, responsible for collecting and

processing visual stimuli, and the retinal pigment epithelium [12].

It is established that the human visual system presents a higher sensitivity to light beams entering the eye near the centre of the pupil than to those entering near the edge of the pupil. This effect is known as the Stiles-Crawford effect of the first kind (SCE I) [28]. The outermost aspect of a photoreceptor, the outer segment, contains a photo pigment that absorbs light, converting it into electrical activity. Outer segments form a distinct retinal layer. Photoreceptor inner segments, which contain many of the organelles of these cells, excluding their nuclei, also constitute a distinct retinal layer. Rods and cones synapse on retinal bipolar cells, which feed into retinal ganglion cells. This photoreceptor → bipolar cell→ ganglion cell arrangement reflects the feed forward or centripetal nature of retinal organization[13]. There are also lateral interconnections that provide for the horizontal transmission of retinal information. In addition to the feed forward and lateral interconnections, there is feedback transmission of information[13]. A vascular network covers the retina, except in what is referred to as the foveal avascular zone, a region that is larger than the foveola, but smaller than the fovea. This adaptation prevents the scattering of light by retinal vessels, maximizing visual resolution provided by the fovea. Metabolic nourishment for (and nonfoveal) cones is provided by the choroid[13].

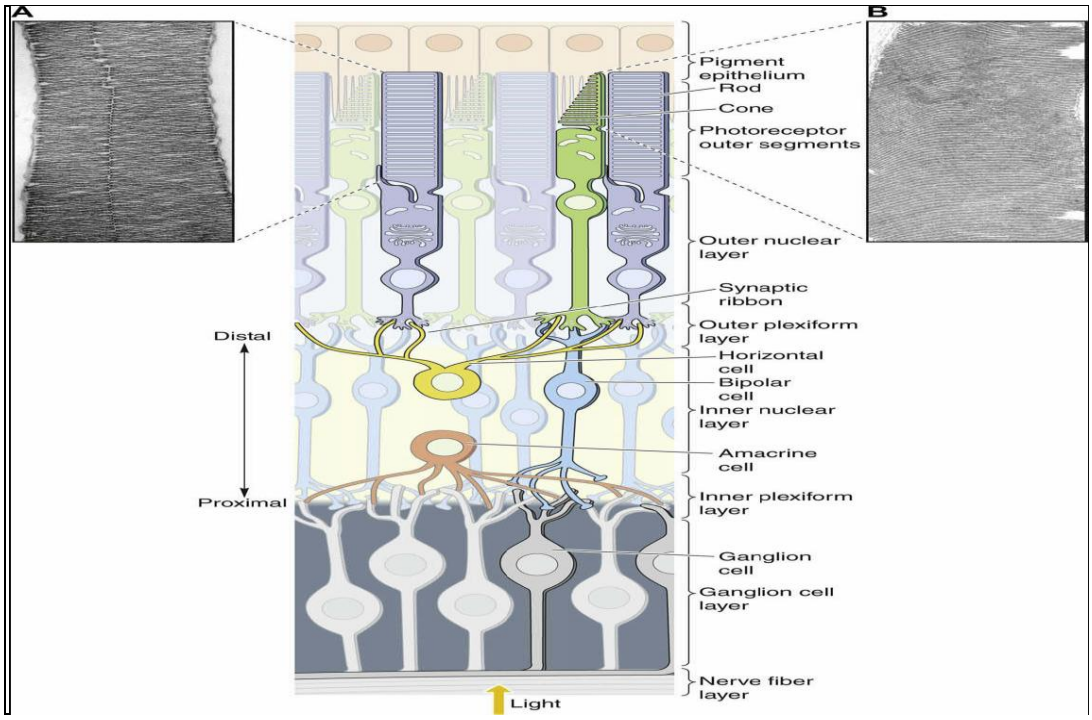


Figure 1.2 Photoreceptors arrangement in the retina[9]

Rod and cone photoreceptors are displayed in a cross-sectional depiction of the retina also showing connections of these photoreceptors to retinal pigment epithelium distally and relaying cells

(bipolar, horizontal, amacrine, ganglion) proximally. Electron microscopic images are shown of a ROS (A) and a COS (B).

The rod structure has a longer outer segment with discs packed without connections to the ciliary membrane, in stark contrast to the COS discs that are continuously connected by the ciliary membrane.

Temporal to the optic disc is the fovea, a specialized retinal region of highly developed visual acuity. A number of anatomical features distinguish the fovea. To maximize vision, neural elements of the inner retina are pushed aside to allow light to fall directly on the photopigment-containing outer segments of cones. This creates a depression or pit with gently sloping borders that is approximately 5 degrees in diameter, approximately the same size as the optic disc. (Figure1.3) The bottom of the pit, the foveola, subtends a visual angle of approximately 1.2 degrees. Cones are the only photoreceptors found in the foveola, where they have a density greater than in any other region of the retina.

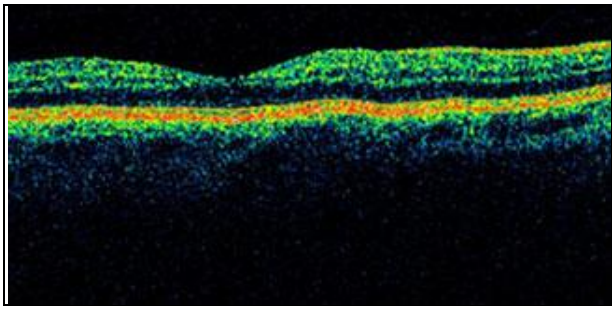


Figure 1.3 OCT showing normal foveal pit.

The mechanism of photoreceptor alignment remains a question without definite answer. The common hypothesis is that this alignment is governed by a phototropic mechanism that actively orients the photoreceptors' axes toward a point close to the pupil centre [29]. Eckmiller et al. [30] proposed a model for photoreceptor alignment whereby light absorption in the outer segment (OS) causes fast membrane and slower cytoplasmic changes that spread from the OS to the myoid, where thy activate feedback-controlled motor functions by cytoskeletal elements (microtubules and microfilaments) to produce a differential local bending that adjusts photoreceptor orientation. Marcos and Burns proposed the alternative hypothesis that the eye's optics and photoreceptors could act as an optimal instrument. They measured the wavefront aberrations and cone directionality function in 24 eyes of 12 subjects and found that although for some eyes the maximum of cone directionality corresponded to the pupil area of best optical quality, this was not general rule. They concluded that in general the ocular optics and cone alignment do not develop

toward an optimal optical design [31].

Using a high-resolution adaptative optics scanning laser ophthalmoscope, Chui et al.[32]demonstrated that in terms of cones per square millimetre, there is a systematic decrease in cone packing density with increasing axial length. They found that cone photoreceptor packing density was significantly lower in myopic eyes than in emmetropic eyes. The density decreased from 27,712 cells/mm^2 to 7,070 cells/mm^2 from a retinal excentricity of 0.30 to 3.40 mm along the superior meridian, although more than 20% of the variance could be accounted for by differences in axial length.

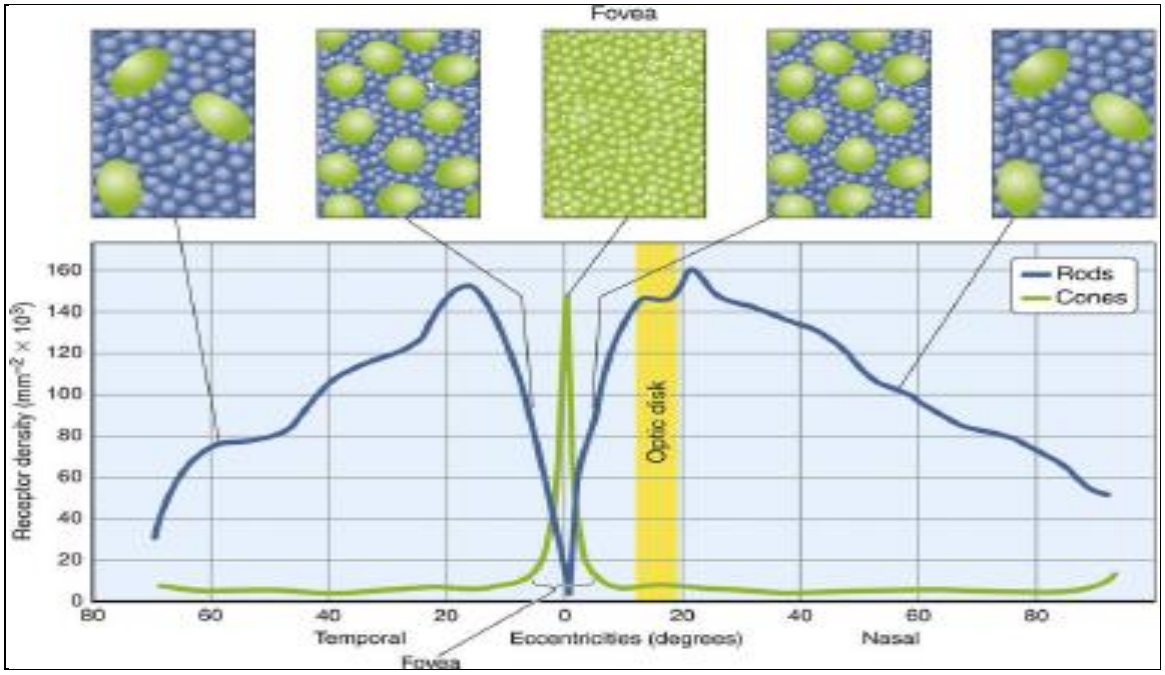


Figure 1.4 Distribution of photoreceptors in the eye [9].

Overall, rods outnumber cones by a ratio of 20:1 in the retina. However, in the fovea, the cone density is the highest and is correlated with visual acuity.

1.1.3 *Ocular barriers.*

The blood- ocular barrier system separates the interior portion of the eye from the blood entering the eye. (Fig.1.5). Of the two blood-ocular barriers, the blood-aqueous barrier (BAB) regulates exchanges between the circulating blood and the aqueous humour, and the blood-retina barrier (BRB) regulates exchanges between the circulating blood and the neural retina [33]. At the blood-ocular barriers, unique distribution of plasma membrane transporters is required to

efficiently supply nutrients to the interior portion of the eye and remove endobiotics and xenobiotics from the same interior portion [34].

The BAB is closely associated with the secretion of aqueous humour. The regulatory role of the BAB is mainly controlled by the ciliary epithelial bilayer consisting of the pigmented ciliary epithelial (PE) layer facing the ciliary stroma and the non-pigmented ciliary epithelial (NPE) layer facing the aqueous humour [33]. Neighbouring cells between the PE and NPE layers are coupled by intercellular gap junctions, thereby, forming a functional syncytium[35].

The BRB plays a primary role in providing a controlled environment of the neural retina, which underpins highly regulated neurotransmission. The retina has two areas of interaction with the blood circulation and thus the BRB consists of two parts, the inner and the outer BRB (Figure 4). The blood supply to the inner two-thirds of the retina comes from the retinal circulation. The choroidal circulation nourishes the outer third of the retina [36]. Unlike retinal capillaries, the vasculature of the choroid has a high blood flow and leaky walls [37].

Because of the continuous diffusional exchanges between blood, ocular tissues, and intraocular fluids, almost any condition that affects the eye or has a marked effect on the blood composition or flow can be expected to have some influence on the blood-ocular barrier system and on the composition of the intraocular fluids [33]. One of the main reasons for the existence of the entire blood-ocular barrier system is to preserve and protect retinal function. It keeps the retina dehydrated in order to maintain its transparency to light. The consequences to the eye of a breakdown of the blood-ocular barrier system are many, depending on the location of the breakdown and the structure involved. Relatively minimal alterations of the BRB may result in a abnormal passage of fluids into the retinal extracellular space and cause retinal oedema, hence lead to visual impairment [33].

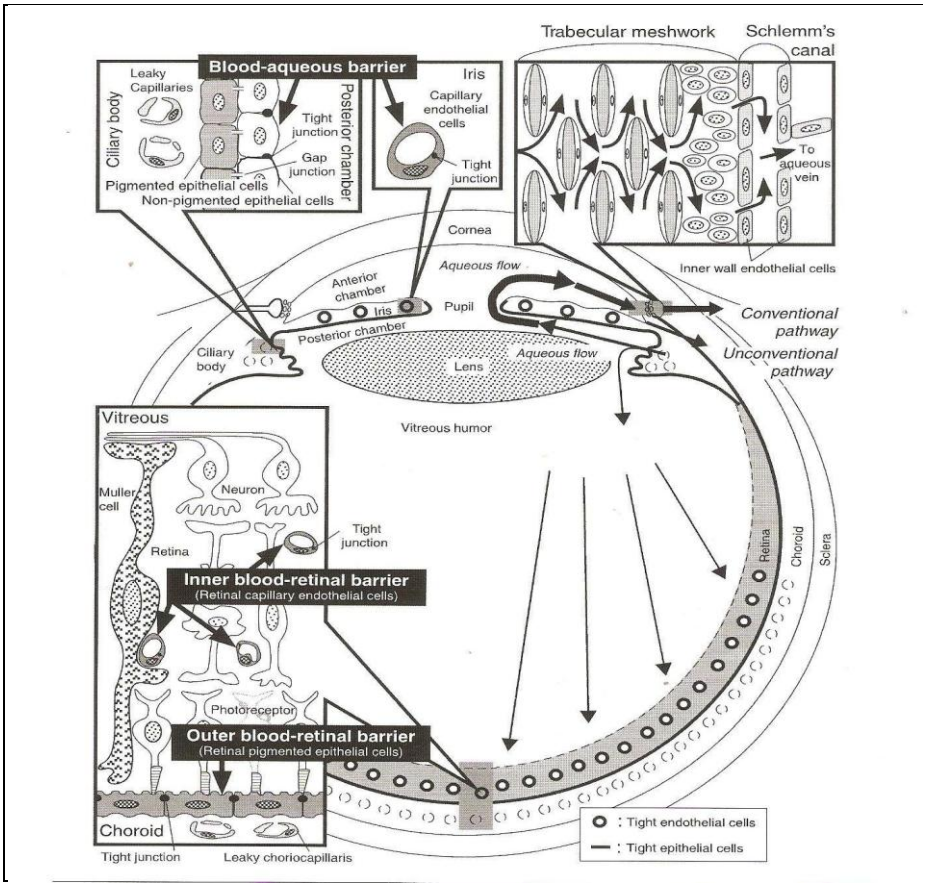


Figure 1.5 Schematic representation of blood-ocular barrier system and aqueous flow. [34]

The interior portion of the eye is separated from the circulating blood by two blood-ocular barriers systems, the BAB and BRB. The BAB consists of ciliary NPE cells and iridial capillary endothelial cells. The BRB consists of retinal capillary endothelial cells (inner BRB) and RPE cells (outer BRB). The aqueous humour is secreted through ciliary NPE cells into the posterior chamber, passes through the pupil into the anterior chamber and then spreads peripherally toward the angle of the anterior chamber. Aqueous humour is mostly drained from the anterior chamber angle either through the trabecular meshwork into the Schlemm's canal and aqueous veins (conventional pathway) or through the ciliary muscle into the suprachoroidal space (unconventional pathway). A part of the aqueous humour is cleared by passing through the vitreous humour and the retina. [28].

1.2 Pathophysiology of uveitis

Uveitis refers to the inflammation of the uvea. It comprises a very diverse group of entities resulting from a variety of causes. This inflammation may lead to significant visual loss [38]. Inflammatory diseases of the eye were known to the ancients, but only recently have the underlying mechanisms to this problem become better defined. During the middle portion of the last century, most cases of uveitis were thought to be caused by infectious agents, such as those responsible for syphilis and tuberculosis. Since then, it has become clear that endogenous mechanisms of immune-modulation play an important role in these disorders, which along with the environmental and genetic factors make up an important triad [2].

It is now established that ocular inflammation is mediated by activated CD4+ T cells. These cells play a central role in the immunogenic mechanisms. When infiltrating the eye, they are harmful to vision-related cells and tissues and cause sight threatening conditions [39]. However, the eye has a unique regional immune system which protects intraocular tissues from these pathogenic activated CD4+ T cells and contributes to the homeostasis of the intraocular microenvironment [40]. The eye is an excellent example of immune privilege site. This organ enjoys immune privilege to protect it from destructive inflammation that may impair vision [41]. The ocular microenvironment is both immunosuppressive and anti-inflammatory. Cultured ocular pigmented epithelium (PE) cells from the iris, ciliary body, and retina can individually suppress T-cells activation via mechanisms that partially overlap [42]. The blood-retina barrier and a special feature named anterior chamber associated immune deviation (ACAID) constitute the immune privilege mechanism which protects the eye from destructive effects of an intraocular cell mediated immune process. These special defence mechanisms contribute to the preservation of vision[43]. Also, we know that the ocular microenvironment is rich with immunosuppressive molecules that influence the activity of immune cells. Many soluble immunomodulators are found in aqueous humour, and are a mixture of growth factors, cytokines, neuropeptides, and soluble receptors. The mechanisms of ocular immune privilege induce apoptosis, promote the production of anti-inflammatory cytokines, and mediate the activation of antigen-specific regulatory immunity. These mechanisms of immune privilege also attempt to impose themselves upon immunity within the uveitic eye [44].

It is generally assumed that this property is severely compromised or eliminated when the inflammation is present within the eye [43]. Tissue damage in uveitis is caused by various chemical mediators derived from either plasma proteins or inflammatory phagocytic

cells, Polymorphonuclear cells (PMNs), and macrophages. These mediators include arachidonic acid metabolites, proteolytic enzymes, and possibly oxygen metabolites [45].

In addition to the uveitogenic antigens resident in its layers, the retina, being an “extension of the brain”, makes it particularly prone to certain neurotropic organisms. Examples include Toxoplasma gondii and many viruses of the herpes family, which \have the propensity for central nervous system tissue. It is also important to remember that under normal circumstances the retinal vasculature has tight junctions; thus it is being impermeable to many molecules. Any perturbation, such as an inflammatory one, that alters this permeability can result in a profound change in retinal functioning. It is interesting to speculate that because the retina maintains a high degree of oxidative metabolism, the potential for the generation of oxygen radicals may lead to autotoxicity[8]. Reactive oxygen metabolites (oxygen free radicals) released by PMNs and macrophages are believed to play an important role during initial phase of inflammation [46],[47]. These free radicals are found to be potent cytotoxic agents that readily cause tissue damage by peroxidation of lipid cell membranes. Recent studies of experimental uveitis indicate that other potent oxidants are generated in uveitis by macrophages[48]. One of these is ONOO-, which is formed from *NO preferentially in the outer retina following iNOS expression. In these phagocytes, outer retinal proteins, especially arrestin are found to be iNOS inducers. Current studies of RPE show that these cells protect the retina from ONOO- mediated damage in uveitis by releasing a novel protein called retinal pigment epithelial protective protein (RPPP). This protein is found to suppress O(-)2 and *NO generation by the phagocytes, both in vitro and in vivo uveitis models [48]. The pro-inflammatory cytokines interleukin (IL)-1beta, IL-2, IL-6, interferon-gamma and tumour necrosis factor-alpha have all been detected within the ocular fluids or tissues in the inflamed eye together with others, such as IL-4, IL-5, IL-10 and transforming growth factor-beta. The chemokines IL-8, monocyte chemoattractant protein-1, macrophage inflammatory protein (MIP)-1alpha, MIP-1beta and fractalkine are also thought to be involved in the associated inflammatory response [49]. Determining the levels of IL-2, -4, -5, -10, TNF-alpha, and IFN-gamma in aqueous humour from patients with panuveitis and anterior uveitis, Ooi et al.[50]found that IFN-gamma is elevated in active uveitis and IL-5 is decreased in posterior. Perez et al.[51]reported elevated IL-6 in the vitreous of patients with active intermediate and posterior uveitis. Cytokines in aqueous humour of infectious uveitis are locally produced, whereas in non-infectious uveitis, IFN-gamma is produced both in the eye and the peripheral blood [52]. IL-6 is responsible for causing ocular inflammation, and it is, at

least partially due to IL-6-dependent Th17 differentiation, a recently discovered IL-17 producing helper $CD4^+$ T-cell subset [53, 54].

Th-17 constitutes a Th cell lineage distinct from Th1 and Th2 cells, and plays a crucial role in several autoimmune diseases by mediating tissue inflammation [55].
IL-17 stimulates IL-17R-expressing cells, and these cells in turn induce the secretion of IL-6, IL-8, PGE2, MCP-1 and G-CSF, causing chronic inflammation [56].
IL-23 has been reported to be responsible for TH17 expansion and crucial for development of autoimmune inflammatory diseases [57, 58].

New studies comparing cells in ocular fluids taken from inflamed eyes with different types have shown a difference in the cytokine profile, so that in visually benign disease interleukin 10 levels are higher than in those which are blinding [59]. Verma et al.[60] found that the concentration of chemokines: IL-8, interferon-inducible protein 10(IP-10), monocyte chemoattractant protein(MCP-1), regulated on activation, normal T-expressed and secreted (RANTES) and macrophage inflammatory protein-1 beta (MIP-1 beta) were significantly increased during the active stages of AU, and correlated with the clinical severity of the disease. These chemo-attractant cytokines probably play a critical role in leukocyte recruitment in acute AU.

Macrophage migration inhibitory factor (MIF) was originally discovered as a T lymphocyte derived factor to inhibit macrophage migration [61]. This pro-inflammatory pituitary and macrophage cytokine is capable of overcoming glucocorticoid mediated inhibition of cytokines, such as tumour necrosis factor α (TNF-α), interleukin (IL)-1ß, IL-6, IL-8, and interferon ɤ (IFN-ɤ) [62, 63]. Although the function of MIF in the eye has not been well studied, Apte et al.[64]demonstrated that MIF shared more than 90% homology with the factor in the aqueous humour which inhibited natural killer (NK) cell mediated lysis of corneal endothelial cells. In patients with uveitis, serum levels of MIF were significantly higher than those in healthy control [65]. Evidences from the work byTaguchi et al.[66]show that aqueous humour and vitreous fluid of patients with uveitis contained significant levels of MIF, and these levels correlated with activity of intraocular inflammation. The authors suggested that intraocular infiltrating cells are upregulated much more actively than PBMC in terms of the capacity to produce MIF.

The explanation for why some patients develop chronic uveitis whereas others have a recurrent self-limiting type of uveitis is unknown. The development of chronicity is not due to inadequate treatment, is unrelated to HLA-B27 and it is likely that host factors are important determinants. Patients with chronic anterior uveitis (CAU) vary in their clinical phenotype. Some develop complications such as cataract, glaucoma and cystoid macular oedema, but others do not [67]. Idiopathic acute anterior uveitis (AAU), in which there is often a severe inflammatory response

in the anterior chamber is the most common type that occurs in the general population. The disease's severity and course vary between individuals, and some patients have ocular complications that can threaten sight [68]. Neutrophil gelatinase-B associated lipocalin (Lcn2/NGAL or NGAL) is a 21-kD protein of the lipocalin superfamily. NGAL is siderophore-binding antimicrobial protein that is upregulated in epithelial tissues during inflammation and seems to play an important role in this process [69]. This protein plays a cytoprotective role by transporting iron into cells, developing antioxidant activity and reducing apoptosis. NGAL is a potent inducer of heme oxygenase-1 (HO-1) and superoxide dismutase (1,2; SOD) [70]. Salom et al. [68] found elevated levels of NGAL in aqueous humour of patients with idiopathic AAU. These findings imply that NGAL is associated with the regulation of inflammation in AAU. In addition, NGAL is strongly upregulated by interleukin (IL) 1-beta [71], and TNF-α in the presence of IL-17 [72], and increased levels of IL-1 have been observed in AAU [73].

In Sympathetic ophthalmia (SO), the loss of vision in the absence of recognizable retinal damage and inflammatory cell infiltration within the retina and choriocapillaris has been an enigma. Parikh et al. [74]demonstrated that in SO, photoreceptor mitochondrial oxidative stress occurs in the absence of leukocytic infiltration of the retina and may lead to photoreceptor apoptosis and subsequent vision loss.

1.2.1 *Immune response mechanisms in uveitis.*

Accumulating evidence shows that the immune response may be a predominant mechanism involved in the development of various uveitis entities [75]. Immune responses have been classically divided into innate and adaptive according to the speed and specificity of the reaction. Innate immune responses act as the first line of defence against infection in every part of our body, including the uvea. [75]. Apparently, innate immune responses play an important role in uveitis induced by infections, such as uveitis caused by toxoplasmosis, tuberculosis, syphilis and Lyme disease. Furthermore, evidence from a number of clinical and experimental studies has also implicated a potential role of innate immune responses to some bacteria and its products in the pathogenesis of several immune-mediated, non-infectious uveitis entities with systemic involvement, including ankylosing spondylitis, sarcoidosis, and Behçet's disease [76-78].

Antigen-presenting cells (APCs) are the critical components of the innate immune response system. These cells can bind to and take up microbial agents and their products by a variety of receptors. APCs can subsequently degrade microbial products or autoantigens to form small

polypeptide fragments and present these polypeptides to the surface of APCs in association with human leukocytes antigens (HLA) [75]. Several autoantigens have been identified as potential triggers for autoimmune uveitis [79-81].

1.2.1.1 *Factors involved in the innate immune response.*

Toll-like Receptors.

TLRs, a family of transmembrane receptors, are among the most important genes involved in innate immunity. Ten TLRs have been described to date in humans which recognize microbial components at the cell surface or endosome [82]. Recognition of pathogen-associated molecular patterns (PAMPs) by these receptors on APCs is able to induce the expression of various pro-inflammatory cytokines, chemokines, co-stimulatory molecules, and MHC molecules. Therefore, these APCs can initiate a rapid host defence against the invading pathogen. Meanwhile, these APCs acquire the ability to activate naive CD4+ T cells and induce their differentiation into Th1, Th2, or Th17 cells. In this way, TLRs may also have an effect on adaptive immune responses. When the activated T cells are self-antigen specific, autoimmune responses may ensure [83-85].

NOD I and NOD2.

The NOD proteins NOD1 and NOD2 are members of the NACHT (domain present in NAIP, CIITA, HET-E, and TP1)-LRR(leucin-rich repeat) family and they are encoded by the caspase-recruitment domain (CARD) 4 gene and CARD 5 gene respectively [86]. Both NOD1 and NOD2 are composed of three domains: a C-terminal LRR domain involved in ligand recognition, a central NOD domain with ATPase-activity-mediated self-oligomerisation, and an N-terminal CARD domain [86]. Watanabe et al. [87, 88] found that NOD2 deficiency may lead to markedly higher IL-12 production and enhance Th1 responses [89]. However, NOD2 was also found to upregulate production of IL-8, TNF, IL-1ß, and IL-10 from APCs mediated by TLRs.

1.2.1.2 *Factors involved in the adaptive immune response.*

HLA Complex.

Antigen recognition is the foundation of all adaptive immune responses. In humans, the capacity of adaptive immune response to an antigen is genetically determined by products of the HLA system. HLA molecules, which are located on chromosome 6 and divided into three classes (class I, II, and III), are highly polymorphic and function as molecules that are capable of presenting antigens. After APCs degrade antigen into peptides, they present these peptides on their surface via HLA molecules. CD4+T cells recognize the peptide HLA complexes by their T-cell receptors (TCRs), which lead to their activation. Thus, appropriate adaptive immune responses are initiated by CD4+Tcells. Co stimulatory signals, such as CD28, are necessary for T- cell activation [75]. The association between the HLA-B27 serotype and anterior uveitis was one of the first identified associations between HLA genes and human disease [90]. HLA-B27 seems to be just one of multiple factors involved in HLA-B27 – associated anterior uveitis, since only about 1% of HLA-B27-positive individuals develop anterior uveitis in their lifetime [91]. Specific HLA alleles do not directly cause uveitis and the real causes for the association between HLA genes and human diseases remains unknown. Up to now, HLA genes have been shown to be associated with a number of uveitis entities including birdshot choroidopathy (HLA-A29), Behçet's disease (HLA-B51), Vogt-Koyanagi-Harada syndrome (HLA-DR1/DR4/DRw53), tubulointerstitial nephritis syndrome(TINU)-(HLA- DRB1*0102), sympathetic ophthalmia (HLA-DRB1*04) [92-94].

Co- stimulatory Molecules.

The specific peptide-HLA-TCR interaction is not sufficient to fully activate the T- cell, and co stimulatory signals must be present on the same cell. The most potent co stimulatory signals are mediated by a CD28-B7 interaction. These two molecules are expressed on T- cells and dendritic cells respectively. The CD28-B7 interaction has been shown to prolong and augment the production of IL-2 and to prevent the induction of tolerance [75].

Investigating the association of CTLA-4 gene polymorphisms (-1661A/G; -318C/T; +49G/A, and CT60) with Behçet's disease and VKH syndrome in Chinese patients, Du et al[95] reported that the frequency of the G allele at the +49 site and the frequency of haplotype-1661A:318C:+49G: CT60G were significantly higher in patients with VKH syndrome than that observed in healthy controls.

1.2.1.3 *Immune response factors contributing to the susceptibility to uveitis.*

Tumor Necrosis Factor (TNF).

In addition to HLA genes, a variety of immune response genes have been shown to be located in HLA gene region. TNF is a multifunctional proinflammatory cytokine located in the HLA gene region. TNF-α is believed to play a pivotal role in Th1-mediated diseases, such as Behçet's disease [75]. Although earlier studies did not support that some polymorphisms in the TNF promoter region played a role in the susceptibility to Behçet's disease [96-98], Ahmad et al. [99] reported that the TNF-1031C allele is independently associated with susceptibility to Behçet's disease in Caucasian patients. These findings have been confirmed by studies in patients from Turkey, Tunisia and Korea [100-103].

MHC Class I Polypeptide-related sequence A (MICA).

Mizuki et al.[104] reported that the (GCT/AGC)(6) allele of microsatellite polymorphism in MICA gene was present in all HLA-B51-positive patients and in an additional 13 HLA-B51- negative patients, suggesting the possibility of primary association of Behçet's disease with MICA rather than HLA-B. This association of MICA polymorphisms with uveitis was implied in subsequent studies [105, 106]. Wallace et al.[107] found that MIC 009 allele was more prevalent among patients compared with controls. Their data also indicated that both MIC-A*009 and the triplet repeats polymorphism of MICA were in strong linkage disequilibrium with HLA-B51; they are unlikely to be susceptibility gene for Behçet's disease, but may be markers for additional risk factors. Subsequently, a study performed on three populations also indicated that the pathogenic gene of Behçet disease id HLA-B51 itself and not other genes located in the vicinity of the HLA-B region [108].

Interleukin (IL)-I

IL-1, a potent pro-inflammatory cytokine, has a critical role in autoimmune diseases, such as Behçet's disease. The polymorphism of IL-1 gene cluster has also been studied in certain uveitis entities [75]. Karasneh et al.[109] investigated the association of IL-1 gene cluster polymorphisms with Behçet's disease and found that IL-1A-889C and IL-1B+5887T haplotype contributed to the susceptibility to Behçet's disease. Other studies have recently also shown an association of an IL-1 polymorphism with the chronicity and complications of anterior uveitis and the recurrence of toxoplasmosis retinochoroiditis [67, 110].

1.2.1.4 *Chemokines.*

Chemokines are chemotactic cytokines playing a critical role in cell migration during immune surveillance and inflammation. More than 50 human chemokines have been described and are now separated into four families (CXCL, CCL, XCL, and CX3CL). Several studies have demonstrated that neutrophils and chemokines are involved in uveitis through directing the migration and infiltration of leukocytes to the uveal sites [75]. A gender-specific association of CCL2 and CCL5 polymorphisms with Behçet's disease has been reported by Chen et al [111]. Wegscheider et al.[112] demonstrated that the frequency of CCL-2518G was significantly higher in patients with HLA-B27 AAU than in HLA-B27 positive controls. Other studies have shown that MCP-1 polymorphisms were associated with idiopathic anterior uveitis and posterior uveitis [113, 114]. The clinical outcome of many autoimmune diseases including different forms of intraocular inflammation appears to be influenced by the balance between inflammatory and down-regulatory cytokines[115],[116].

1.3 Classification of Uveitis.

In 2008, the International Uveitis Study Group (IUSG) designed a simplified, clinical classification system based on aetiological criteria. It has 3 main categories, as followed:

- Infectious (e.g., bacterial, viral, fungal, parasitic). Infectious agents such as toxoplasma gondii, herpes virus, Syphilis, CMV, HIV, onchocerciasis are well recognized [117],[118].
- Non-infectious (e.g., known systemic association, no known systemic association). In the majority of patients the cause of the intraocular inflammation is unknown, but in some cases is a manifestation of a systemic disease process, such as sarcoidosis[119, 120], Behcet's disease (BD), juvenile idiopathic arthritis(JIA), multiple sclerosis(MS), ankylosing spondylitis (AS), Inflammatory bowel/Crohn's disease, SLE, Wegener's granulomatosis, VKH[121, 122], whilst others may be associated with various conditions such as the HLA-B27-related group of diseases[45].
- Masquerade: Neoplastic and non neoplastic.

However, the most widely used classification of uveitis is the Standard Uveitis Nomenclature (SUN) devised by International Uveitis Study Group (IUSG) in 1987, based on the anatomical location of the inflammation [123]. According to this, uveitis should be categorised as anterior, intermediate, posterior or panuveitis.

Descriptors of the onset and course of the uveitis were addressed at the 2005 SUN workshop, and it was agreed that the condition should be described as acute, chronic or recurrent. Acute if of sudden onset and duration less than 3 months, chronic if the duration exceeds 3 months, and recurrent if after interrupting treatment the disease flares up after 3 months.[124]

1.3.1 *Anterior uveitis.*

Anterior uveitis refers to inflammation involving the iris and ciliary body, and is the commonest form of uveitis. In most patients, the aetiology is unknown, but the association with HLA-B27, a genetic marker, is present in about 50% of patients [122]. Ankylosing spondylitis (AS), an idiopathic, common, chronic arthritis is strongly associated with acute anterior uveitis. AS usually affects young men in the second or third decade; women are also affected to a lesser extend [125]. About 97% of AS patients are HLA-B27 positive and about 25% of AS patients will develop uveitis [90]. Systemic diseases, such as sarcoidosis or Behçet's disease may be present as an anterior uveitis, but more

usually as panuveitis [126]. Juvenile idiopathic arthritis (JIA) describes a heterogenous group of idiopathic arthritides occurring in children under the age of 16 years. This is the commonest disease association with anterior uveitis in childhood [127]. Though no correlation exists between disease activity in the joint and eye inflammation, an association between the mode of onset of JIA and risk of eye inflammation is well recognised.

Patients with pauciarticular involvement, in the absence of systemic features, carry the highest risk of eye involvement, especially in the presence of anti-nuclear antibodies [127, 128]. In the majority of patients, arthritis precedes the uveitis that has an insidious onset on routine slit-lamp examination [129].

1.3.2 *Intermediate uveitis.*

Intermediate uveitis (IU) refers to a subset of uveitis in which inflammation is primarily observed in the vitreous cavity. It is characterised by low-grade, chronic inflammation of the posterior part of the ciliary body, the vitreous base and peripheral retina. This accounts for 4-8% of the uveitis cases. Children and young adults are typically affected. The inflammation is bilateral in the majority of patients. Some patients may have underlying systemic diseases like multiple sclerosis and sarcoidosis [126]. The diagnostic term pars planitis should be used only for that subset of IU where there is snow bank or snowball formation occurring in the absence of an associated infection or systemic disease [130]. The aetiology is unknown but there are several associated diseases: multiple sclerosis, idiopathic optic neuritis, autoimmune corneal endotheliopathy, sarcoidosis, thyroid diseases and inflammatory bowel diseases [131]. Intermediate uveitis of childhood might exhibit a self-limiting course after several years [132].

1.3.3 *Posterior uveitis*

Posterior uveitis (PU) refers to inflammation of the choroid and retina and may result from localized ocular inflammation (focal, multifocal or diffuse choroiditis, chorioretinitis, retinitis, and neuroretinitis), or from a systemic condition [133, 134]. The aetiology is unknown in many patients, but systemic inflammatory diseases, such as sarcoidosis, Behçet's disease and Vogt-Koyanagi-Harada syndrome, and infectious causes like Mycobacterium tuberculosis, syphilis, herpes group of viruses, toxoplasmosis and ocular toxocara need to be considered in the differential diagnosis [120]. Non infectious posterior uveitis may result in permanent vision loss. The inflammation can be constant, or characterised by periodic exacerbations on an underlying baseline of inflammation. Recent

studies indicate that vision loss often results from cumulative damage over multiple recurrences of inflammation, rather than from a single initiating event [135].

1.3.4 *Panuveitis.*

Panuveitis involves inflammation of the anterior, intermediate, and posterior uveal structures, and the differential diagnosis is similar to that of posterior uveitis. Herpetic viral retinitides may also present as panuveitis or posterior uveitis in both immunosuppressed and immunocompetent individuals.[133]

1.3.5 *Masquerade Syndromes.*

The term masquerade syndrome is classically used in ophthalmology to describe those conditions that include as part of their manifestation the presence of intraocular cells, but that are not due to immune-mediated uveitis entities [136]. The two underlying disorders for which the term masquerade is most commonly used are intraocular infection and intraocular lymphoma. Both can appear to be a chronic panuveitis with little in the way of other signs.[137] Acute endophthalmitis occurs within a few days after surgery and is usually recognised, but delayed onset endophthalmitis may occur weeks or months after the surgery, and can be much more difficult to diagnose. Aqueous and vitreous sampling may not yield viable organisms which can be grown on laboratory media, and the inflammation may be partially suppressed by corticosteroids.[137] Patients with intraocular lymphoma may be perfectly well with no systemic or neurological symptoms and signs, and few other ocular signs except cells, predominantly in the vitreous, with some in the anterior chamber. Vitreous sampling may not yield enough cells for the diagnosis to be confidently established, and the vitritis may be steroid sensitive, at least initially[137].

1.3.5.1 *Lymphoid malignancies.*

A. *Primary CNS lymphoma in immunocompetent patients****.***

In a review of 828 consecutive patients seen in a tertiary referral clinic, Rothova et al found a frequency of neoplastic masquerade syndromes of 2.3% (19 patients). Of these, 13 patients (68%) had intraocular lymphoma, confirming the impression of many that intraocular lymphoma is the most common neoplastic “masquerader” [138]. Approximately 98% of primary intraocular lymphoma are extranodal, non-Hodgkin’s B cell lymphomas, which, as the name implies, are localized to the intraocular structures: vitreous, retina, subretinal, and sub-retinal pigment epithelial

spaces [136]. Approximately 2% of PCNSL are T cell lymphomas, with the very rare occurrence of other primary CNS neoplasms, such as Ki-1 lymphoma, lymphomatoid granulomatosis, T cell-rich B cell lymphoma, signet-ring cell lymphoma, angiotrophic lymphoma, Hodgkin's disease, and plasmocytoma [139]. PCNSL is generally considered a rare condition, but its incidence is increasing. Data from the National Cancer Institute reveal that 2.7 cases per 10 million people were reported from 1972 to 1974, as compared with 7.5 cases per 10 million people from 1982 to 1984 [140]. A continuing increase has been reported during the years subsequent to these data [141-143].
Despite this increase, the risk of an immunocompetent individual developing PCNSL is very low [144].

When the lymphoma involves the vitreous and the retina, the diagnosis may be more apparent, but it may still be difficult to establish definitively in the absence of CNS findings.
Clinically described as creamy yellow subretinal infiltrates, with overlying retinal pigment epithelial detachment [145], but they may take on many forms, such as discrete white lesions, suggestive of acute retinal necrosis, toxoplasmosis, and frosted branch angiitis [146], branch retinal artery obstruction with coexistent multifocal chorioretinal scars [147], and retinal vasculitis [148].

B. *Primary CNS lymphoma in patients with acquired immunodeficiency syndrome (AIDS).*

Immunocompromised patients have an increased risk of malignancy, of which lymphoproliferative disease is an important type, non-Hodgkin's lymphoma being the second most common malignancy associated with AIDS [149]. Compared with nonimmunosuppressed patients, those with AIDS have a much greater risk of developing clinical CNS disease, ranging from 2-6% [150-152].

C. *CNS lymphoma secondary to systemic lymphoma.*

T cell lymphoma and HTLV-1 lymphoma

Ocular involvement in primary CNS lymphoma is typically different from that resulting from secondary involvement of the eye by systemic lymphoma [136]. Although the majority of intraocular lymphomas are of a B cell nature, there is increasing recognition of the existence of intraocular T cell lymphomas [148, 153, 154]. It is interesting that in the majority of case reports involving T cell lymphomas, patients present with primarily an anterior involvement, mimicking an anterior uveitis [136]. In contrast to these cases, Reim et al. [155] reported the presence of T cell lymphomas with primarily posterior findings. HTLV-1 is a retrovirus that has been reported as a cause of adult T-

cell leukemia/lymphoma [156]. A variety of ocular manifestations have been reported with HTLV-1 infection, including retinal vasculitis [157], cotton-wool spots, granulomatous iridocyclitis, and vitritis [158], and subretinal infiltrative lesions [159]. Yoshimura et al.[160] described the clinical features of uveitis associated with seropositivity for HTLV-1 in 93 patients. They found that the incredibly nonspecific symptom of floaters was the only complaint found more commonly in HTLV-1 patients compared to non-HTLV-1 patients with uveitis that reached statistical significance. In addition the findings of vitreous opacities, retinal vasculitis and intermediate uveitis were significantly higher in HTLV-1 positive patients than seronegative patients. The possibility of HTLV-1 virus associated uveitis and adult T cell leukaemia/lymphoma must thus be always kept in mind in the setting of intraocular inflammation, especially in patients who have been in endemic areas [136].

Systemic B cell lymphoma.

Ocular disease can be the presenting sign of systemic lymphoma [161, 162]. Although conjunctival or orbital involvement with systemic B cell lymphomas is relatively common [163], intraocular involvement is rare [161, 163, 164]. In general, systemic lymphomas arising from visceral organ tend to involve the uvea. This is in contrast to CNS lymphomas which typically involve the vitreous, retina, subretinal and sub-RPE areas [136]. Ocular involvement with systemic non-Hodgkin's lymphoma usually carries a poor prognosis, with an average longevity of 31 months after diagnosis [165]. (Fig.1.6)

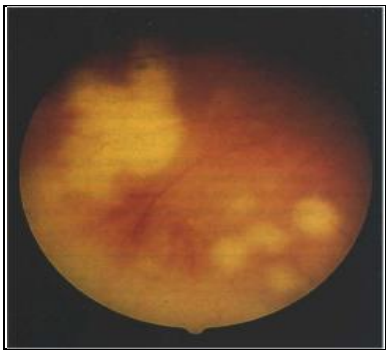


Figure 1.6 Fundus photograph of a patient with choroidal infiltrates due to ocular lymphoma.

The association of uveitis in patients with both systemic and intracranial lymphoma is now well known and, should rank high in the differential diagnosis of chronic vitreous inflammation, especially in patients who respond poorly to anti-inflammatory and immunosuppressive therapy [136].

Leukemia.

Intraocular findings occur in 28-75% of patients with acute leukaemia, less in patients with chronic leukaemia [166]. Retinal findings are common, including intraretinal haemorrhages, cotton wool spots, white-centered haemorrhage (Roth spots), microaneurysms, and peripheral neovascularisation.

Occasionally, leukemic cells can break through the internal limiting membrane into the vitreous cavity, simulating vitritis. When the choroid is involved by the leukemic process, exudative retinal detachment may result. Angiographically, this may assume the typical pattern of Vogt-Koyanagi-Harada disease or posterior scleritis, with multiple, pinpoint serous detachments of the retina and RPE [166]. Other masquerade presentations can include anterior "hypopyon uveitis", with spontaneous hyphema, heterochromia iridis, or pseudohypopyon which is typically gray-yellow in colour [167].

1.3.5.2 *Non- lymphoid malignancies.*

A. *Uveal Melanoma.*

Uveal melanomas may present with clinical features suggestive of intraocular or orbital inflammation. In a series of 450 enucleated eyes with malignant melanoma of the uvea, Fraser et al found that 4.9% of patients presented with ocular inflammation. Clinical presentation included episcleritis, anterior and/ or posterior uveitis, endophthalmitis [168].

B. *Retinoblastoma.*

Although the classic presenting signs of retinoblastoma are leukocoria or strabismus, an inflammatory presentation may also occur in 1-3% of cases, usually in the relatively rare variant of diffuse infiltrating retinoblastoma which presents around 6 years of age [169, 170]. Clinical signs may include conjunctival chemosis, pseudohypopyon, and vitritis. The hypopyon typically shifts with changes of head position [171]. An important morphological clue is that, in contrast to the typically yellowish hypopyon of inflammation, the pseudohypopyon of retinoblastoma is usually white [136].

C*. Metastatic tumors.*

Metastatic tumours are the most common intraocular malignancy in adults. These lesions may involve the uvea, the retina, or optic nerve and produce findings that may be rarely be confused with uveitis [172].

Uveal Metastasis.

Tumour metastatic to the uvea most commonly involves the posterior segment. They tend to be plateau-shaped, yellow in colour, and associated with subretinal fluid [173]. Posterior segment metastatic lesions are infrequently misinterpreted as uveitis conditions [136]. In a series of 40 patients with masquerade syndrome, Rothova et al.[138] reported only one case of metastatic disease (lung carcinoma) to the posterior uvea.

In addition to the posterior uvea, metastasis can present in the anterior segment. In this case, lesions may present with cells in the aqueous humour, as well as other features that are occasionally present in uveitis, such as iris nodules, rubeosis iridis, and elevated intraocular pressure [174-176]. Primary tumour sites commonly reported with anterior uvea metastasis from the lung and breast [174, 176,177].

Retinal Metastasis.

Metastatic tumour isolated to the retina is extremely rare [178]. Although metastatic tumours to the retina can present with vitreous cells, those in metastatic melanoma are described as large brown spherules, whereas metastatic carcinoma typically has a white to yellow colour and may result in perivascular sheathing, possibly simulating a retinal vasculitis or necrotising retinitis [136].

The first International Workshop on standardization of uveitis nomenclature for reporting clinical data agreed that the onset of uveitis should be reported either as sudden or insidious. It was also recommended that the course of an attack of uveitis should be described as either limited or persistent, if it is 3 months or less or greater than 3 months in duration respectively[124]. The term acute should be used when describing the course of specific syndromes characterized by sudden onset and limited duration such as HLA-B27-associated “acute anterior uveitis”[179].

The workshop also recommended that when reporting on the course of the disease, repeated episodes separated by periods of inactivity of at least 3 months duration without treatment should be labeled as recurrent, the term chronic should be reserved for those cases with persistent uveitis characterized by prompt relapse in less than 3 months after discontinuation of therapy[124]

1.4 Ancillary tests.

***A**. Imaging.*

In recent years enormous progress has been achieved in investigational procedures for uveitis. Imaging is one such example with the advent of new methods such as indocyanine green angiography, ultrasound biomicroscopy and optical coherence tomography [180]

Ultrasonography.

Ultrasonography is usually an invaluable tool in the examination of the uveitis patients, allowing evaluation of the posterior segment of eyes with opaque media, and in determining the presence of thickening of the choroid [136] (Fig.1.7)

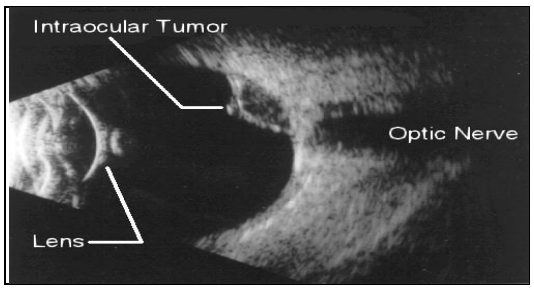
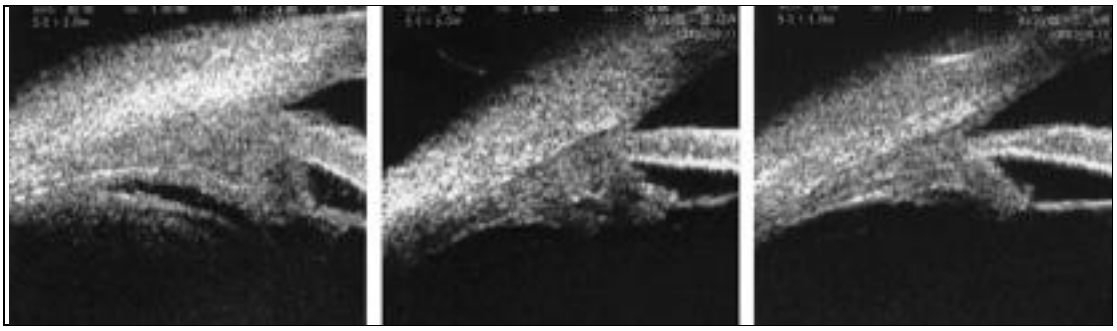


Figure 1.7 BScan ultrasound image

Ultrasound Biomicroscopy.

During the past two decades, ultrasound biomicroscopy (UBM) has become available for the appraisal of the pathophysiology of the anterior segment [181-184]. UBM is based on high-frequency transducers incorporated into a B-mode clinical scanner. This technology allows quasi-histological sections up to 5mm in depth to be obtained in vivo [185]. A recent study by Tran et al suggested that UBM is of great clinical value in the assessment of inflammatory lesions of the iris, ciliary body, pars plana and peripheral vitreous [182]. Using UBM, Yang et al reported a variety of abnormalities in the posterior chamber, anterior chamber angle, and the ciliary body and its surrounding tissues in eyes with AAU (Fig.1.8).

Their findings suggested that the involvement of the ciliary body is perhaps a universal sign of AAU, whereas in slit-lamp microscopy, the inflammation is seen to affect the iris only in some patients. The authors concluded that UBM is not only useful for evaluating changes in the anterior segment which cannot be seen by slit-lamp microscopy, but represents a valuable tool for the guidance of treatment of patients with AAU [185].



A B C

Figure 1.8 Changes in the anterior segment revealed by ultrasound biomicroscopy (UBM) in acute anterior uveitis.

*(*A) At 13 days after uveitis attack, UBM shows numerous cells in the posterior chamber and anterior vitreous body, striking oedema in the iris/ciliary body and irregular exudates adjacent to it. (B) At 26 days after uveitis onset, UBM shows an open angle, improved oedema of the iris/ciliary body and few exudates adjacent to it or in the anterior vitreous. (C) At 45 days after uveitis onset, UBM shows an open angle, and no cells or exudates in the anterior chamber, posterior chamber or anterior vitreous [186].

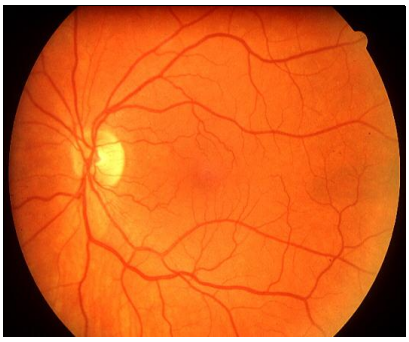
Laser Flare Photometry (LFP).

Clinical determination of aqueous humour protein levels (“flare”) has been considered less important. This belief may have evolved from the greater difficulty in clinically identifying changes in protein levels. Whereas cells can be counted, the quantification of aqueous humour protein levels by slit-lamp biomicroscopy is more subjective, based on the perceived intensity of light reflected off protein molecules within the aqueous humour [186].

Laser flare photometry provides a more precise way to identify changes in aqueous humour proteins. The Kowa FM-500 Flare Meter projects a diode laser beam into the anterior chamber and measures the amount of light scattered by protein molecules in the aqueous humour [187]. Using this method, Gonzales et al.[188] have demonstrated the associations between elevated laser flare photometry values and posterior synechiae, low intraocular pressure (< 10mmHg), history of cataract, and macular oedema in patients uveitis.

Fundus color photography.

Mostly used in posterior uveitis, allows the mapping of lesions. Comparisons can be made with subsequent photos to determine whether the lesion has regressed, stabilized, or increased.



Figue 1.9 Normal colour fundus photograph.

Fundus autofluorescence (FAF)

Fundus autofluorescence (FAF) has been used for the evaluation of RPE in degenerative, inflammatory, and neoplastic conditions [189, 190]. The FAF signal is derived primarily from lipofuscin accumulation within the RPE and may be indicative of altered structure and function [191, 192]. The white dot syndromes (WDSs) classically include acute posterior multifocal placoid pigment epithelium epitheliopathy (AMPPEE), serpiginous choroidopathy (SC), birdshot retinochoroidopathy (BSCR), multiple evanescent white dots syndrome (MEWDS), and multifocal choroiditis (MFC) , and are characterized by multiple lesions of the posterior pole due to inflammation of the choroid, retinal pigment epithelium, and retina [193, 194]. Yeh et al.[195] found that FAF imaging was valuable in the evaluation of WDSs. They observed that foveal hypoautofluorescence appeared to be a marker for moderate to severe visual impairment. Fundus autofluorescence seems to be a very sensitive imaging technique for detecting damage of the RPE in acute episodes of serpiginous choroiditis. A sequence of autofluorescence changes reflects the passage from activation to

resolution of new lesions [196]. McBrain et al.[197] have shown that it can be used as a rapid, non invasive technique in the diagnosis of CMO.

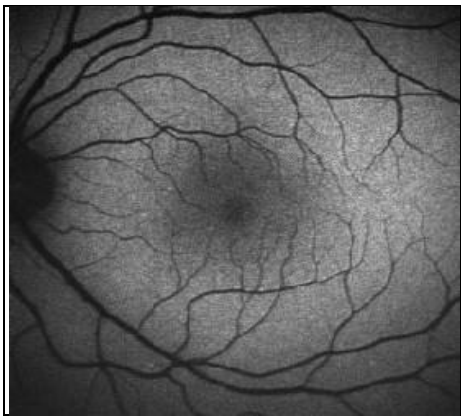


Figure 1.10 Normal FAF

Roesel et al. [198] found that increased FAF in uveitic CMO is associated with poor vision. Wang et al. [199] reported that hyper-autofluorescence in the foveola is a non-specific manifestation of photoreceptor-retinal pigment epithelium dysfunction. Investigating the characteristics of fundus autofluorescence in birdshot, Koizumi et al.[200] found that FAF demonstrated the RPE atrophy, which was hard to see by other means of investigations. They found that the areas of RPE atrophy did not necessarily correspond to the hypopigmented lesions, which suggested that both the choroid and the RPE can be affected independently.

Fundus fluorescein angiography (FFA) and Indocyanine green angiography (ICGA).

Angiography may be performed to confirm elements already revealed by clinical examination or other investigational methods such as optical coherence tomography (OCT). A second reason to perform an angiography is for better grading of the inflammation of the fundus. A third reason is to make a good baseline inventory of inflammatory involvement to subsequently use it for follow-up purposes. In follow-up situations, angiography is usually performed to monitor disease intensity and impact of therapy [180].

Fluorescein angiography has been performed for over 4 decades. Fluorescein sodium (FNa) is injected intravenously to analyze the blood circulation of the ocular fundus, mainly the retina. It is a small hydrosoluble molecule of 354 daltons of which 80% is bound to proteins and 20% is free, the latter free portion being responsible for the emission of fluorescing light [180, 201].

Two crucial principles characterise FNa. (1) Fluorescein has a micromolecular behaviour. This means that it easily gets out,

at the slightest breakdown of the hemato-retinal barrier, from the usually impermeable retinal vessels. (2) Fluorescein fluoresces at 520-530 nanometers within the wavelengths of visible light ,and is therefore blocked by the RPE, giving no useful information on choroidal circulation, except on the choriocapillaris during the first 40-60 seconds of angiography [180].

Increased fluorescence can be due to three main mechanisms: (1) leakage producing pooling (in a space) or staining (in tissues); (2) increased transmission of fluorescence due to fundus atrophy with removal of the RPE producing larger hyperfluorescent areas or due to smaller window-defects produced by areas of RPE defects; (3) presence of abnormal vessels (retinal vessels or choroidal neovascular membranes) [180].

Decreased fluorescence can be either due to transmission decrease (blockage), or filling defect (vascular delayed perfusion or non perfusion) [180]. FFA furnishes three types of information on the retinal circulation which include: (1) imaging of inflammatory damage to vessel walls in retinal vasculitis, (2) display occlusive vasculopathy of retinal arteries or arterioles, and (3) detection of retinal new vessels situated at the disc (NVD) or elsewhere (NVE) [180]. Macular ischemia is best detected using FFA and has to be looked for in case of severe fundus inflammation such as Behçet's uveitis [202, 203]. CMO is visible by funduscopy if it is sufficiently pronounced. However, until recently, FFA was recommended to determine the extent of CMO. Two grading systems of CMO have been put forward by the groups of Miyake and Yanuzzi [204, 205]. Cassoux et al. [206] reviewed the fluorescein angiographic findings in 44 patients with ocular and CNS lymphomas and reported punctuate hyperfluorescence window defects in 54.5%, round hypofluorescent lesions in 34%, vasculitis in 13.6%, papilloedema in 3.7%, and cystoid macular oedema in 2.5%.

For about 15 years, a second angiographic procedure is being used, using indocyanine green, a dye that fluoresces in the infrared wavelengths (830nm). Besides the different wavelength at which ICG fluoresces, the crucial difference between FNa and ICG comes from their binding affinity to proteins. The ICG molecule is nearly completely protein bound and predominantly so to large sized proteins (lipoproteins) [207, 208]. This procedure, in contrast to FFA, often gives additional information undetected by clinical examination or FFA or OCT. Therefore, ICGA is indispensable in the proper assessment of inflammatory involvement in uveitis as it gives information, which is otherwise lost. Very often, ICGA has a diagnostic value, rarely the case for FFA. For all these reasons, in most cases where angiographic work-up is required and choroidal involvement cannot be excluded, dual FFA and ICGA should be performed [209-211]. Fluorescein leaks readily from slightly inflamed retinal vessels with minor damage to the blood-retinal barrier and readily impregnates tissues, whereas only major damage to retinal vessels allows ICG to leak [212]. When analysing ICGA

in posterior inflammatory disorders, crucial differences with FFA interpretation have to be borne in mind to correctly analyse the images obtained [213]. Altan-Yaycioglu et al. [214] reported that the combined use of FFA and ICGA helps gauge the severity of inflammation in the choroid and the retina during active inflammation. In quiescent stages, however, ICGA does not give any additional information.

Optical coherence tomography (OCT).

Optical coherence tomography is an imaging technique able to provide cross-sectional high-resolution images of the retina. OCT is useful for the evaluation and diagnosis of several macular diseases, such as macular oedema, macular holes, epiretinal membranes, central serous chorioretiopathy, and age-related macular degeneration. OCT provides information for the diagnosis and follow-up of macular oedema caused by inflammatory diseases, diabetic retinopathy, vascular occlusions and macular degenerations [215-217]. It is an important technique providing information about inflammatory macular oedema [218]. OCT has a high sensitivity in showing epiretinal membranes and the presence of potential vitreoretinal abnormalities in the macular area, suggesting the hypothesis of a tractional mechanism as a probable origin or cofactor of onset of macular oedema during uveitis [219-221]. Using OCT, Moreno-Arrones et al found that patients suffering an AAU showed an increase in macular volume and superior RFNL thickness versus control eyes in the acute episode [222].

Chest and joint x-rays and neuroimaging.

Plain postero-anterior and lateral chest X-rays may assist in the diagnosis of both tuberculosis and sarcoidosis [119, 223]. Chest x-ray findings are present in one-third of patients with extrapulmonary tuberculosis, although pulmonary disease is inactive in most cases. There may be a healed primary lesion visible as peripheral calcified pulmonary nodules and/or calcified hilar lymph nodes [224].

Radiological examination of the joints is often of value in diagnosing the seronegative spondyloarthropathies. In particular, sacro-iliitis may be visible as juxta-articular sclerosis, blurring of the joint margins and erosive changes on pelvic X-rays [225].

When suspecting a primary CNS lymphoma, computed axial tomography scans of immunocompetent patients typically show multiple, diffuse, periventricular lesions with high-density tumour before contrast injection. After contrast injection, dense periventricular

enhancement appears and may involve the corpus callosum. Magnetic resonance imaging (MRI) shows isointense lesions on T1, and iso- to hyperintense lesions on T2. Periventricular contrast enhancement is strong in 75% of cases [155].

B. *Laboratory tests.*

The aetiology of uveitis remains uncertain or unknown in 30-70% of cases after noninvasive investigations [226]. The diagnosis is often based on history, detailed clinical examination, and selected investigations [227]. Unless a thorough history suggests a systemic problem or there are additional suspicious clinical signs, adults with an isolated unilateral acute anterior uveitis are not usually investigated for systemic associations. Such cases are likely to be confined to the eye. However, chronic anterior uveitis or recurrent acute disease, bilateral uveitis and all childhood inflammations demand investigation. Commonly requested tests include: Full blood count, HLA-B27, B51 typing, serum angiotensin I-converting enzyme (ACE) measurement, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), syphilis serology, rheumatoid factor (RF), and anti-nuclear antibodies (ANA). Tuberculin test is reserved for those individuals in high-risk groups [224].

It is obviously important to be able to distinguish between infectious, non-infectious, and malignant causes of uveitis. Infections are reported to be the cause in approximately 20% of cases of uveitis [228, 229]. Infections and intraocular malignancies often masquerade as immune-mediated conditions and present with similar clinical features [137].

Advances in molecular biology, microbiology, and cytopathologic techniques have been applied to the diagnosis of many diseases [230, 231].

Polymerase chain reaction (PCR) analysis of peripheral blood, serologic testing of peripheral blood or both is not informative about the cause of inflammation in the eye. The accurate and timely diagnosis of infectious uveitis, however, is essential in providing appropriate treatment; immunosuppressive therapy commonly used to treat non-infectious uveitis may prolong or worsen any infectious process [232].

Vitreous aspiration needle tap seems to provide a safe method for acquiring ocular fluid in cases of uveitis in which the pathogenesis is unknown, permitting subsequent cytopathologic, microbiologic, and molecular analysis of the material, which in combination with the clinical features helps identify the aetiology of the disease process [233-235]. Lobo et al reported that ocular sample collected by vitreous aspiration permitted the relevant diagnostic test to be carried out and the diagnosis to be made in 92% of patients. It allowed immunosuppressive treatment to be given to

50% of the patients, having excluded intraocular malignancy [227]. In the United States, diagnostic vitrectomy is used in patients with atypical or severe presenting symptoms [236].

The diagnosis of intraocular lymphoma from vitreous specimens depends on proper handling of the specimens, methods of aspiration, concentration, fixation, and staining [237, 238]. Prior treatment of patients with steroids reduces the number of viable lymphoma cells, because central nervous system lymphoma cells have an unique sensitivity to corticosteroids, which are known to be cytolytic [238].

It is now possible to apply novel PCR techniques to vitreous samples to determine immunoglobulin H rearrangement and t (14; 18) translocation of the bcl-2 gene and show monoclonality [239, 240]. Herpes viruses such as varicella-zoster and herpes simplex are common agents inciting ocular inflammation in immunocompromised and immunocompetent individuals, whereas CMV is the major cause of retinitis in patients with immunodeficiency virus/AIDS. PCR analysis of ocular fluid samples in the early phases assists diagnosis and initiation of appropriate treatment, because retinitis can progress very rapidly [241, 242].

Analysis of aqueous samples obtained by anterior chamber tap (paracentesis) is an underused approach [243-247]. A volume of approximately100 to 200µl aqueous allows analysis for multiple pathogens at real-time PCR for the detection of the infectious pathogen itself and the determination of the Goldmann-Witmer coefficient (GWC) as a parameter of intraocular production of specific antibodies [243, 248]. It has been demonstrated that the combination of both assays, PCR and GWC, improves the efficacy of intraocular fluid analysis of infectious uveitis [243, 247-249].

Rothova et al.[232] considered it a clinically meaningful approach to perform aqueous analysis in PU patients with active inflammation and negative results of the initial uveitis screening and in severe cases when early diagnosis and treatment are essential. When positive results confirm the suspected diagnosis, optimal treatment can be used and vitrectomy is not necessary. In the event of negative results, unsatisfactory clinical development, or both, the authors proceeded with diagnostic vitrectomy. Only in very severe cases when retinal evaluation is not possible (such as possibility of endophthalmitis) and in those with a strong suspicion of malignancy did the authors opt for primary vitreous biopsy. Despite the posterior location of inflammation, aqueous analysis yields a high frequency of positive results [232].

1.5 Visual acuity.

Visual acuity is the single most-widely used eye test. It informs about a major aspect of a patient's visual function in an easily administered form In its routine application it is a test of

resolution in the central fovea[250]. Foveal acuity and peripheral acuity are two important subject factors related to visual search performance [251].

1.5.1 *Foveal acuity.*

Foveal acuity is the ability to discriminate fine details and is a visual function important for many tasks. It measures the capability of the visual system[252].

1.5.2 *Visual acuity measurement.*

Visual acuity can be measured and analysed using a variety of strategies [253]. The Early Treatment Diabetic Retinopathy Study (ETDRS) protocol was designed in the 1980s based on recommendations from the National Academy of Science's Working Group[254] and is similar to a chart created by Bailey and Lovie [255] and allows for standard reproducible visual acuity measurements as described in details by Ferris et al. [256, 257]. The ETDRS charts have the advantage of using a regular geometric progression of letter size and spacing [256, 257]. A 3-line change in visual acuity (± 15 letters) using ETDRS charts is equivalent to a doubling or halving of the visual angle regardless of the baseline visual acuity measurement [256, 258]. This chart has been shown to be accurate and reliable [259] at high and low levels of visual acuity [255, 256]. Even low visual acuity as poor as 20/800 can be calculated by moving the patient closer to the chart from a distance of 4 metres to 1 meter [256].

The Bailey–Lovie distance visual acuity chart was developed to overcome the inaccuracies of the Snellen chart and has been widely accepted as an accurate and efficient measure of visual acuity, particularly for assessing patients with low vision [255, 260]. The chart has approximately equally legible letters on each row and the separation of letters within rows and between rows is uniform so that contour interaction is controlled. The visual task at each level of the chart is therefore the same irrespective of acuity or test distance [255]. The Bailey-Lovie chart employs a logarithmic progression of sizes and the log MAR visual acuity notation, which has been shown to represent a good approximation to an equal discriminability scale [261], and has been recognized by many investigators as the most logical measure of visual acuity [260, 262, 263]. The major advantage of the log MAR visual acuity notation and the use of the Bailey-Lovie chart for research purposes is the ability to measure and score low visual acuities accurately, which can thus be included in statistical analysis [264]. The log MAR visual acuity scoring method allows arithmetic procedures, including regression analysis and parametric statistics, to be applied legitimately to visual acuity scores,

because by the use of appropriate variations in test distances, the visual acuity scale is not truncated, as is the conventional Snellen visual acuity [265, 266].

Routine clinical practice usually relies on the Snellen charts to measure visual acuity. The Snellen chart has well documented limitations, including inconsistent progression in letter size from one line to the next, large gaps between visual acuity levels at the lower end of the chart (20/80-20/800), unequal legibility of letters used, and unequal and unrelated spacing between letters and rows [267-269]. Furthermore, there is no "one" Snellen scale, either in consistent number of letters or consistent lines on the chart, and as a result, visual acuity measurements can vary based on variations from chart to chart [253]. The Snellen chart is designed to measure visual acuity in angular units in which the numerator is the testing distance (in feet or meters), and the denominator is the distance at which a letter subtends the standard visual angle of 5 minutes of arc. Thus, on the 20/40 line, the letters subtend an angle of 5 minutes of arc when viewed at 20 feet [270]. The reciprocal of the Snellen fraction represents the minimum angle of resolution (MAR) [270]. The negative base 10 logarithm of the reciprocal Snellen fraction is the logarithm of the minimum angle resolution (log MAR), which converts the geometric Snellen progression into a linear function well suited for statistical manipulations [270]. The usual practice in retrospective research when using Snellen visual acuity measurements is to convert Snellen visual fractions to log MAR units, perform statistical calculations, and then report the visual acuity measurements as log MAR units[270].

The accuracy of visual acuity measurements using a Snellen chart is poor because at low visual acuity, there are few letters on each line and each line represents a large interval change in visual acuity [253]. Nevertheless, Snellen visual acuity is relied on in many retrospective studies that report statistical results, and most retrospective data collection for clinical studies should use Snellen fraction nearest the line that was fully read with the likelihood that this Snellen fraction would be the most reproducible [253].

1.6 Epidemiology of uveitis.

Uveitis is a relatively common inflammatory eye condition with reported annual incidences between 17 and 22.6 per 100,000 populations[271-273], and a prevalence between 38 and 370 per 100,000 populations [274]. It may occur at any age, but most commonly afflicts those aged between 20 and 59 years [275]. The total population prevalence being reported as 38 per 100,000 in France[276] and 68-76.6 per 100,000 in Finland [277]. One study from the USA in the early sixties showed a prevalence of around 200 per 100,000 [278]. In the largest population-based uveitis study in the USA

to date, Gritz et al.[279] found an incidence of 52.4/100.00 person-years and a period prevalence of 115.3/100.000 persons. The incidence and prevalence were lowest in the paediatric age groups, and highest in patients aged 65 or older. It was also shown in this study that women had a higher prevalence of ongoing uveitis than men, and this difference was highest in the older age group. The incidence found was approximately 3 times that of previous US estimates and increased with the increasing age of patients.

Many of the past and current epidemiological studies in uveitis have limitations [274]. These include the effects of referral or selection bias; the heterogeneity of diagnostic criteria, workup, and the availability of investigations in different study centres; and the lack of uniform classification systems or definitions of various uveitis entities, making comparisons of epidemiological data from different populations or regions difficult [134].

McCannel et al. [280] illustrated the significance of a referral bias, reporting a much higher proportion of patients with anterior uveitis in community-based practices and, in contrast, observing a shift in the relative frequency of uveitis cases in the tertiary referral centre toward posterior uveitis and panuveitis. Most of the hospital-based studies are not representative of the general population as they only include patients seeking treatment [93].

It is estimated that the population-based incidence and prevalence of uveitis in children is 5 to 10-fold lower than in adults, children constituting only about 5% to 10% of patients with uveitis in most tertiary uveitis clinics [281], and up to 16% in some reports [282],[127].

In the elderly, different cohorts report an incidence and prevalence of 6-21.8%.[283-285]. Limited epidemiological data suggest that the incidence of uveitis may be increasing, at least in the western world, perhaps reflecting the general rise in autoimmune diseases, although this needs confirmation by appropriately designed studies [279]. Suhler et al.[286] in 2008 looking at the incidence and prevalence of uveitis in Veterans Affairs Medical Centers of the Pacific Northwest found a crude incidence of 25.6 cases/100.000 person-years, and a prevalence of 69 cases/100.000 persons. There are similarities and distinct differences in the patterns of uveitis in the various geographic regions. Such patterns of uveitis are influenced by combinations of geographical, environmental and genetic factors [274]. In different studies, anterior uveitis is reported to be the commonest form of uveitis. Wakefield et al.[287] in Australia report 76% of AU, Rodriguez et al.[228, 288-292]in the United States and all European series report 49-92% of anterior uveitis. In a series from the south-eastern of the US, panuveitis was the most common form of uveitis with 38% of all cases of uveitis, AU and PU accounting for 25% and 24% respectively [293]. In Japan, Kotake et al.[294] reported PU

being the most common type with 69%, followed by AU (29%) and PU (2%). In London, Perkins et al.[295] in 1984 reported 63% of AU, 19% and 18% for panuveitis and posterior uveitis respectively. Comparing this pattern to the one of uveitis in Iowa, the authors concluded that genetic factors were more important than geographic location in determining the types of uveitis.

Uveitis is the fifth most common cause of visual loss in the developed world and is estimated to be responsible for up to 20% of legal blindness worldwide [296].

1.7 Definitions of Visual Impairment and Blindness.

In the US definition, bilateral blindness is defined as BCVA ≤ 6/60 in the better-seeing eye (log MAR ≥1.00), and visual impairment is defined as BCVA < 6/12 but >6/60 in the better-seeing eye (log MAR >0.30 to < 1.00). In the WHO definition, bilateral blindness is defined as BCVA < 6/120 in the better-seeing eye (log MAR >1.30) and/or visual field < 10°; visual impairment is defined as BCVA < 6/18 but ≥ 6/120 in the better-seeing eye (log MAR > 0.48 to ≤1.30).
The SUN group came to a consensus that key visual acuity thresholds that should form the basis for reporting results of uveitis studies include 6/15 or worse (visual impairment) and 6/60 or worse (severe visual loss or blindness)[124].

1.8 Causes of visual loss worldwide and the part of uveitis.

For the past 35 years, the World Health Organisation Programme for the Prevention of Blindness and Deafness has maintained a global data Bank on visual impairment with the purpose of storing available data on blindness and low vision. In 2002, 208 population-based studies on visual impairment for 68 countries were reported [297].

In a WHO report, it was estimated that more than 161million people were visually impaired worldwide. Of these, 37 million were blind and 124 million had low vision, the main causes of visual loss being cataract, glaucoma, AMD and diabetic retinopathy [298]. While many individual ocular inflammatory diseases are quite rare, ocular inflammation is one of the more common causes for visual disability, including blindness, in the developed world [93],[299].

Although the impact of uveitis on vision is well known, there are very few data on its prevalence and the incidence among the visually impaired or blind population in the literature; and in surveys on the causes of blindness uveitis is usually not included and is probably underestimated

[300]. The sequelae of uveitis are considered to be the direct causes of visual loss while the primary cause of the disease (uveitis) is not mentioned [301].

It has been estimated that 5%-20% of blindness in the United States is due to the complications of ocular inflammation. Nussenblatt et al.[302] reported that uveitis accounted for 10% to 15% of all cases of total blindness. Iwase et al.[303] looking at the prevalence and causes of low vision and blindness in a Japanese adult population found that uveitis accounted for 7%.
A population based assessment of uveitis in an urban population in Southern India reported that 1 in 370 people will develop a visual impairment of less than 6/18 in at least one eye and 1 in 625 people a visual loss of 6/60 in at least one eye [271].

In a hospital survey on blindness in Sierra Leone where secondary cataract and glaucoma were correctly attributed to Uveitis, this disease was the second leading cause of blindness, indicating how large the proportion of patients with uveitis is among the blind [304]. Williams et al.[305] in Scotland reported a prevalence of sight-threatening uveitis of 14.8 per 100,000 within the population. Recently, a Hospital based study in Malawi reported 3.6% of bilateral blindness caused by uveitis [306].

Reviewing the causes of visual loss in England and Wales as recorded on BD8 certificates during the year April 1999 to March 2000, uveitis was not counted; Bunce et al.[307] noted an increase in the three main causes of visual impairment e.g. diabetic retinopathy, AMD and glaucoma comparing to the 1990-1991 period and suggested that there is a need to improve the collection of good quality data and causes of visual loss. Childhood uveitis is associated with unique diagnostic and management issues, tendency for chronic disease, high complication rates, with severe visual impairment in up to one-third of all children with uveitis[127],[308]. The rate and spectrum of vision threatening complications of paediatric uveitis are significant [309]. Delayed diagnosis, extended burden of disease over lifetime, limited treatment options in children, difficult examinations, and the risk of amblyopia are all challenges specific to childhood uveitis [310, 311]. De Boer et al. [308] reported that even after the average follow up limited to 3 years, 19% of young patients with uveitis will develop at least one legally blind eye. Kump et al. and Friling et al. [312, 313] reported respectively 23% and 17% of all children with uveitis having their best corrected visual acuity (BCVA) < 6/12. Looking at the course of disease in childhood uveitis, Smith et al. [314] in the USA recently reported that the proportion of patients with vision ≤ 6/60 was 9.2% at baseline, 6.5% at 1 year, 3.2% at 3 years, 15.1% at 5 years, and 7.7% at 10 years [309].

Edelsten et al., in retrospective, multicenter, observational study from three primary and two referral ophthalmic units in England found that 17% of paediatric uveitic patients had a visual loss of < 6/12 in at least one eye.

Recent population-based studies have demonstrated that glaucoma, cataract and macular degeneration are the major causes of visual impairment in industrialised societies and their prevalence increases markedly with age [315]. The main sight-threatening complications of uveitis are cataract formation, glaucoma and maculopathy; these complications also have an increasing prevalence in the normal elderly population [300]. In most forms of uveitis, visual morbidity usually does not occur from a single episode of uveitis; rather recurrent episodes of inflammation cause cumulative damage. However some patients with severe disease can develop refractory cystoid macular oedema at an early stage whereas patients with Behçet's disease can develop devastating visual loss within days despite intensive immunosuppression [296]. Suttorp-Schulten et al. [3]reporting on the main causes of vision loss in the 20-60 years age group found diabetic retinopathy (20%), tapetoretinal degenerations (20%), congenital anomalies (20%), uveitis (10%), and trauma (5%). There is little information on the relation of increasing age of onset to the prevalence of complications in the adult uveitis population apart from a reported decrease in prevalence of intermediate uveitis and an increase in secondary hypertension [316]. Recent epidemiological studies looking at serious eye diseases and blindness do not even mention uveitis [226, 317-319]. There are few studies documenting the frequency of visual loss in the general uveitis population. In a hospital based study from Minnesota from 1962, Darrell et al found a rate of visual loss (defined as < 25% of vision) in patients with uveitis of 6% [278]. Rothova reported that 35% of uveitis patients suffered from significant visual loss or visual impairment and found a similar rate of severe visual loss (< 6/60) in a mixed primary and secondary referral centre over 30 years later [278, 300]. The latter study found cystoid macular oedema, corneal opacities, and macular inflammatory lesions to be the major causes of visual loss resulting from intraocular inflammation. Durrani et al.[296] looking at the degree, duration and causes of visual loss in uveitis reported that 69.9% of patients had visual loss of ≤ 6/18 in at least one eye of which 45.4% had moderate visual loss (6/18-6/36), and 54.5% had severe visual loss of ≤ 6/60. Some degree of permanent visual damage was found in 24.5% of patients. Of the whole population in this series, 11.4% of patients met the WHO blindness criteria.

The authors reported panuveitis, Indian or Pakistani origin, increasing patient age, bilateral inflammation and increasing duration of visual loss as strong predictor factors of visual loss [296].

The prevalence of visual loss reported in the later study was higher than those reported in other studies [3, 300, 317]. Some degree of referral bias is likely to be present in these studies as they investigate patients under treatment in secondary and tertiary centres [120].

Visual prognosis is worse in cases that present with severe intraocular inflammation, due primarily to retinal and uveal tissue damage in the form of vascular leakage, cystoid macular oedema, and other alterations, such as secondary cataract, secondary glaucoma, vitreous opacities, retinal scars, optic neuropathy and pthisis bulbi [300],[296].

In a recent study, Forooghian et al. [320] reported that intraocular inflammation in a variety of uveitic syndromes could result in foveal atrophy. The cause of this is multifactorial and may include dysfunction and atrophy of the retinal pigment epithelium and choroid, CMO, macular ischemia secondary to occlusive retinal vasculitis, choroidal neovascularisation, retinal detachment, and possibly antibody-mediated damage directed against photoreceptors.

Uveitis will continue to be, and perhaps, become increasingly more important as a group of potentially sight-threatening inflammatory eye diseases that have a significant impact on both the visual and systemic health of the generally young adult population that is affected [321].

1.8.1 *Cystoid macular oedema.*

The healthy BRB is impermeable to plasma proteins, whereas the BAB is partly permeable to plasma proteins. Small amounts of IgG can be found in the aqueous of healthy eyes [322]. Macular oedema is a common cause of decreased visual acuity in many ophthalmic diseases. It results from disruption of the blood-retinal barrier and subsequent accumulation of fluid leading to increased retinal thickness [323]. Patients with uveitis have elevated levels of intraocular IgG, particularly those with CMO, retinal ischemia or both. These observations indicate that a damaged BRB leads to both an accumulation of fluid in the macula and increased IgG concentration[324].

Elevated levels of pro-inflammatory cytokines and vascular endothelial growth factor were found in all types of CMO [325]. Numerous molecules may induce the retinal vascular hyperpermeability that leads to macular oedema. Depending on the underlying entity, these may include prostaglandins and leukotrienes, protein kinase C, nitric oxide, and various cytokines such as vascular endothelial growth factor (VEGF), tumour necrosis factor α (TNF-α), insulin-like growth factor-1, and interleukins [326-328].

A factor that often contributes to vascular leakage is the endothelial damage resulting from leukocyte adherence to vessel walls (leukostasis), a phenomenon mediated by nitric oxide, adhesion molecules, and other inflammatory mediators [328],[329]. In the normal healthy retina, the transretinal water fluxes are mediated by glial and pigment epithelial cells. These water fluxes are inevitably coupled to fluxes of osmolytes; in the case of glial (Muller) cells, to K+ clearance currents. Ischemic/hypoxic alterations of the retinal microvasculature result in gliotic responses which involve down-regulation of K+ channels in the perivascular Muller cell end-feet. This means closure of the main pathway which normally generates the osmotic drive for the redistribution of water from the inner retina into the blood. The result is intracellular K+ accumulation which, then, osmotically drives water from the blood into the glial cells (i.e., in the opposite direction) and causes glial cell swelling, oedema, and cyst formation [330],[331].

Clinical CMO that is responsible for a low visual acuity must be differentiated from angiographic CMO that can albeit uncommonly be present even without any decrease in visual acuity. Fluid progressively accumulates into the outer plexiform layer of the retina and pools into cystic spaces. Fluid accumulation can now be better seen with optical coherence tomography (OCT). In chronic CMO fluid accumulation is associated with thinning of the retina and fibrosis. At this stage CMO may or may not respond to medical therapies, but vision does not improve. Failure of vision to improve is because of the thinning and scarring [332].

Fluorescein angiography identifies the anatomical location and pattern of vascular leakage and is a qualitative and functional study, whereas OCT allows morphologic assessment of macular oedema by producing two or three dimensional images of the retinal tissue [333]. FFA and OCT are commonly used in conjunction with each other; correlating information obtained by these two imaging technologies is important to help understand the patho physiology of macular oedema. Some authors have found that macular oedema detected by either FFA or time-domain OCT was occasionally not present on the other imaging modality [323, 334, 335].

Spectral domain OCT allows the study of structural alterations in the different retinal layers and subtle changes associated with disease process [336].

Using OCT to describe the morphologic characteristics of uveitic macular oedema, Markomichelakis et al.[337] reported 3 patterns of macular oedema: diffuse macular oedema (DMO), cystoid macular oedema (CMO), serous retinal detachment (RD), and found that epiretinal membrane (ERM) coexisted in a significant percentage of patients. The irreversible loss of visual acuity in macular oedema is usually attributed to permanent loss of photoreceptor cells, although there is hardly any information on changes in photoreceptor function in macular oedema. Assessing photoreceptor function in various stages of macular oedema, Lardenoye et al.[338] found that eyes with inflammatory or diabetic macular oedema showed decreased directional sensitivity and visual pigment density in the macular area. Kiss et al.[339, 340] reported a marked reduction in central retinal sensitivity in eyes with active macular oedema and substantial impairment at resolution of macular oedema. They also found that reading acuity and reading speed are significantly impaired in eyes with macular oedema. In one study, cystoid macular oedema was noted in 33% of all uveitis patients, of whom 44% had visual acuity of 20/60 or less in at least 1 eye. Of all uveitis patients, 35% had visual acuity of 20/60 or less in at least 1 eye, which was caused by CMO in 42%. Poor visual acuity in patients with CMO was associated with the advanced age of the patients, chronic inflammation, and various specific uveitis entities.[341]

Nussenblatt et al.[342] suggested that macular thickening, and not the presence of macular oedema, is significantly correlated with visual acuity. Traditionally, the presence of CMO has implied that retinal thickening exists concurrently. However, Jun et al.[343] reported cases of cystoid spaces within the retina accompanied by normal foveal thickness and contour on OCT. Brar et al.[323] hypothesised that visual acuity correlates with the number, size, and location of the cysts and not just the presence or absence of cysts. The reliable prognostic factors distinguishing eyes with CMO with a potential for improvement from the eyes with definitively damaged visual acuity are not yet known. Regardless of the various pathogenic mechanisms causing macular oedema, the resulting visual acuity depends on many factors in addition to macular thickening, including duration of oedema, macular ischemia, photoreceptor impairment and/or loss, retinal pigment epithelium dysfunction, flat optical coherence tomography indicating atrophic macula, media opacities as well as poor contrast sensitivity, impaired colour vision and advanced age [325, 344, 345]. Sivaprasad et al.[346] reported that OCT is an important tool in monitoring the treatment response of uveitic macular oedema.

They found that assessing the patterns of uveitic macular oedema by OCT gives more useful information on the prognosis than the central macular thickness. Inner retinal cystoid oedema is more resistant to treatment than any other patterns of oedema and cysts in the inner retinal layers may indicate the presence of ERM that is difficult to define clinically[346].

Fundus autofluorescence (FAF) imaging with confocal scanning laser ophthalmoscopy is increasingly becoming accepted as it is a noninvasive and rapid procedure for diagnosing macular diseases [189]. FAF in normal eyes is determined by the lipofuscin distribution in the retinal pigment epithelium. FAF is also influenced by macular pigments in the outer nuclear and outer nuclear and outer plexiform layers and in the fibers of Henle and inner nuclear layer of the retina [347]. As the concentration of macular pigments is highest in the foveal area, normal FAF exhibits a central dip in this area [198]. FAF is increased in many uveitis patients. However, Roesel et al.[198] report only 50% of pathologic FAF in eyes with angiographically proven CMO. McBain et al.[197] found an 81% sensitivity and 69% specificity of FAF imaging for diagnosing macular oedema when compared with standard fluorescein angiography. This limitation indicates that FAF may not replace FFA or OCT for the detection and follow up of macular oedema [198].

1.8.2 *Uveitic glaucoma.*

Secondary glaucoma represents a frequent complication especially in chronic forms of uveitis. Different immunological and mechanical alterations can be responsible for the elevation of intraocular pressure(IOP) [348]. Uveitic secondary glaucoma is difficult and challenging to manage and may jeopardize a favourable visual therapeutic outcome in uveitis patients [349]. The delicate tissues of the anterior segment may become swollen, scarred, and distorted, or rendered malfunctional by the inflammatory response [350], leading to increase of intraocular pressure, glaucomatous damage to the optic nerve, and subsequent loss of visual field [351]. During the past 5 decades, more light has been shed on cellular and biochemical modifications leading to uveitic glaucoma [352]. In a healthy eye, proteins concentration in aqueous humour varies between 10 to 20mg/100ml. This concentration reaches 2300mg/ml in uveitic eyes[353]. In inflamed eyes, the breakdown of the blood-ocular barrier occurs with subsequent influx of proteins as well as inflammatory and immune-competent cells[354].

Though the conventional aqueous outflow route is well characterised[355], the unconventional or uveoscleral outflow route is less well understood [356],[357],[358].

The latter, studied by Bill et al.[359] showed aqueous humour flow through interstitial spaces of the ciliary muscle into the suprachoroidal spaces, moving into the sclera. While removal of proteins from the eye is critical for optical clarity, the clearance route of these proteins has been unclear under the assumption that the eye is devoid of lymphatics[360]. Fairly recently, using endothelial cell markers, podoplanin, a transmembrane mucin- type glycoprotein, specifically detected with D2-40 antibody [361] and lymphatic endothelial hyaluronan receptor-1(lymphatic vessels endothelium-1) (LYVE-1)[362], Yucel et al.[360] determined the presence of lymphatic channels in the human ciliary body.

Lymphatics are highly permeable to large macromolecules, pathogens and migrant cells as they lack continuous basement membrane and pericytes [363],[364],[365].

Several mechanisms are involved in the pathogenesis of inflammatory glaucoma, including obstruction of the trabecular meshwork by inflammatory cells and proteins, trabeculitis, formation of anterior and/or posterior synechiae, pupillary block, neovascularisation, and anterior rotation of the lens-iris diaphragm. In addition, the use of steroids to control intraocular inflammation may cause secondary elevation of IOP [366],[354].

Inflammatory cells have a cytotoxic effect on tissues and induce the formation of arachidonic acid, cytokines, proteolytic enzymes, and free radical molecules. Inflammation and tissue necrosis could trigger the IOP rise by a direct action on trabecular endothelial cells, by the formation of peripheral anterior synechiae or by a combination of both mechanisms [352].

Looking at the relationship between aqueous humour protein level and outflow facility in patients with uveitis, Ladas et al.[367] found that the aqueous flow is significantly reduced in uveitic eyes with elevated protein concentration in the anterior chamber when compared with eyes with active uveitis but with low aqueous protein level. This suggests that the role of inflammatory cells in the trabeculum meshwork blockage mechanism is minor, and is mostly played by proteins [367]. There is not always a relationship between the amount of inflammation, as measured by cells and flare, and inflammation induced rise of intraocular pressure. One therefore cannot predict in which patients intraocular pressure will drop when steroid therapy is increased [368].

Myocilin also called trabecular meshwork-inducible glucocorticoid response protein (TIGR) is another protein excreted by the trabeculum, the sclera, the ciliary body and the retina [369, 370].

Wentz-Hunter et al.[371, 372] had demonstrated that the hyper expression of TIGR/Myocilin on cultured human trabecular endothelial cells induce alterations of their adhesive properties. These alterations within the trabecular meshwork increase the outflow resistance [373]. Many different types of uveitis have been associated with glaucoma, but certain disorders may have a relatively higher risk. For example, glaucoma is believed to be the major long term threat to vision in patients with Fuchs' heterochromic iridocyclitis [374]. Glaucoma is also a major component of the Posner-Schlossman syndrome (glaucomatocyclitic crisis) [375].

In children, Edelsten et al.[376] suggested that the presence of complications early in the course of the disease may cause irreversible anterior segment changes that lead to cataract and glaucoma. Several lines of evidences report glaucoma and elevated IOP to be the most common complication in children with chronic anterior uveitis [310],[377].

1.8.3 *Epiretinal membranes.*

Macular alterations are frequently seen in intraocular inflammatory diseases and include, apart from macular oedema: neovascularisation, both subretinal and retinal; pre-retinal membranes and macular holes [378]. A macular epiretinal membrane (ERM) is a disorder of the vitreomacular interface characterized by fibrocellular proliferation on the anterior surface of the internal limiting membrane (ILM) of the macula [379]. Epiretinal membranes are a common and treatable cause of vision loss, occurring in about 7% of the population [380]. Prieto-del-Cura et al.[381] reported 4.1%, a cumulative prevalence of epiretinal membranes, choroidal neovascular membranes and macular necrosis in complications of uveitis. Khaja et al.[382] found that ERMs occur in approximately 1 in 21000 children and are most frequently associated with a traumatic, idiopathic, or uveitic cause. Gass[383] proposed grading the severity of ERMs on the following clinical scale: translucent membranes unassociated with retinal distortion, grade 0; membranes causing irregular wrinkling of the inner retina, grade 1; and opaque membranes causing obscuration of the underlying vessels and marked retinal distortion, grade 2.

The natural history of epiretinal membranes is variable, with recent studies suggesting that the condition in some patients may be non progressive over time with a mild effect on vision [384, 385].

The initial progress of idiopathic ERM formation does not usually cause any clinically important reduction in vision; however, when advanced, visual acuity can significantly be reduced. Macular morphologic and functional abnormalities caused by tractional force generated by ERM such as damage to the neurons in the inner retinal layers (similar to macular oedema) and the outer retina [386, 387], reduction in perifoveal circulation [388], and macular morphologic changes [389-391] have been suggested to be related to a decrease in visual acuity.Gomes et al.[392] hypothesized that with time, accumulation of cellular debris in the foveal region results from either photoreceptors damage or RPE proliferation. Several studies have shown that foveal thickening is negatively correlated with visual acuity [389, 390, 393]. Because alignment of the discs is necessary for normal functioning of the photoreceptors, the presence of a normal IS/OS junction on OCT images indicates normally functioning photoreceptors [394]. In non operated ERM cases, it has been reported that defects in the IS/OS junction are related to poor visual acuity[395]. Photoreceptor disruption detected by OCT is found to be a predictor of poor visual outcome in eyes with ERM [391, 394]. Suh et al.[391] found that this disruption may be irreversible. Thus, early membrane peeling may beneficially prevent further progression of photoreceptor damage in ERM patients with photoreceptor disruption. The authors also emphasised that membrane removals should be performed carefully to avoid further photoreceptor disruption. Although surgical intervention may not be required, different studies have found that a significant proportion of patients have worsening metamorphopsia and declining visual acuity requiring surgery [396, 397]. Also spontaneous recovery has been reported with PVD. Despite a 70% to 80% success rate of an improved visual acuity of more than 2 Snellen lines [396, 398, 399], limited improvement of visual acuity of less than 2 Snellen lines may occur after successful ERM removal in the absence of significance complications [400]. Chronic untreated ERMs can induce permanent changes in the outer layers of the retina secondary to longstanding tractional forces [392]. Known prognostic factors such as preoperative visual acuity and duration of symptoms cannot fully explain limited visual improvement after successful surgery [396, 398].

1.8.4 *Cataract.*

Cataract formation is a common finding in uveitis patients either as a direct consequence of the disease process or as sequel of long-term corticosteroid use [401, 402]. Some forms of uveitis, such as Fuchs' heterochromic cyclitis or uveitis associated with juvenile idiopathic arthritis(JIA), commonly feature cataract as part of the disease process, whereas others result from topical, periocular, or systemic corticosteroids used to treat uveitis[403].

A specific diagnosis may guide clinical approach as well as surgical technique, thus, a comprehensive ocular and systemic history along with appropriate laboratory analysis is essential, including investigation for possible infectious and autoimmune causes [404],[405] The importance of such efforts is evidenced by BenEzra et al.[406] who found increased post-operative inflammation in patients with juvenile idiopathic arthritis (JIA)-associated uveitis and least complicated postoperative course in those with idiopathic disease. Moreover, increased rates of cataract development are encountered with JIA-associated uveitis, though the reported incidence of cataract development in children with uveitis varies widely [407].

The uveitic cataract poses for the surgeon special challenges given the commonly encountered consequences of chronic inflammation, which can include a miotic "stuck down" pupil, iris atrophy, posterior synechiae, pupillary membrane, band keratopathy, and bleeding from abnormal fragile iris vessels [408]. The goal of most cataract surgery is to improve vision. In young children, there is an additional aim to prevent amblyopia [408].

Visual results of cataract surgery depend on different uveitic entities and on posterior segment abnormalities. Fuchs' heterochromic cyclitis has historically been thought to have a good prognosis after cataract surgery even with incomplete control of anterior chamber cell [409],[410]. Patients with observed preoperative macular lesions are at risk for poor visual outcome[411]. Belair et al.[412] reported an incidence of CMO of 12% at 1 month post cataract surgery in uveitic eyes without a statistically significant difference when compared with non inflamed eyes. They found an incidence of CMO of 8% at 3 months, whereas in non uveitic eyes, there was no CMO at 3 months post-op. They reported a 7-fold reduction in postoperative CMO with perioperative oral corticosteroids, and an increased risk of postoperative CMO in uveitic eyes with active inflammation within 3 months before surgery.

Cataract surgery in eyes with uveitis leads to an improvement of vision in the majority of cases. Severe postoperative uveitis is the most common postoperative complication and is associated with a significant risk of macular oedema in those with anterior disease. In the posterior group, poor visual outcome after surgery is most commonly the result of preoperative vision-limiting conditions [413, 414].

1.8.5 *Retinal vasculitis and ischemia.*

Optimal retinal neuronal cell function requires an appropriate, tightly regulated environment, provided by cellular barriers, which separate functional compartments, maintain their homeostasis, and control metabolic substrate transport. Correctly regulated hemodynamics and delivery of oxygen and metabolic substrates, as well as intact blood-retinal barriers are necessary requirements for the maintenance of retinal structure and function [415].

Retinal vasculitis is a rare, but potentially blinding intraocular inflammatory condition with diverse aetiology [416],[417]. It belongs to a spectrum of inflammatory disorders involving the posterior segment of the eye, collectively assigned a variety of titles including posterior uveitis, uveoretinitis or posterior segment intraocular inflammation (PSII). The term PSII encompasses inflammatory disease of the choroid, retina, retinal vessels, vitreous and/or ciliary body and pertains to broad range of aetiological and pathological process [416]. Retinal vasculitis represents small-vessel inflammation involving the arterioles, the capillaries, and the postcapillary venules, either singly or in various combinations. The signs of retinal vasculitis that involves the arterial side of the vasculature include attenuation, sheathing and, in some cases, cotton-wool spots representing microinfarcts. Sometimes large parts of the superficial retina may become opaque owing to the inflammation of the terminal retinal arterioles. Inflammation involving the venous side of the circulation, on the other hand, usually produces retinal haemorrhage, oedema, telangiectasia, and microaneurysms, although attenuation and sheathing may also be present [418]. The diagnosis of retinal vasculitis is clinical, based on an abnormal appearance of retinal vasculature due to inflammation. In many cases, abnormalities of retinal vessels may be caused by perivascular changes rather than true disease in the vessel wall itself [419].

A strict definition of retinal vasculitis excludes forms of vasculopathy due to non-inflammatory process such as atherosclerosis, congenital anomalies, or increased blood viscosity. Inflammation may involve retinal arteries, veins, or capillaries, although venous involvement is more commonly recognised [419].

In 2005, the standardization of uveitis nomenclature (SUN) working group came to a consensus that the term retinal vasculitis is a descriptive term for those situations in which there is evidence of ocular inflammation and retinal vascular changes. The presence of occlusive retinal vasculpathy, in the absence of visible inflammation such as in antiphospholipid antibody syndrome, should not be considered retinal vasculitis[124].

Although the group provisionally agreed to consider perivascular sheathing and vascular leakage or occlusion on fluorescein angiogram as evidence of retinal vascular disease for the classification of retinal vasculitis, there was consensus that the definition of retinal vasculitis required more work. For example, it was unsolved as to how to distinguish between retinal vasculitis and the peripheral vascular sheathing sometimes seen in intermediate uveitis[124]. Retinal vasculitis detected by the ophthalmologist can be presenting sign of a systemic disease and has therefore to be approached in a multidisciplinary fashion [420]. The list of associated diseases is extensive and includes systemic diseases such as Behçet's disease (BD), multiple sclerosis (MS), sarcoidosis, as well as a number of ocular diseases as shown in table 2.2.1 [421]. With a wide variety of disease associations, a search for an underlying aetiology should be undertaken based on a meticulous history, review of systems, and physical examination. The laboratory evaluation of patients with retinal vasculitis is an essential component of the work-up to facilitate detection of any underlying disease or to establish a limited differential diagnosis [421].

The pathogenesis of retinal vasculitis is presumed to be an autoimmune phenomenon. Numerous studies have demonstrated the presence of CD4+ T cells within and surrounding the retinal vessels in patients with retinal vasculitis[422],[423],[424]. However, humoral immunity and immune complex formation may also participate in the immunopathogenesis of retinal vasculitis [425].

Retinal vasculitis is characterised pathologically by migration of leucocytes across the blood-retinal barrier leading to oedema and photoreceptor cell dysfunction [426]. Wallace et al have evidenced that serum levels of the chemokine macrophage inflammatory protein-1 beta (MIP-1 beta) were significantly raised in patients with retinal vasculitis, whether active or not, demonstrating that chemokines are involved in the pathogenesis of retinal vasculitis [427]. In vivo and in vitro studies suggest that antinuclear cytoplasmic antibodies (ANCA) have a role in the pathogenesis of vasculitis [428-430]. When activated primed neutrophils degranulate, they generate free oxygen radicals [431, 432] which are directly toxic to vascular endothelial cells [432, 433]. ANCA are serum autoantibodies directed against neutrophils.

ANCA show two principal patterns of staining in immunofluorescence testing: a diffuse cytoplasmic pattern and a perinuclear pattern, designated cANCA and pANCA respectively [429]. The development of an enzyme immunoassay has revealed that cANCA is directed mainly against proteinase3 (PR3), while pANCA is directed mainly against myeloperoxidase (MPO), leading to new terminology for cANCA and pANCA: PR3-ANCA and MPO-ANCA, respectively [434-436]. The serum positivity of ANCA was found to be associated with several types of diseases that affect small blood vessels, including capillaries, venules, and arterioles, and sometimes involve middle-sized arteries [437, 438]. The role of cANCA testing is well recognized to aid in the diagnosis of Wegener granulomatosis in general setting as well as in an ophthalmological presentation [439-441]. In contrast, pANCA testing is useful for the differential diagnosis of glomerulonephritis and systemic vasculitis; however, its role in the ophthalmological setting remains to be established [429].

ANCA are useful diagnostic serological markers for the most common forms of necrotising vasculitis. Gallagher et al.[442] advocated the testing of all patients with retinal vasculitis for serum ANCA. Matsuo et al.[429] report that posterior segment manifestations such as retinal vein occlusion, anterior ischemic optic neuropathy (AION) and AMPPE were seen in patients with pANCA-associated vasculitis.

Retinal blood flow is autoregulated by the interaction of myogenic and metabolic mechanisms through the release of vasoactive substances by the vascular endothelium and retinal tissue surrounding the arteriolar wall. The close interaction between nitric oxide (NO), lactate, arachidonic acid metabolites released by the neuronal and glial cells during neuronal activity and energy-generating reactions of the retina strive to optimize blood flow according to metabolic needs of the tissues. During the evolution of ischemic microangiopathies, impairment of structure and function of the retinal neural tissue and endothelium affect the interaction of these metabolic pathways, leading to a disturbed blood flow regulation. The resulting ischemia, tissue hypoxia and alterations in the blood barrier trigger the formation of macular oedema and neovascularisation [415].

Vasculitis may result in leakage or occlusion of the lumen, and these sequelae account for the more advanced signs and symptoms of the disease. Leakage leads to retinal swelling, exudation and oedema, whereas retinal venous occlusion results in intraretinal haemorrhage, cotton wool spots (corresponding to hold up of axoplasmic flow in areas of ischemic nerve fibre layer) and retinal and optic nerve oedema. Venous occlusion may result in capillary nonperfusion and ischemia, with subsequent retinal neovascularisation and vitreous haemorrhage leading to further visual loss and, in the most severe cases tractional retinal detachment and anterior segment neovascularisation leading to secondary glaucoma [416]. Chronic complications are often associated with a poor visual prognosis and include branch vein occlusion, central vessel occlusion, macular ischemia, persistent

neovascularisation, vitreous haemorrhage, and tractional retinal detachment [421]. Palmer et al.[443] reported that patients with ischemic retinal vasculitis had a worse visual outcome when compared to those with non ischemic vasculitis. Bentley et al. [202] suggested that a poor visual outcome in some patients with posterior uveitis may be predicted by the presence of macular ischemia on fluorescein angiography. Macular ischemia secondary to retinal vasculitis can also lead to foveal atrophy as demonstrated by Forooghian et al.[320]

1.9 Diagnostic criteria for different types of uveitis and complications.

1.9.1 *Anterior uveitis.*

Anterior uveitis describes inflammation confined to the anterior segment that involves the iris or ciliary body. AU may be associated with multiple systemic diseases. While all these diseases share the ability to cause inflammation in the anterior uveal tract, the entities often can be distinguished by their presentation and course[444]. The sine qua non to diagnose anterior uveitis is the presence of leukocytes in the anterior chamber of the eye as detected by slit lamp examination. Normal aqueous humour should be virtually acellular. The detection of white cells in the aqueous humour is pathognomonic for anterior uveitis [445]. Anterior uveitis can present with acute, chronic or recurrent attacks. Anterior uveitis is the commonest type of intraocular inflammation and commonly presents as a unilateral sore red eye with pain or photophobia, circumlimbal redness and anterior chamber cells and flare. (Fig.1.11). Patients with anterior uveitis usually complain of pain, redness, blurred vision, photophobia, and watering. Blurring of vision, which is perhaps the commonest symptom, is caused by turbidity of the aqueous. Photophobia is commonly due to ciliary muscle spasm but anterior chamber cellular infiltration, corneal epithelial oedema and pupillary muscle involvement can also contribute. Varying degrees of pain seen in anterior uveitis can be attributed to ciliary muscle spasm. It is usually a dull aching type of pain or a throbbing sensation. Severe pain can be associated with raised intraocular pressure[186].

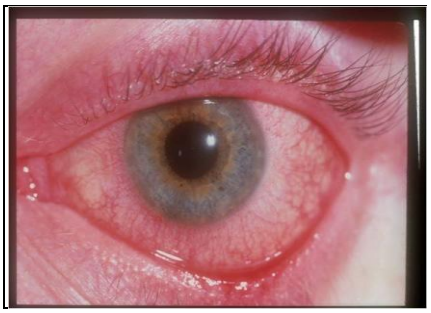


Figure 1.11 Left eye with anterior uveitis.

Investigations are rarely undertaken at the first episode of an acute non-granulomatous anterior uveitis or in Fuchs' heterochromic iridocyclitis.

In other cases, the following investigations were requested as appropriate.

a. Complete Blood Count:-Baseline, Leucocytosis in infectious aetiology

b. Erythrocyte sedimentation rate (ESR): Nonspecific indication of a systemic disease.
c. Mantoux test: when suspecting prior exposure to tubercle bacilli.
d. Venereal disease research laboratory test (VDRL) to rule out syphilis.
e. Treponema pallidum hemagglutination test (TPHA): Highly specific for syphilis.
f. Human leukocyte antigen (HLA) B27: Done in some patients with recurrent attacks of anterior uveitis. Not all patients were screened for this.
g. Antinuclear Antibodies in vasculitis and collagen vascular diseases.
h. Serum Angiotensin Converting Enzyme in active sarcoidosis. However it can be normal in patients with sarcoidosis and it can be physiologically elevated in chronic smokers and in children. Interpretation of serum ACE test has to be done in conjunction with clinical findings. S ACE is also raised in TB.
i. Chest X-ray for Tuberculosis, hilar lymphadenopathy in Sarcoidosis;
j. Sacroiliac joint X-ray: Ankylosing Spondylitis (done less now as superceded by MRI which is done by the rheumatologist).
k. High resolution CT scan chest: Sarcoidosis (done by the physician as necessary)
l. Others as indicated by clinical history and examination.

The above listed tests have to be done on a tailored basis and not all the tests are usually required in all patients with anterior uveitis.

Anterior uveitis was classified as acute when the inflammation episode lasted for less than 3 months and chronic for cases where the inflammation was present for more than 3 months. Recurrent anterior uveitis describes repeated episodes of inflammation separated by periods of inactivity without treatment.

Fuchs' heterochromic iridocyclitis (FHC).

FHC is characterized by idiopathic non-granulomatous anterior uveitis. It is of insidious onset and chronic in nature. It's commonly seen in young females, mostly unilateral, and patients commonly present with blurring of vision in a white eye. Classical presentation of uveitis in Fuchs' heterochromic iridocyclitis is occasional to 1+ anterior chamber cells, aqueous flare of 1+ to 2+, diffuse white stellate keratic precipitates on the endothelium which are non-pigmented non-confluent in nature (Fig.1.12). Absence of posterior synechiae is a pathognomic sign of Fuchs' heterochromic iridocyclitis. Most patients will present with findings at a routine optometry visit with signs of complications, e.g. posterior subcapsular lens opacification (PSCLO), or vitritis. Raised IOP is

present in about 30% over the course of the disease which may be many years. Patients with FHC do not require topical steroids to control the inflammation as they do not work. Heterochromia iridium is another feature of the disease due to iris stromal atrophy [446-448] but may also occur in other types of chronic anterior uveitis as well. There is no systemic association. Patients may have vitritis and require vitrectomy.

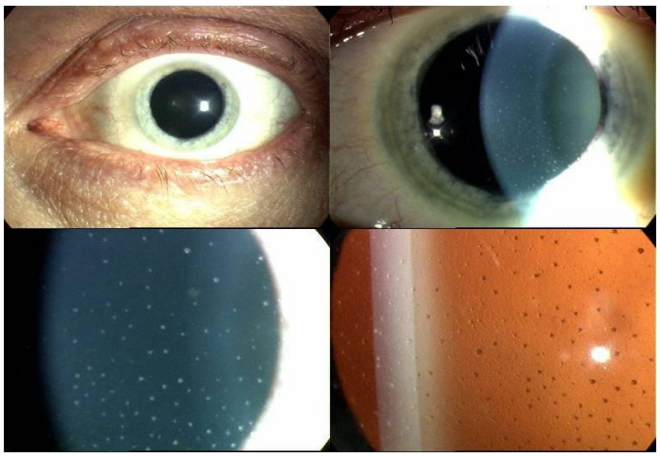


Figure 1.12 Fuchs' heterochromia uveitis showing a white eye with fine KPs.

1.9.2 *Intermediate uveitis.*

Intermediate uveitis is intraocular inflammation involving the anterior vitreous, peripheral retina and pars plana. It usually affects patients from 5 to 30 years old, without gender or racial preferences. It may be unassociated with any systemic disease, but can be associated with multiple sclerosis, sarcoidosis, inflammatory bowel disease and others. Symptoms are blurry vision, floaters and distortion of central vision. The syndrome is bilateral in 80% of the patients and chronic with periods of exacerbation and remission. Clinical presentation includes: mild to moderate anterior chamber inflammation, small keratic precipitates in the inferior portion of the cornea, vitritis, vasculitis in the peripheral retina, intravitreal "snowballs," retinal "snowbanking," optic neuritis and cystoid macular oedema [131] (Fig.1.13). In the Standardization of Uveitis Nomenclature (SUN) working groups international workshop for reporting clinical data the consensus reached was that the term IU should be used for that subset of uveitis where the vitreous is the major site of the inflammation and if there is an associated infection (for example, Lyme disease) or systemic disease (for example, sarcoidosis). The diagnostic term pars planitis should be used only for that subset of IU where there is snow bank formation.[449]

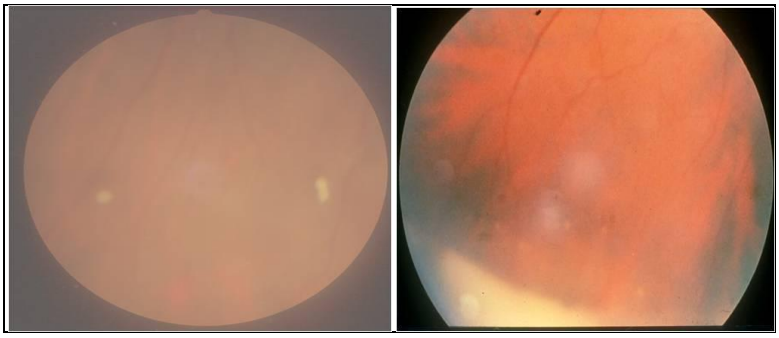


Figure 1.13 Intermediate uveitis with snowballs (left) and snowbank (right).

1.9.3 *Multifocal choroiditis (MFC)*

Multifocal choroiditis (MFC) is conventionally diagnosed when multiple yellowish white 50- to 1000-µm spots are seen at the level of the retinal pigment epithelium and inner choroidal layer, often accompanied by inflammatory cells in the vitreous and/or anterior chamber, optic disc swelling and macular oedema.(Fig.1.14) It can be associated with diseases such as sarcoidosis. Patients with MCP are usually older (median age 45) [450]. Many MCP patients develop inflammation related structural complications such as cataract, CMO, optic neuropathy and epiretinal membrane [450].

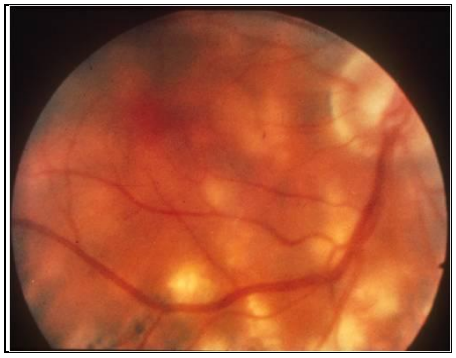


Figure 1.14 Multifocal choroiditis in a patient with sarcoidosis.

1.9.4 *Punctate inner choroidopathy (PIC)*

Punctate inner choroidopathy (PIC) affects healthy young women with moderate myopia and manifest a high frequency of bilateral involvement [451]. Slit-lamp biomicroscopy is characterised by the absence of cells in the anterior chamber and vitreous cavity. Fundus examination reveals multiple (12-25), small (about 100--300 mm in diameter), gray or yellow, opaque round lesions scattered throughout the posterior pole in a random or occasionally linear pattern [452] (Fig.1.15). The lesions are under the neurosensory retina at the level of the RPE and

inner choroid, and there may be a neurosensory retinal detachment overlying them [450]. In 77% of cases, patients with PIC will present with CNVM [450].

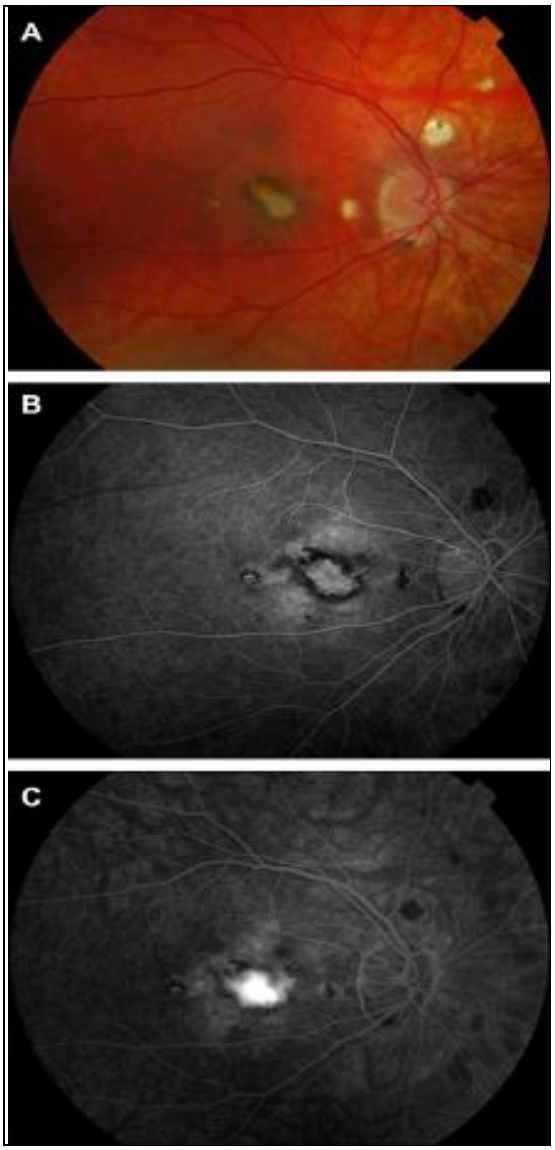


Figure 1.15 Fundus photographs of Punctate inner choroidopathy.

1.9.5 *Acute multifocal placoid pigment epitheliopathy (AMPPE)*

Acute multifocal placoid pigment epitheliopathy(AMPPE) is an inflammatory retinochoroidal disease characterised by sudden loss of vision and the appearance of multiple yellow-white, flat inflammatory lesions at the level of the RPE and choriocapillaris in the acute phase [453](Fig.1.16). The lesions tend to fade after a few days, and after 2 weeks they are replaced by partly depigmented pigment epithelium clumps [454] (Fig.1.17). Depending on the localisation of the lesions, patients may develop central or paracentral visual loss. The overlying retina usually appears normal. It has

predilection for young healthy adults, with peak occurrence between the ages of 20 and 30 years [450]. AMPPE lesions are much larger than those seen in PIC and demonstrate hypofluorescence in the early phases of the angiogram with late hyperfluorescence [450]. Acute posterior multifocal placoid pigment epitheliopathy has been described in association with many common illnesses, including mumps, adenoviral infection, and Lyme disease; administration of vaccines for varicella, and hepatitis B; and in patients with Wegener's granulomatosis [455-460]. Vascular inflammation is thought to be a component as evidenced by its association with neurosensory hearing loss [461] and central retinal vein occlusions[462]. Patients can present with headache, and some patients develop cerebral vasculitis and ischemia [463-466].

Figure 1.16 Colour fundus photographs of AMMPE in acute phase.

Figure 1.17 Colour fundus photograph of AMPPE in chronic phase with scarring.

1.9.6 *Serpiginous choroidopathy.*

Serpiginous choroidopathy is an inflammatory chorioretinopathy characterised by inflammatory yellow-grey choroidal lesions that eventually evolve into geographic areas of chorioretinal atrophy in both eyes [467-469]. These typically occur in the peripapillary region and then spread in a helicoid pattern along the major vascular arcades towards the macula and midperipheral retina (Fig.1.18). These lesions are much larger than those observed in PIC. Recurrences are common and manifest as yellow-grey extensions at the level of the RPE/choriocapillaris, contiguous or as satellites to existing areas of chorioretinal atrophy [470-473].

In approximately one-third of cases inflammatory cells are seen in the vitreous [474]. Chorioretinal atrophy and pigmentary changes are prominent in previously affected areas. Visual disability may result directly from retinal lesions affecting the central macula, or secondary to the development of CNVM as a result of disruption of the Bruch's membrane- RPE complex [475, 476].

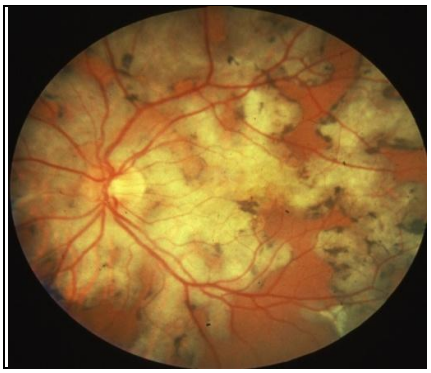


Figure 1.18 Serpiginous choroidopathy

1.9.7 *Birdshot retinochoroidopathy (BSRC).*

Birdshot retinochoroidopathy (BSRC) is an inflammatory condition characterised by the presence of multiple depigmented spots at the level of the RPE and choriocapillaris [477, 478]. The disease tends to occur between the ages of 35 and 70, with an average age of presentation of 50 [450]. It is a slowly progressive disease with profound dysfunction of vision that may not be reflected in Snellen visual acuity [479]. Patients with BSRC most commonly present with varying degrees of gradual and painless visual loss [453, 480]. Floaters, photophobia, nyctalopia, and disturbances of color vision are frequently reported [481-483].

The diagnosis of BSRC is clinical. Ryan and Maumenee[478] described the fundus lesions as ''multiple, small, white spots that frequently have the pattern seen with birdshot in the scatter from a shotgun.'' These lesions are found in the midperipheral and peripheral retina.(Fig. 1.19)

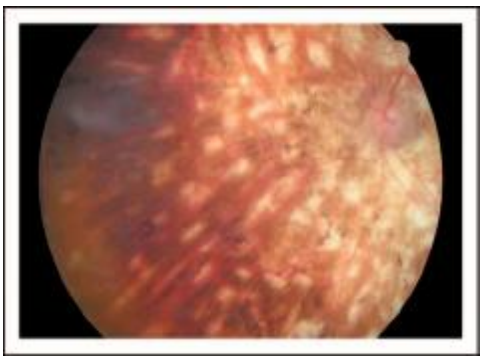


Figure 1.19 Fundus color photograph of Birdshot choroidopathy.

In addition to its characteristic ocular features, the condition is unique from the immunogenetic standpoint by its association with the HLA-A29 allele which is one of the strongest link between an HLA class I antigen and a disease [484, 485].

Diagnostic criteria include the presence of "birdshot lesions" and intraocular inflammation in both eyes. HLA-A29 is supportive of the diagnosis, but not required [486]. Macular oedema is the most frequent cause of decreased visual acuity. Macular atrophy, as reflected in OCT evidence of macular thinning and mfERG evidence of poor macular function, occurs in patients with long-standing birdshot retinochoroidopathy. Measurement of retinal layer thickness by frequency-domain OCT suggests that the atrophy occurs primarily in the outer retina [487].

Retinal capillary hyperpermeability and resultant cystoid macular oedema are common. The main objective of fluorescein angiography in patients with BSCR is the assessment of the retinal vasculature, and the following can be observed: attenuated vessels in 83%, irregular veins in 72%, and arteriovenous filling time longer than 10s in 6% of patients [488]. Choroidal neovascular membrane can also be detected. The cause of visual loss can be determined by this mean.

ERG assessment of rods and cones is abnormal in a great number of patients, with a variable degree of impairment. ERG parameters may show early retinal dysfunction. Typical results show an electronegative pattern with a b-wave smaller than the normal or attenuated a-wave resulting in a low b:a ratio [481, 489].

Autofluorescence photography can demonstrate the RPE atrophy, which may not be seen by other means of investigation. The areas of RPE atrophy do not necessarily correspond to the hypopigmented lesions, which suggest that both the choroid and the RPE can be affected independently. Retinal pigment epithelium atrophy in the macula may be an important cause of poor central visual acuity in eyes with BSCR [200].

1.9.8 *Sympathetic ophthalmia (SO).*

Sympathetic ophthalmia presents as (SO) presents as a bilateral, granulomatous uveitis following trauma to one eye[490]. Penetrating injuries and surgical procedures are the most common causes of SO. Other, less common causes are plaque brachytherapy[491], fungal keratitis[492], and cyclodestructive procedures[493]. The eye sustaining the injury or surgery is referred to as the inciting eye and the fellow eye is called sympathising eye. The time between the ocular injury or surgery of the inciting eye to the development of SO is quite varied. The sympathising eye usually presents with inflammation within 3 months after the injury but the range has been noted to be from 2 weeks to 50 years[494]. About 80% of cases occur within a 3-month time frame and 90% occur within 1 year [495, 496].

Patients can present with bilateral acute anterior uveitis with mutton-fat keratic precipitates [490, 497]. Lymphocytic infiltration of the iris can lead to thickening and synechiae while change in the intraocular pressure may be due to ciliary body shutdown or blockage of trabecular meshwork [490]. In the posterior segment, SO can manifest itself in the form of moderate to severe vitritis, inflammation of the ciliary body, choroiditis, peripapillary choroidal atrophy and optic nerve oedema[490, 497, 498]. Serous retinal detachment and macular oedema may also be present[499]. Yellow-white lesions at the level of retinal pigment epithelium correspond to Dalen-Fuchs nodules [500, 501](Fig.1.20). In a recent pilot study Furusato et al.[500, 501]demonstrated that M1 macrophages are the predominant inflammatory cells within granulomas and DFN of SO. They further observed high levels of IL-17 within granulomas and the presence of Th1 and M1 cells.

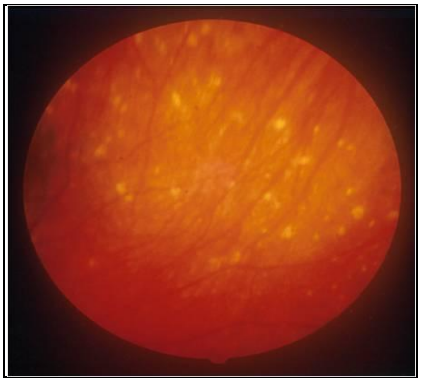


Figure 1.20 Dalen-Fuchs nodules in SO.

Before diagnosing a patient with sympathetic ophthalmia, it is necessary to rule out other causes of granulomatous uveitis. The diagnosis is made clinically, Dalen-Fuchs nodules are not a prerequisite for diagnosis, and histological proof is not required[502].

If the patient has sustained previous trauma, one must rule out uveal effusion syndrome, lens induced uveitis, and post-traumatic iridocyclitis. Autoimmune illnesses including Vogt-Koyanagi-Harada syndrome (VKH), sarcoidosis, multifocal choroiditis can be very similar to SO. Dalen-Fuchs nodules, choroiditis and papillitis can be found in SO and sarcoidosis. Infiltration by T lymphocytes can occur in VKH, SO and sarcoidosis and antibodies to retinal antigens can be identified in both SO and VKH[495].

Intraocular lymphoma and bilateral phacoanaphylaxis can also have a similar presentation to SO. Landolfi et al.[503]reported a case where sympathetic ophthalmia presented like multiple evanescent white dot syndrome. Atypical presentations have also been reported and include progressive subretinal fibrosis with multifocal granulomatous chorioretinitis with the patient having antiretinal antibodies [504]. Fluorescein angiography is used commonly to confirm and assess the extent of SO. Characteristic findings include multiple fluorescing spots in the pigment epithelium during the venous phase of the study corresponding to areas of flourescein leak[505]. In the

presence of retinal vasculitis or Dalen-Fuchs nodules, the flourescein leaks will correspond to these regions. Staining of optic nerve can also be observed [506].

1.9.9 *Ocular toxoplasmosis (OT).*

The hallmark of ocular toxoplasmosis is the characteristic clinical picture of disease reactivation (secondary infection), which often makes it unnecessary to refer patients for laboratory testing [507]. The typical ocular lesion consists of focal necrotising chorioretinitis accompanied by vitreous inflammatory reaction, frequently associated with an adjacent old pigmented scar indicative of previous infection [508]. The classic"headlight in the fog" appearance is attributable to the presence of active retinal lesions with severe inflammatory reaction[509].(Fig.1.21) Chorioretinitis in individuals with acute acquired toxoplasmosis can arise sporadically or in the context of an outbreak of acute disease[510]. Satellite lesions develop in 80% of patients compared with 20% with isolated lesions [511]. It is noteworthy that 72% of patients attending for the first time already have a combination of an active lesion with a healed retinal scar, indicating that these patients had a previously unnoticed retinal lesion [511]. Less typical manifestations comprise large, eventually multiple and/or bilateral lesions, endophthalmitis like presentations, punctate outer retinitis, neuroretinitis, and scleritis [117, 511-514]. Complications like granulomatous iritis, high intraocular pressure, retinal vasculitis and vascular occlusions, rhegmatogenous and serous retinal detachments, and diverse forms of secondary pigmentary retinopathies might disguise the original toxoplasmic lesion and make the correct diagnosis difficult [511, 512, 514]. OT is typically characterised by 8- to 16-week active periods of intraocular inflammation in which new retinal lesions are formed and by long, disease-free intervals, which may extend for several years. Complications can include fibrous bands, secondary serous or rhegmatogenous retinal detachments, optic neuritis and neuropathy, cataracts, increased intraocular pressure during active infection, and choroidal neovascular membranes.

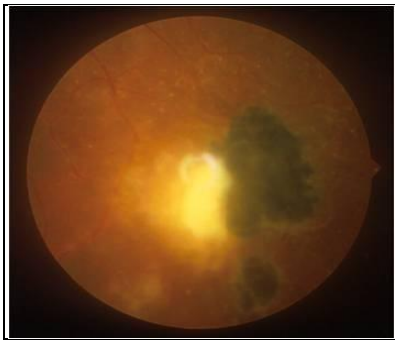


Figure 1.21 Ocular toxoplasmosis showing an old scar with a satellite active reactivation lesion.

Recurrences in untreated congenital toxoplasmosis can occur in the teenage years[515]. The causes of visual loss include location of toxoplasmic lesion in the macular area and retinal detachment [511]. Clinical diagnosis of OT, frequently used in practice, is only presumed and reliable when typical [516]. Although serology is crucial in acute infections where antitoxoplasma IgM is raised, it is not helpful in most of OT patients, who typically have low IgG antibody levels [508]. Even though toxoplasmosis is well recognised as the most common form of posterior uveitis worldwide and the etiologic agent has been known for over 100 years, there are still significant discrepancies regarding how to best diagnose and treat the condition [507].

1.9.10 *Retinal vasculitis.*

Retinal vasculitis is a sight-threatening inflammatory eye condition that involves the retinal vessels. It may occur as an isolated idiopathic condition, as a complication of infective or neoplastic disorders, or in association with systemic inflammatory disease [417]. The term vasculitis is not used in its original histopathological sense of vessel wall inflammation but in the sense of visible clinical vessel wall changes seen by ophthalmoscopy and/or fundus fluorescein angiography [517]. The most common symptoms reported by patients with retinal vasculitis are blurred vision, scotomata, and floaters. Less common symptoms include alteration of color vision, metamorphopsia, and rarely pain [518]. Some patients may have minimal or no symptoms if the vasculitis is confined to the retinal periphery. Systemic symptoms and signs may be present and suggest an underlying aetiology. Important systemic manifestations include oral and genital ulcers, skin lesions ulceration, arthritis, rash, neurologic disease, and evidence of embolic disease [519].

Detection of retinal vasculitis is made clinically, and is confirmed with the help of fundus fluorescein angiography. Active vascular disease is characterised by thickening and cellular infiltrates surrounding the basement membrane and retinal vascular wall resulting in white sheathing or cuffing of the affected vessels, which may be segmental (skip lesions) or confluent [517].(Fig.1.22) In some patients, the peripheral retinal vessels may be preferentially affected. The vasculitis may involve the retinal arteries, veins, and/or capillaries although the retinal veins are most commonly affected. Minimal anterior chamber cells as well as vitritis, inferior vitreous snowballs, and posterior vitreous detachment are also common. Additional findings include retinal haemorrhages, cystoid macular oedema, optic disc oedema, or optic atrophy [421].

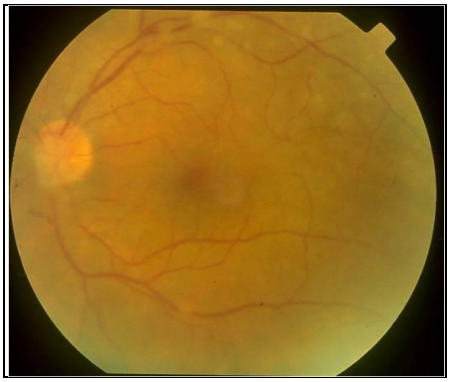


Figure 1.22 Colour fundus photograph showing retinal vascular sheathing.

Characteristic features seen on fluorescein angiography include inflammatory and ischemic manifestations such as vascular staining and leakage with typical “skip lesions”, capillary nonperfusion, retinal neovascularisation, and sclerosis of vessels. Diffuse capillary leakage is also a common finding in many patients [421]. (Fig. 1.23)

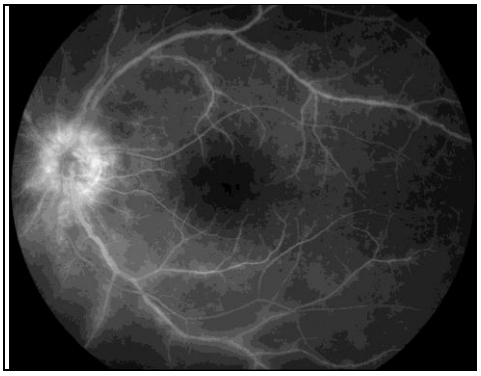


Figure 1.23 Diffuse capillary leakage on fluorescein angiography.

Table 1.1 Summary of diseases associated with retinal vasculitis[417] .

Ocular disease	Infectious diseases	Systemic diseases
Idiopathic	Toxoplasmosis	Behçet disease
Eales disease	Tuberculosis	Sarcoidosis
Birdshot retinochoroidopathy	Syphilis	Multiple sclerosis
Intermediate uveitis	Lyme disease	Crohn's disease
Frosted branch angeitis	Cytomegalovirus	Systemic lupus erythematosus
Idiopathic retinal vasculitis and neuro-retinitis(IRVAN)	Herpes simplex Varicella zoster	Wegener granulomatosis Ankylosing spondylitis
Vogt-Koyanagi-Harada Syndrome	Whipple disease	Polyartheritis nodosa
Sympathetic ophthalmia		Burger disease
Acute multifocal haemorrhagic retinal vasculitis	Human T-cell lymphotropic virus Brucellosis	Relapsing polychondritis Antiphospholipid syndrome
Multifocal choroidopathy	Hepatitis	Chug-Strauss syndrome
Panuveitis	Cat scratch disease	Sjögren's disease
	AIDS	Polymyositis
		Rheumatoid arthritis
		Dermatomyositis
		Takayasu disease
		Primary central nervous system lymphoma
		Acute leukaemia
		Cancer-associated retinopathy

Less commonly, inflammation of the retinal vasculature may occur as an isolated disorder. These cases of retinal vasculitis without an associated systemic or ocular disease are termed idiopathic retinal vasculitis (IRV). Patients with IRV are typically young adults with no signs or symptoms suggestive of an underlying systemic or ocular disease e.g. Eale's disease. [520]. Once the diagnosis of retinal vasculitis is made, investigations can be initiated, the diagnostic work-up being tailored according to the patient's medical history, review of systems, and physical examination.

Acute inner retinal ischemia develops secondary to occlusion of the larger retinal vessels. The retinal appearance in the affected area depends on whether the occlusion is total or relative, or whether it affects an arteriole or a venule. After total occlusion of the arteriolar supply, the inner retina is emptied of blood and develops a characteristic whitish ischemic oedema in the inner layers[521]. Relative occlusion of the retinal arteriolar supply may lead to the development of haemorrhages and microaneurysms in the affected area, sometimes accompanied by a yellowish retinal oedema[522].

Chronic inner retinal ischemia is primarily observed as capillary occlusion in the retinal midperiphery and periphery. It is diagnosed on the basis of its angiographic appearance: areas of capillary non-perfusion consist of localised, well defined dark areas caused by closure of the retinal capillaries. In these areas, the choroidal contours are blurred, probably as a result of the accumulation of a serous material between the pigment epithelium and the retinal photoreceptors[523](Fig.1.24; 1.25)

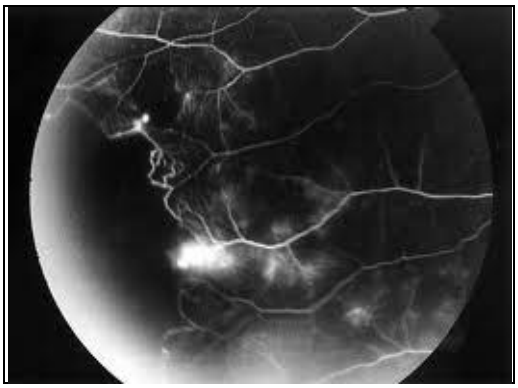


Figure 1.24 Peripheral capillary nonperfusion

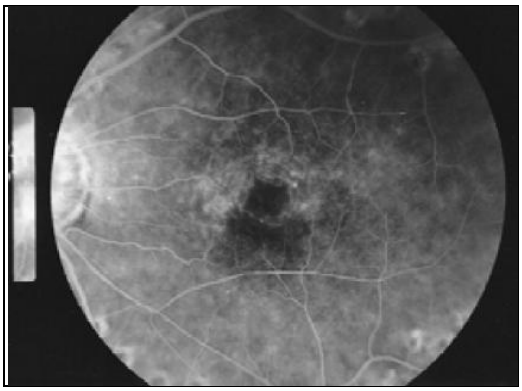


Figure 1.25 Capillary phase of fluorescein angiogram showing focal dropout of the perifoveal papillary arcade indicative of macular ischemia.

Three patterns of retinal ischemia may be identified by FFA. Peripheral capillary closure is a feature of tuberculosis, sarcoidosis, Eale's disease, and, in rare instances, multiple sclerosis, Behçet syndrome, and slow-flow retinopathy. Ischemic branch retinal vein occlusions are characteristic of Behçet syndrome and have also been reported in sarcoidosis[524]. Focal capillary dropout at the fovea (macular ischemia) is often missed because of either media opacity or a failure to identify the fovea at the appropriate phase of the angiogram run[524]. This is an important sign because its presence often explains a poor visual outcome despite adequate suppression of disease [525].

1.9.11 *Neovascularisation.*

Both retinal neovascularisation at the disc (NVD) (Fig.1.26), elsewhere (NVE) (Fig.1.27) and choroidal new vessels leak fluorescein profusely in the late phase of fluorescein angiography. The neovascular response may occur secondary to widespread capillary closure or as a direct consequence of intraocular inflammation[524]. It is important to identify the presence or absence of retinal ischemia in this situation because the management is different. In the former case, laser photocoagulation may be indicated (although there is a risk of exacerbating macula oedema), whereas in the latter, adequate immunosuppression will usually induce regression of the neovascular response[526].

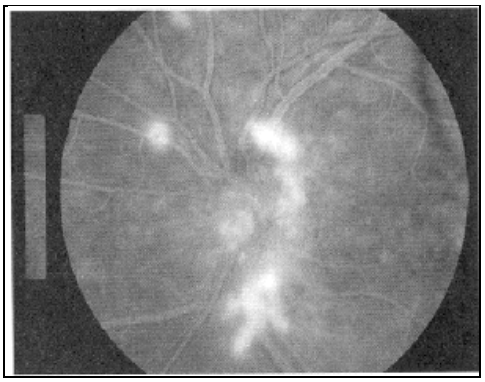


Figure 1.26 Neovascularisation of the optic disc.

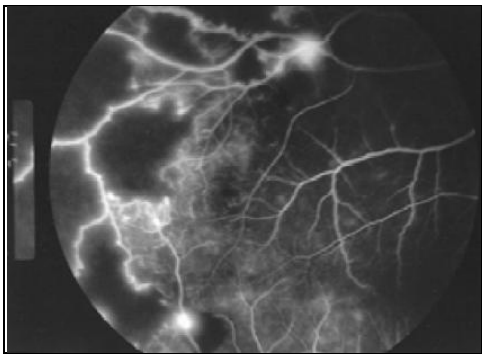


Figure 1.27 Peripheral capillary closure and early NVE.

1.9.12 *Retinal vein occlusions (RVOs)*

Depending on the location of the obstruction, RVOs can be divided into central retinal vein occlusion (CRVO) (Fig.1.28) and branch retinal vein occlusion (BRVO) (Fig.1.29). In BRVO, the obstruction is located in one of the branches of the central vein, affecting only part of the posterior pole and the portion of the peripheral retina drained by the occluded branch. In CRVO, it is located in the central vein, at the level of the optic nerve, so most of the retina is affected[527]. Both BRVO and CRVO can be subdivided in two types: ischemic (if more than 10 disc areas of capillary nonperfusion are noted on fluorescein angiography) and nonischemic (if fewer than 10 disc areas of retinal capillary nonperfusion are identified) [528]. Although most patients with CRVO are over the age of 50, it can occur in younger patients, commonly termed papillophlebitis. Younger patients frequently have an associated inflammatory cause[529] or coagulopathy [530, 531]. CRVO has also been reported in association with glaucoma[532, 533], ocular syphilis[534], acute posterior multifocal placoid pigment epitheliopathy [535]" tuberculosis and uveitis[536].

A CRVO is characterised by what is often called a "blood and thunder" appearance with extensive, widespread intraretinal haemorrhages radiating from the optic nerve head, and dilated and tortuous retinal veins [537]. Other conditions associated with BRVO include BD, sarcoidosis, antiphospholipids syndromes, SLE and toxoplasmosis [538-541]. Risk factors for CRVO include high blood pressure, high cholesterol. It may occur as part of disease process or secondary to complications such as hypertension or secondary glaucoma.

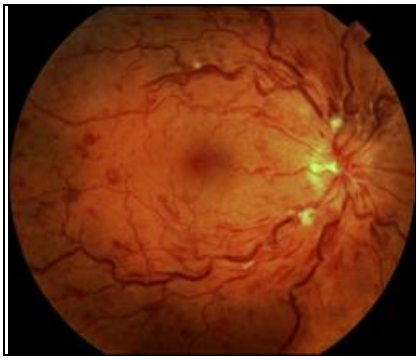


Figure 1.28 Central retinal vein occlusion(CRVO)

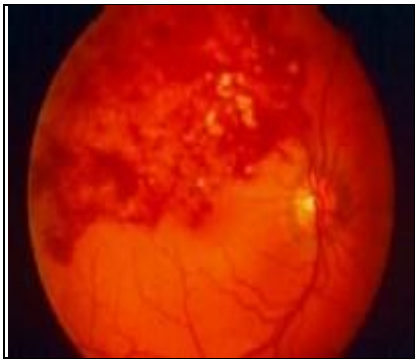


Figure 1.29 Branch retinal vein occlusion (BRVO).

1.9.13 *Retinal artery occlusion (RAO).*

Branch retinal artery occlusions (BRAOs) typically occur at vessel bifurcations, with temporal vessels being involved 98% of the time[542]. Branch retinal arteries are mainly distributed in the nerve fibber layer of the retina, and branches of the capillary form the inner capillary and outer capillary plexus. The inner capillary plexus is mainly distributed in the ganglion cell layer while the outer capillary plexus is mainly distributed in the inner nuclear cell layer. Therefore, obstruction of the central retinal artery or branch retinal artery causes ischemic damage in various retinal layers mentioned above [543]. When retinal artery occlusions occur in association with CRVO, the arterial component is, in most cases, probably secondary to the CRVO, CRVO causing compression of artery in sheath portion with central retina artery [529].

Central retinal artery occlusion (CRAO) (Fig.1.30) and BRAO (Fig.1.31) have been reported in association with antiphospholipid syndromes, SLE and collagen diseases [544-546].

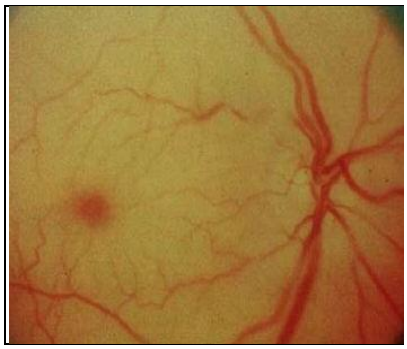


Figure 1.30 Central retinal artery occlusion (CRAO) showing the typical “cherry-red” spot.

Figure 1.31 Branch retinal artery occlusion (BRAO).

1.9.14 *Vogt-Koyanagi-Harada syndrome (VKH).*

VKH (Vogt-Koyanagi-Harada) syndrome is an autoimmune disease. Also known as uveomeningitic syndrome, is an idiopathic inflammatory disease characterised by bilateral, chronic, diffuse granulomatous panuveitis frequently associated with neurological, auditory, and integumentary manifestations [547]. It is an autoimmune disease against melanin. The prevalence of the disease varies among different populations of the world, and it commonly affects pigmented races and people of certain genetic predispositions [548]. The most common complaints of VKH patients include visual loss in one or both eyes, eye pain, and hearing disturbance. They typically show a prodromal aseptic meningitis-like syndrome, such as headache, vertigo, nuchal rigidity, vomiting, and low-grade fever. Although considered a systemic condition, VKH can present with disease findings limited to intraocular inflammation. In patients with acute VKH, 54% had only ocular manifestations, whereas in chronic disease, 40.9% had findings limited to the eyes[549]. Early ocular findings may include diffuse multiple choroidal granulomas more typical, optic disc swelling, and exudative retinal detachment. (Fig.1.32) Late ocular findings include depigmentation of the fundus (sunset glow fundus) and occasionally subretinal neovascularisation. According to the clinical features, the course of VKH was classically classified as four distinct phases: prodromal, acute uveitic, chronic, and chronic recurrent stages [550]. The diagnosis is essentially clinical, no blood investigations are helpful. It is interesting to note that VKH disease can present in patients with clinical features limited to the eye in the acute phase in the form of bilateral uveitis associated with exudative retinal detachment, whereas in the chronic phase VKH patients may present with sunset glow fundus without extraocular findings. Recognition of this isolated ocular variant of acute and chronic VKH is important for prompt diagnosis. In patients with bilateral uveitis, the importance of exudative retinal detachment and sunset glow fundus changes as the main diagnostic findings in acute and chronic VKH, respectively[551]. In patients with uveitis without clinically apparent exudative retinal detachment, ultrasonography and fluorescein

angiography can detect choroidal and retinal findings [552-555]. To exclude infection when there are meningo-encephalitic signs/symptoms, a lumbar puncture may be required and classically shows a lymphocytosis.

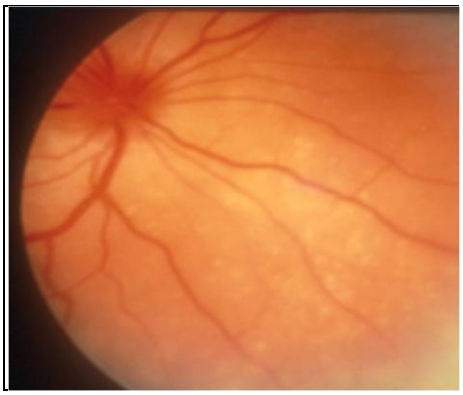


Figure 1.32 VKH syndrome with pink optic disc and white choroidal granulomas.

1.9.15 *Behçet's disease (BD).*

Behçet's disease (BD) is a multisystem disorder that was described in 1937 by the Turkish dermatologist, Hulusi Behçet (1889-1948) as consisting of the triad of ocular inflammation and oral and genital ulcers. Other systemic manifestations include erythema nodosum, cutaneous thrombophlebitis, arthropathy, gastrointestinal disturbances, and, less commonly, central nervous system involvement and major vessel thrombosis [556].

The diagnosis of BD is entirely clinical as there is no specific diagnostic test. According to the International Study group for Behcet's disease, it requires recurrent oral ulcerations as an essential symptom plus any two or more symptoms of genital ulcerations, eye lesions, skin lesions and a positive pathergy test [557]. The underlying pathology of Behçet's disease (BD) is an obliterative and necrotizing vasculitis and typically presents itself in the eye as an anterior or posterior uveitis or, more commonly, as a panuveitis[558].(Fig.1.33)

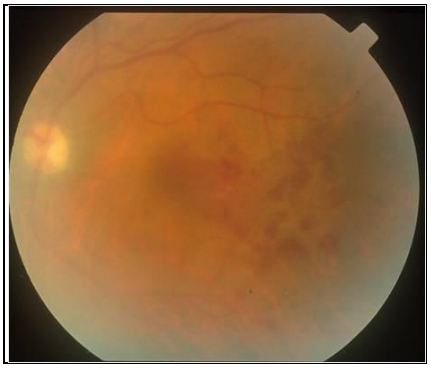


Figure 1.33 Panuveitis in Behçet's disease.

The incidence of posterior segment involvement is reported to be 50–93% [558-560]. An anterior uveitis or iridocyclitis is seen frequently, with an associated hypopyon in about a third of cases in some series and in 10% of Europeans [561].

Retinal disease is characterised by severe, often bilateral ischemic retinal vasculitis with retinitis which may involve the macula and optic nerve. These recurrent vaso-occlusive episodes ultimately result in extensive retinal damage with consequent profound visual loss [556]. Fluorescein angiography may show diffuse retinal vascular leakage, late staining of vasculature, leakage from the disc, macular oedema, areas of capillary dropout, and neovascularisation [517]

1.9.16 *Sarcoidosis.*

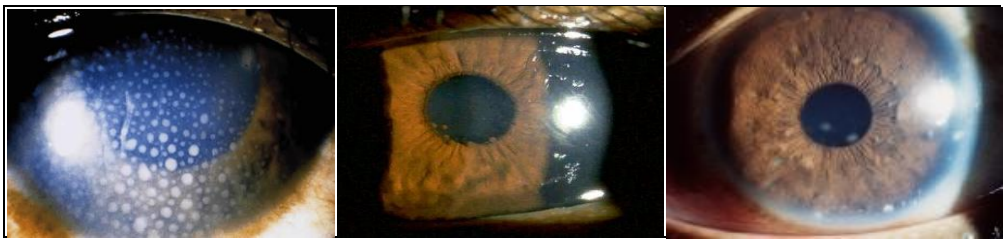
Sarcoidosis is a chronic inflammatory disorder with an unknown aetiology characterised by noncaseating granulomas[562]. It is universally accepted that the gold standard for the diagnosis of sarcoidosis is histological proof on biopsy tissue showing noncaseating granulomas, and exclusion of other diseases that produce granulomatous lesions, such as tuberculosis [563]. Skin, peripheral lymph nodes, and lungs are the common biopsy sites for sarcoidosis [564].

Many reports in the literature described granulomatous uveitis as the hallmark of sarcoidosis. The criteria used to establish the diagnosis was in line with the 1st International Workshop on Ocular Sarcoidosis (IWOS) held in 2006 in Tokyo, Japan. According to their report, the following clinical signs were most suggestive for ocular sarcoidosis [565]:

1. Mutton-fat/granulomatous keratic precipitates (KPs) and/or iris nodules (Koeppe/Busacca) (Fig.1.34)

These two signs are the expression of granulomatous changes in the anterior segment of the eye. KPs can be large (mutton-fat KPs) or can take the form of smaller granulomatous KPs. The nodules at

the pupillary margin (Koeppe nodules) and those in the iris stroma (Busacca nodules) are classic manifestations of chronic anterior granulomatous uveitis.



A B C

Figure 1.34 Mutton-fat KPs (A), Koeppe nodules (B) and Bussaca nodules(C).

2. Trabecular meshwork (TM) nodules (Berlin Nodules) and/or Tent-shaped peripheral anterior synechiae (PAS). Small nodules are commonly seen on the surface of the TM. The small size of the nodules and their colour (white or whitish grey) on the TM (white) make them difficult to find. Careful gonioscopic examination with high magnification may help to detect the TM nodules. Tent-shaped PAS is considered to be the consequence of the resolution and scarring of TM nodules representing the same pathology at a different stage of inflammation. TM nodules can disappear soon after treatment with topical or systemic corticosteroids, while tent-shaped PAS stay there and can be found at any time once they have occurred.

3. Snowballs/string of pearls vitreous opacities.

These types of vitreous opacities represent granulomatous changes in the vitreous. These vitreous opacities are usually located at the inferior segment of ocular fundus, and can be single or multiple and forming a “string of pearls” configuration.(Fig.1.35) They are commonly seen in sarcoidosis, but also can be seen in pars planitis and intermediate uveitis associated with multiple sclerosis.

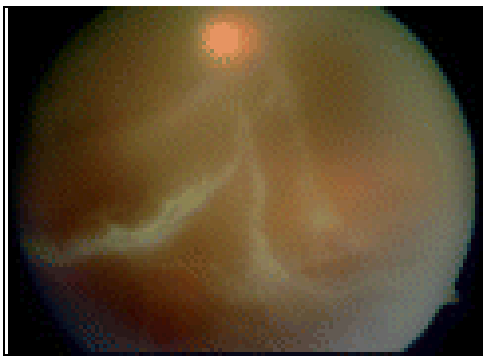


Figure 1.35 Vitreous opacities/ String of pearls.

4. Multiple chorioretinal peripheral lesions (active and/or atrophic)

Multiple chorioretinal lesions in sarcoidosis are small, round, white or whitish-yellow, and present in clusters, located at random in the periphery up to 360°, but are most commonly seen inferiorly.(Fig.1.36) The lesions are more whitish when active and become more yellowish-greyish with more sharp margins when cicatricial.

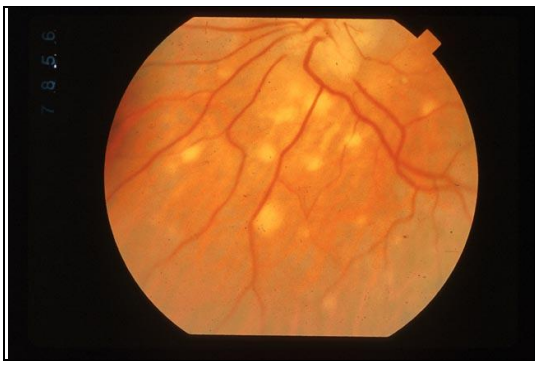


Figure 1.36 Chorioretinal lesions in sarcoidosis

5. Nodular and/or segmental periphlebitis (candlewax drippings). (Fig.1.37)

Nodular or segmental sheathing of retinal veins is a typical manifestation of retinal vasculitis in sarcoidosis. It can cause obstruction of the retinal veins, resulting in retinal vein occlusion which may be associated with areas of nonperfusion, causing retinal neovascularisation. In addition to these, the presence of macroaneurysms in an inflamed eye may be a rare ocular sign of sarcoidosis.

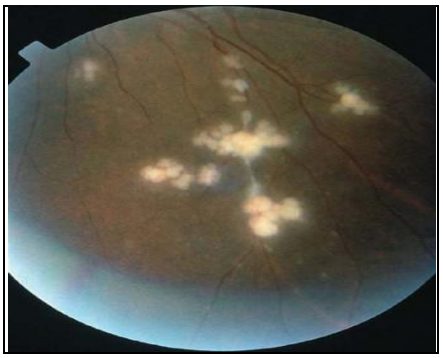


Figure 1.37 Candlewax dripping feature in sarcoidosis.

6. Optic disc nodules/granulomas and/or solitary choroidal nodule.

Although these two signs are rare, they are very typical signs of granulomatous uveitis such as sarcoidosis and tuberculosis. Optic disc nodules can be large or small. (Fig.1.38) The solitary choroidal nodule is usually round and whitish-grey (Fig.1.39).

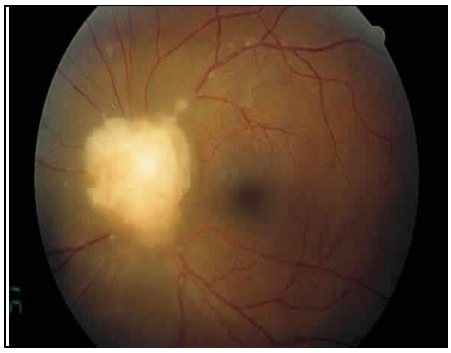


Figure 1.38 Large optic nerve head granuloma in sarcoidosis.

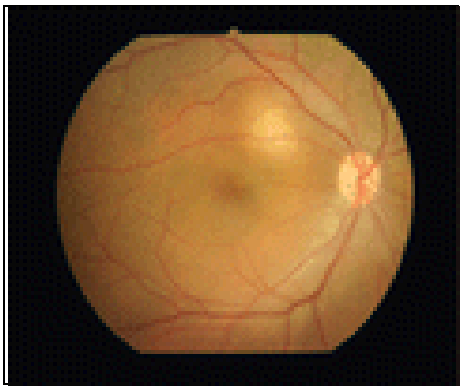


Figure 1.39 Solitary choroidal granuloma in sarcoidosis.

7. Bilaterality.

More than 80% of patients with ocular sarcoidosis have bilateral uveitis [566]. Bilaterality can be established either by clinical examination or by adjuvant methods capable of showing subclinical disease. Bilaterality can also be documented when, in addition to activity in one eye, there are sequels of previous inflammation in the other eye, such as PAS found on gonioscopic examination.

To support the diagnosis of ocular sarcoidosis, the following investigations/laboratory tests are recommended by the IWOS:

-Chest X-ray: Showing bilateral hilar lymphadenopathy (BHL).

- Chest CT scan in patients with a negative chest X-ray

-Negative Tuberculin test in a BCG-vaccinated patient or in a patient with previously positive tuberculin skin test. This state of immune unresponsiveness is known as anergy. It is induced when the T-cell's antigen receptor is stimulated, effectively freezing T-cell responses.

-Elevated serum Angiotensin Converting Enzyme (ACE) and/or elevated serum lysozyme.

-Abnormal liver enzyme tests: three times the upper limit of normal values for alkaline phosphatase or elevation twice over the upper limit of two of the following liver enzymes: aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), or alkaline phosphatase.

-Interferon Gamma Release Assays (IGRAs) testing for the exclusion of TB might be useful in the diagnosis of ocular sarcoidosis.

Classic ocular features of OS will be:

- Anterior uveitis with mutton-fat KPs and/or iris nodules(Koeppe/Busacca)
- Intermediate uveitis/ posterior uveitis: snowballs/ strings of pearls vitreous opacities, multiple choriretinal lesions, BRVO with vitritis, optic nerve nodules.
  Patients who had the diagnosis of ocular sarcoidosis confirmed were jointly followed up by a chest physician and the uveitis team.

1.9.17 *Neurosarcoidosis.*

The incidence of nervous system involvement in sarcoidosis is about 5% [567]. Neurosarcoidosis characteristically presents with the onset of cranial nerve palsies or endocrine and electrolyte disturbances in a patient with known systemic sarcoid [568]. Cranial nerve involvement is the most common neurological manifestation [569], acute lower motor neurone facial palsy the most frequently seen. Many patients also have anterior uveitis. Patients with neurological symptoms and associated intraocular inflammation should have a routine work-up for sarcoidosis and the differential diagnosis may include multiple sclerosis. Investigations should include MRI scan of the brain and orbits and lumbar puncture in selected cases. Tissue biopsy should be attempted when clinically accessible lesions are available i.e., conjunctiva or lacrimal gland [569].

1.9.18 *Multiple sclerosis (MS).*

Multiple sclerosis is primarily an inflammatory disorder of the brain and spinal cord in which focal lymphocytic infiltration leads to damage of myelin and axons. Initially, inflammation is transient and remyelination occurs but is not durable. Hence, the early course of disease is characterised by

episodes of neurological dysfunction that usually recover [570]. It is the most common chronic immune-mediated central nervous system disorder among young adults [571]. In most patients, clinical manifestations indicate the involvement of motor, sensory, visual, and autonomic systems but many other symptoms and signs can occur (Table 1.2). Few of the clinical features are disease-specific, but particularly characteristic are Lhermitte's symptom (an electrical sensation running down the spine or limbs on neck flexion) and the Uhthoff phenomenon (transient worsening of symptoms and signs when core body temperature increases, such as after exercise or a hot bath) [570].

Table 1.2 Symptoms and signs of multiple sclerosis.[570]

Site	Symptoms	Signs
Cerebrum	Cognitive impairment	Deficit in attention, reasoning, and executive function (early); dementia (late).
	Hemisensory and motor	Upper motor neuron signs.
	Affective	Mainly depression
	Epilepsy(rare)	
	Focal cortical deficits(rare)	
Eye		Intermediate uveitis, retinal vasculitis, retinal vein closure
Optic nerve	Unilateral painful loss of vision	Scotomata, reduced visual acuity, colour vision, and RAPD
Cerebellum and Cerebellar pathways	Tremor	Postural and action tremor, dysathria
	Clumsiness and poor balance	Limb incoordination and gait ataxia
Brainstem	Diplopia, oscillopsia	Nystagmus, internuclear and other complex ophthalmoplegias.
	Vertigo	
	Impaired swallowing	Dysarthria
	Impaired speech and emotional lability.	Pseudobulbar palsy
	Paroxysmal symptoms	
Spinal cord	Weakness	Upper motor neuron signs
	Stiffness and painful spasms	Spasticity
	Bladder dysfunction	
	Erectile impotence	
	Constipation	
Others	Fatigue	
	Temperature sensitivity and exercise intolerance	

In many situations, clinical evidence is sufficient for establishment of the diagnosis and laboratory studies are superfluous; but, when the diagnosis is ambiguous, investigations can help. MRI shows focal or confluent abnormalities in white matter in more than 95% of patients. Their presence alone, however, does not make the diagnosis of multiple sclerosis; characteristic radiological lesions can appear in people without clinical signs of disease and many individuals older

than 50 years have non-specific white matter cerebral lesions [570]. The presence of oligoclonal bands after protein electrophoresis of the cerebrospinal fluid, which is seen in about 90% of patients, suggests intrathecal immunoglobulin synthesis [570]. The reported frequency of uveitis in MS patients varies widely, from 0.4% to 26.9% [572, 573]. The prevalence of MS in the total population of patients with uveitis is 1% to 2% [574]. The most common type is intermediate uveitis [575-577] which may be mild or severe with vaso-occlusive disease [578, 579]. The diagnosis of MS is always made by a neurologist.

1.9.19 *Juvenile idiopathic arthritis (JIA).*

JIA is a collection of heterogeneous chronic childhood arthritides with onset before 16 years of age and persisting 6 weeks or longer with likely distinct pathophysiologic mechanisms that lead to a common pattern of tissue destruction [580]. There are four subtypes of JIA: persistent oligoarticular (four or less joints involved throughout course of disease), extended oligoarticular (four or less joints involved during first 6 months and five or more joints involved thereafter), rheumatoid factor-positive polyarticular and rheumatoid factor-negative polyarticular. The female : male ratio in oligoarticular JIA is 3 : 1[580]. Susceptibility to JIA is inherited; siblings of patients with JIA have a 15–30-fold higher risk of developing JIA compared with the general population [581].
JIA subtypes associated with antinuclear antibodies and those classified among the undifferentiated spondyloarthropathies carry the highest risk of ocular involvement [582-585]. The risk of ocular involvement is highest in pauciarticular JIA, which predominantly affects girls before 5 years of age. The risk of uveitis persists for years after arthritis onset, extending into adulthood [586]. Ocular signs include white eyes with intraocular inflammation.(Fig.1.40) In patients with uveitis, AU is present in 83% of cases, IU in 9%, pan/posterior uveitis in 8%[587]. The functional symptoms are subtle, resulting in delayed diagnosis, and contributing to the severity of the ocular involvement [588]. Most common ocular complications include posterior synechiae reported in 68%, cataract in 59.6%, band keratopathy and glaucoma in 48% and 25% respectively[589] The diagnosis of JIA was usually made by a paediatrician.

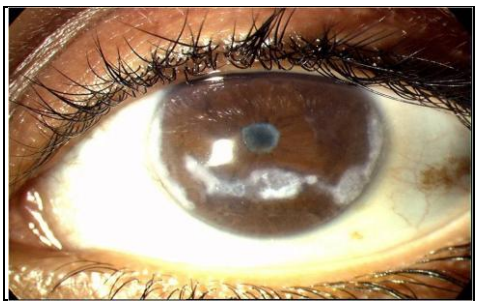


Figure 1.40 JIA uveitis. Note a white eye with posterior synechiae and band keratopathy.

1.9.20 *Ankylosing spondylitis (AS).*

Ankylosing spondylitis (AS) is a chronic inflammatory disease that mainly affects the sacroiliac joints and is characterised by restricted spinal mobility. Disease may be accompanied by peripheral joint symptoms and enthesitis or extraarticular involvement such as uveitis. When preceding symptoms occur in individuals ≤ 16 years of age and followed by radiographic sacroiliitis in later stages, the disease is termed juvenile onset AS (JOAS) [590]. JOAS differs from its counterpart, adult onset AS (AOAS), with clinical features and pattern at onset of high prevalence of peripheral expression and low prevalence of axial involvement [591, 592]. Almost 90% of patients with ankylosing spondylitis are HLA-B27 antigen positive [593]. Diagnosing early spondyloarthritis (SpA) in young patients presenting with symptoms of inflammatory back pain (IBP) and normal findings on plain radiographs of the sacroiliac joints (SIJ) remains a challenge in routine practice. This is reflected by a substantial diagnostic delay of 5 to 7 years in many cases [594].

Radiography displays postinflammatory structural changes in the subchondral bone of the SIJ that are often visible only after symptom duration of several years [595, 596]. Magnetic resonance imaging (MRI) shows early inflammatory changes in bone marrow and soft tissues and is regarded as the most sensitive imaging modality for detecting early SpA. It may therefore display early inflammatory abnormalities in the SIJ and the spine before the appearance of structural lesions on radiography. MRI may allow a confirmation of a diagnosis of early SpA suspected on clinical grounds as early as 4 months after symptom onset [597]. The most frequent extraarticular manifestation in SpA is eye involvement, which is found in 30%-50% of patients.

Prevalence of uveitis increases with duration of disease[598]. Uveitis associated with AS is characterised by acute nongranulamatous anterior uveitis with recurrent episodes in most patients. Diagnosis is made according to typical clinical features and radiological evidence of bilateral sacroiliitis [599]. AAU associated with AS is often recurrent and unilateral, but may flip to the alternative eye with subsequent epsodes[600]. The ocular disease may be associated with macular oedema and may also become chronic [601].

1.9.21 *Systemic lupus erythematosus (SLE).*

Systemic lupus erythematosus (SLE) is a chronic, relapsing and remitting, autoimmune disorder. The clinical presentations are diverse and depend on the organ systems involved [602]. A pathologic immune response involving the production of autoantibodies and immune complex-mediated tissue damage is thought to play a central role in the disease process[603]. Women with SLE outnumber men by 9 : 1 and the peak age of onset ranges from the late teens to the fourth

decade of life [604]. Individuals of African or Asian descent appear to be at greatest risk for developing the condition [604]. The diagnosis of SLE is based upon the presence of four or more of the 11 criteria from the American College of Rheumatology. These criteria are malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis (pleuritis or pericarditis), renal disorder (proteinuria or cellular casts), neurologic disorder (seizures or psychosis), hematologic disorder (haemolytic anaemia or leucopoenia or lymphopenia or thrombocytopenia), immunologic disorder (positive tests for antiphospholipid antibodies or anti-DNA antibodies or anti-Sm antibodies or false positive serologic test for syphilis), and presence of antinuclear antibodies [605, 606].

Retinal vascular changes are a significant ophthalmic finding, as they appear to correlate to the degree of systemic disease activity [607]. The retinal microangiopathy associated with SLE is thought to result from immune complex-mediated vascular injury and microvascular thrombosis. Antiphospholipid antibodies (anticardiolipin antibodies or lupus anticoagulant) may play a critical role in some patients [602]. Antiphospholipid antibodies are present in 77% of patients with lupus related retinal or optic nerve disease, compared with only 29% of SLE patients without such ocular involvement [608]. Retinal findings most commonly associated with lupus are cotton wool spots and intraretinal haemorrhages[609].(Fig.1.41) Other retinal manifestations may include microaneurysms, vascular tortuosity, arteriolar narrowing, retinal oedema, or exudates [610-612]. Fluorescein angiography may be helpful in patient evaluation [610-612].(Fig.1.42)

Severe vaso-occlusive retinopathy(Fig.1.43) is a rare but well described entity that is associated with widespread retinal capillary nonperfusion, multiple branch retinal artery occlusions, ocular neovascularisation, vitreous haemorrhage, and significant resultant visual loss [613, 614]. Patients may also develop opportunistic infections of the retina (HZV, HSV, CMV, Toxo) as a consequence of their immunosuppressive treatment.

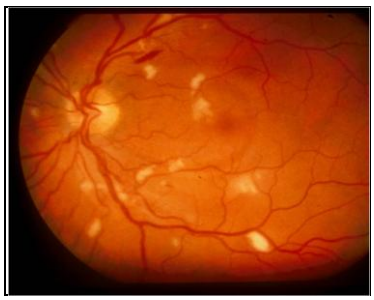


Figure 1.41. Retinal microangiopathy in SLE.

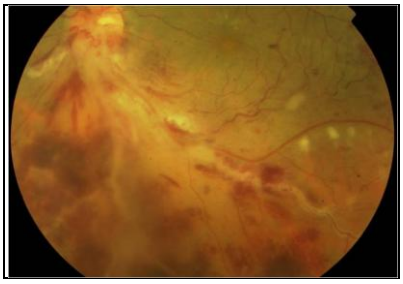


Figure 1.42 Severe retinal vaso occlusion in SLE.

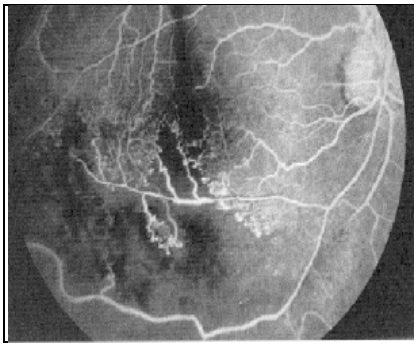


Figure 1.43 Capillary nonperfusion with neovascularisation in SLE.

1.9.22 *Diabetes.*

There is an underlining association between AU and type I and type 2 diabetes [615-617]. Diabetic patients presenting with uveitis, whatever the aetiology, may have severe inflammation, reduced vision, and poor glycaemic control [618]. All patients included in this study had a baseline blood sugar test and subsequent glycaemic checks, especially for those started on systemic steroids. Patients with visual loss due to diabetic retinopathy were excluded from this study.

1.10 Definition of complications seen in this study.

1.10.1 *Cystoid macular oedema (CMO).*

Cystoid macular oedema is defined as perifoveal macular oedema evident on biomicroscopy and confirmed by fluorescein angiography and/or optical coherence tomography.

On fluorescein angiography, CMO is recognised as a classic “flower petal” leakage pattern.
CMO appears as cavitations of the outer plexiform and inner nuclear layers in the OCT scan.(Fig.1.44)

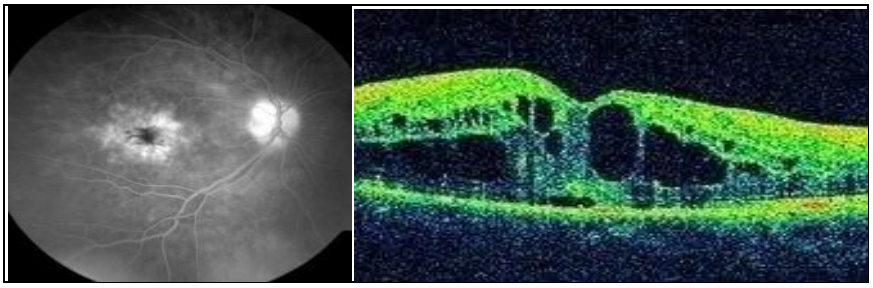


Figure 1.44 CMO on fluorescein (Left), on OCT (Right)

1.10.2 *Epiretinal membrane (ERM).*

Epiretinal membrane, also referred to as retinal folds, wrinkling of the internal retinal surface, preretinal gliosis, preretinal macular fibrosis, cellophane maculopathy, and macular pucker, is a condition characterized by proliferation of abnormal tissues on the surface of the macula or central retina of the eye [379, 619, 620].(Fig.1.45) ERMs are associated with a variety of ocular diseases, such as vascular occlusion, diabetic retinopathy, cataract, retinal detachment surgery, and posterior vitreous detachment, and also occur after photocoagulation, inflammation, or prior trauma [621-624]. The majority of patients who develop epiretinal membranes are over age 50 years [379, 625, 626]. Occasionally, epiretinal membranes can develop in children and young adults [627].
In early stages, epiretinal membranes may be asymptomatic or may create a mild reduction in visual acuity, which seldom progresses below 6/60 [625, 628-630]. Metamorphopsia, central blurring, and distortion of the Amsler grid pattern develop once the foveal centre is involved. Absolute scotomas are rare. In some cases, membrane contraction may exert tangential traction on the macular retina causing severe vision loss [619]. Clinically, epiretinal membranes start as a mild glinting, water-silk, shifting light reflex on ophthalmoscopic examination [379, 630] known as cellophane macular reflex (CMR).

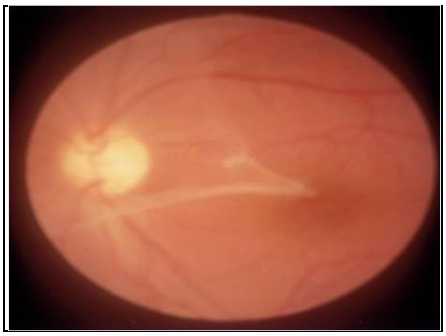


Figure 1.45 Epiretinal membrane.

At this time, superficial retinal vessels cast visible shadows on the pigment epithelium with the oblique slit-lamp illumination. As the membrane thickens and contracts, superficial retinal folds or

traction lines appear and a glinting reflex becomes opaque and gray, and is seen as clumps or bands extending over the retinal surface known as preretinal macular fibrosis (PMF). As the retinal traction lines develop, the small vessels become increasingly tortuous and macular oedema may develop. This change is often apparent on fluorescein angiography [380, 631-635]. OCTs, especially Spectral Domain are more sensitive than clinical examination in detecting ERM and vitreo macular traction syndrome (VMT)[219]. Epiretinal membrane-induced retinal damage associated with visual acuity reduction is located within the outer retina external to the inner plexiform layer [636]. In most uveitis patients, it is secondary to CMO. It may spontaneously separate, or may require surgical removal if causing visual loss

1.10.3 *Chronic macular damage.*

These occur as a result of cumulative damage over multiple recurrences of inflammation. They include macular changes due to long lasting CMO, ERMs, RPE mottling from retinal detachments, lamellar macular holes etc.

A lamellar macular hole is by definition a partial thickness macular hole where the inner layers of the fovea are involved with traction and detached from the underlying cellular layers of the fovea. Lamellar macular holes typically appear as a round or irregular-shaped, well-circumscribed reddish lesion on biomicropscopy, but clinical detection of lamellar holes at an early stage can be difficult [637]. On OCT, lamellar macular holes are easily diagnosed, and their characteristic features of an irregular foveal contour, break in the inner fovea, intraretinal split and an absence of a full-thickness foveal defect with intact foveal photoreceptors are well recognised [638].

Macular pseudo holes (MPH) were originally described as being caused by epiretinal membrane contraction, which surrounds but does not cover the foveal area [639].(Fig.1.46) Biomicroscopically, they often cannot be differentiated from lamellar and full-thickness macular holes. In TD-OCT, they are described as having a steep fovea contour and a normal or slightly elevated central and paracentral retinal thickness [640].

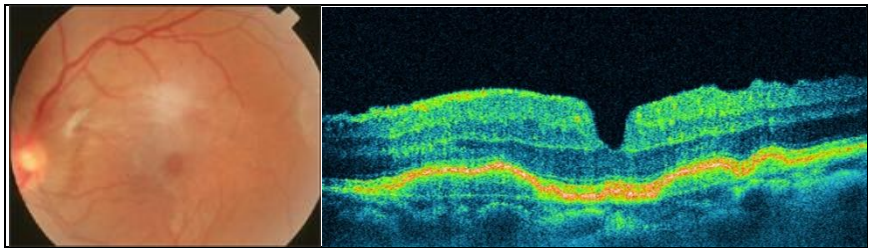


Figure 1.46 Fundus colour photograph of macular pseudo hole (left), OCT (Right)

Pigmentary changes are seen on funduscopy and can be documented with FAF. Since retina autofluorescence is mainly derived from lipofuscin fluorophores [8,9], this method is a valid tool for retinal evaluation, providing additional information on RPE viability and function [191, 192]. In contrast to normal background fluorescence, hyper- and hypofluorescence seem to be focal hallmarks of changes in health and metabolism of RPE and photoreceptor cells. Hypofluorescence is mainly attributed to either atrophy of RPE cells or light absorption by melanin pigmentation, haemorrhage, or intraretinal exudates [641].

1.10.4 *Choroidal neovascular membrane (CNVM).*

Choroidal neovascular membrane (CNVM) formation is a well-documented sight-threatening complication of posterior segment intraocular inflammation (PSII). Patients present with reduced visual acuity and distortion. Fundus examination reveals an elevated macula with grey appearance and haemorrhages.(Fig.1.47) Based on their histology, Gass classified CNVMs into Type 1 and Type 2 [642]. In Type 1, the sub epithelial CNVM grows between the basement membrane of the RPE and the inner collagenous zone of Bruch's membrane. The CNVMs associated with punctate inner choroidopathy (PIC), and with other PSII are assumed to be type 2 membranes; so called inflammatory membranes [643]. There is a correlation between leakage on FFA from an active CNVM and increased retinal thickness on OCT [644, 645]. OCT diagnostic accuracy, compared to FFA as gold standard, is improved with the use of additional colour photographs [646].

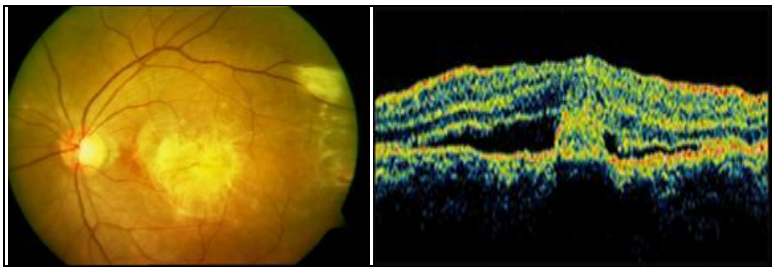


Figure 1.47 Colour fundus photograph of CNVM (Left), OCT (Right).

1.10.5 *Optic atrophy.*

Optic atrophy is a clinical term used to describe an optic disc that is paler than normal. (Fig.1.48) Optic atrophy is not a diagnosis but an ophthalmoscopic sign. Evidence of visual loss (acuity, colour vision, central vision) and afferent pupillary defect are often present. Most optic

atrophy is diffuse and nonspecific, but historical and examination clues exist that help differentiate the many causes of optic atrophy [647, 648].

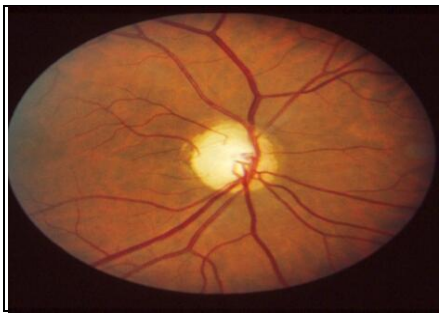


Figure 1.48 Optic atrophy.

Optic neuritis is a common feature of inflammatory diseases of the central nervous-system such as multiple sclerosis and neuromyelitis optica. It may also reveal systemic inflammatory disorders including sarcoidosis, lupus, Sjogren's syndrome, Behcet's disease, or infections such as neurosyphilis or with Bartonella [649-651]. Optic disc swelling is a common finding associated with Vogt-Koyanagi-Harada disease[652]. In patients with an acute unilateral optic neuropathy, optic neuritis in the young patient and ischemic optic neuropathy in the older patient are common aetiologies of optic atrophy [647, 648]. Patients with unexplained optic atrophy should be evaluated with magnetic resonance imaging to exclude a compressive lesion. Most patients with optic atrophy were seen by a neurologist.

1.10.6 *Cataract.*

The diagnosis of cataract, mainly PSCLO (Fig.1.49) in type was made on slit lamp examination. The clinical diagnosis was made if the lens opacity had a significant impact on vision. Patients with a lens opacification that would prevent fundus view had a B-scan ultrasound to rule out a possible retinal detachment before being listed for cataract surgery.

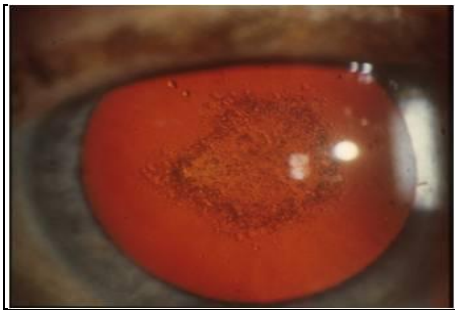


Figure 1.49 Posterior subcapsular cataract.

Patients were started on aggressive steroid regimen prior to surgery if macular oedema or posterior segment inflammation had occurred. Surgery was performed only when the inflammation was well controlled for three months and if visual acuity was reduced to the level where it caused functional impairment. The vast majority of patients underwent phacoemulsification with intraocular lens (IOL) insertion, most commonly the foldable Acrylic soft lens.

1.10.7 *Glaucoma.*

The diagnosis of glaucoma was made in situations where the intraocular pressure (IOP) was greater than 21 mmHg in association with optic disc cupping (Fig.1.50) and/or typical visual fields defects.

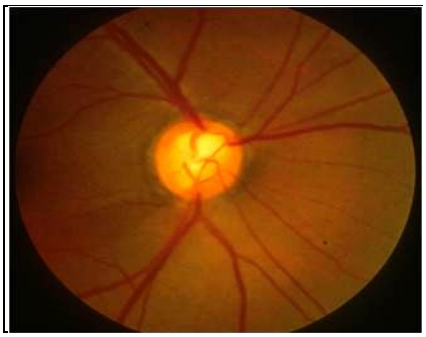


Figure 1.50 Glaucoma cupped disc.

1.10.8 *Ocular hypertension.*

The term ocular hypertension was reserved for cases where the intraocular pressure (IOP) was above 21mmHg on more than two examinations, but with normal visual fields and normal optic disc appearance.

1.10.9 *Steroid responder.*

Steroid-induced ocular hypertension/glaucoma is a form of open-angle glaucoma usually associated with topical steroid use, but may develop following oral, intravenous, inhaled, or periocular steroid administration. In the majority of cases, the IOP lowers spontaneously to baseline levels after the steroid therapy is discontinued [653]. Steroid responders were defined as having an increase in intraocular pressure (IOP) of ?6 mmHg and an absolute IOP ?21 mmHg when on steroid

together with an anatomically open anterior chamber angle and minimal inflammation[654]. Thus steroid-induced OHT/glaucoma can be differentiated from uveitic OHT/glaucoma.

1.10.10 *Hypotony.*

Hypotony is low intraocular pressure (5 mmHg or less). This can be acute, transient, chronic or permanent in an individual eye, leading to functional changes. It can be asymptomatic or symptomatic and structural changes can be reversible or irreversible [655]. Acute hypotony is any immediate lowering of IOP, a process that is often readily reversible. If it can be reversed in 15 days to one month, the hypotony is retrospectively termed transient. Transient hypotony is associated with severe uveitis and ciliary body dysfunction, retinal detachment, cilioretinal detachment and usually is without irreversible functional loss.

Chronic (prolonged or persistent) hypotony does not reverse itself easily after two to four weeks. Because it is not known how long an individual eye will tolerate a given low pressure, there is the danger of irreversible structural and functional changes. Permanent hypotony denotes irreversible structural and functional change that, on the continuum of severity, is close to phthisis [656]. The commonest causes are chronic retinal detachment, cyclitic membranes, and chronic intractable uveitis. Chronic hypotension shrinks and thickens the sclera. Epiretinal and intraretinal gliosis may cause loss of photoreceptors. Proliferation of the non pigmented epithelium of the anterior vitreous base then often leads to the formation of a cyclitic membrane in the end- stage [657] . Breakdown of the blood-aqueous barrier and the impairment of intraocular fluid dynamics ultimately results in corneal oedema, cataract, and dystrophic calcification of the corneal epithelium(band kerathopathy), pigment epithelium, and inner choroid [656].

1.10.11 *Phthisis bulbi.*

Phthisis bulbi defines the end stage appearance of the globe after any multitude of insults (i.e. injury or infection or inflammation). The intraocular structures are not easily identifiable, by physical exam or with imaging, and there is often calcification within the eye. The globe is small, shrunken (Fig.1.51) and anatomically disfigured, with generalised disorganization of the intraocular contents.

There is a reduced axial length on A-scan ultrasound as compared to the other eye.

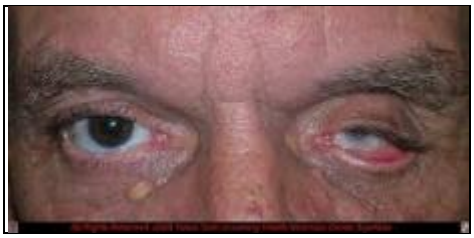


Figure 1.51 Phthisical left eye.

1.10.12 *Band keratopathy (BK).*

Calcium deposition in the Bowman's membrane and the stroma of the cornea that appearing as an opaque gray streak(Fig.1.52) and occurs in hypocalcaemia and various chronic inflammatory conditions of the eye e.g. JIA, chronic posterior uveitis.

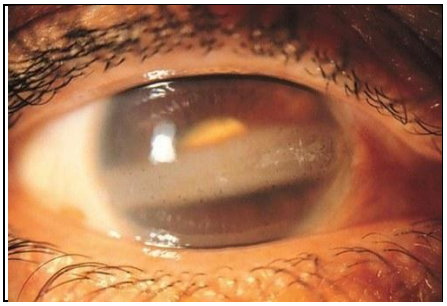


Figure 1.52 Band keratopathy.

1.10.13 *Retinal detachment (RD).*

Clinical signs of retinal detachment include sudden visual loss typically occurring like a curtain or peripheral visual field defect. Retinal detachment was diagnosed on clinical examination using biomicroscopy and indirect ophthalmoscopy. (Fig.1.53) When the retina is detached, but the macula is not, the patients have more subtle physical findings than when the macula is off because the visual centre is still functional[658].

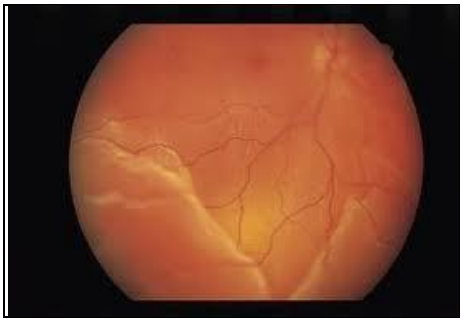


Figure 1.53 Retinal detachment.

In uveitis, RD can be rhegmatogenous, serous or tractional. Retinal detachment can be accurately characterised using ultrasonography, and the size of the detachment can be correctly identified within a small sector of the eye (3 clock hours) in 94.2% of cases [659]. Retinal detachment is a known complication in uveitis and has been reported in up to 8.3% of cases of pars planitis[660]. Brockhurst et al. showed that retinal detachment secondary to peripheral uveitis can be either rhegmatogenous or exudative[661]. Retinoschisis has also been reported as a complication of intermediate uveitis [661-663], especially following snowbank regression.

Rhegmatogenous retinal detachment (RRD) is a potentially blinding ocular pathology. The pathogenesis of RRD is a complex process resulting from inherited and/or age-related changes in vitreous structure and vitreoretinal adhesion, which predisposes to retinal break formation initiating separation of the neural retina from the underlying retinal pigment epithelium (RPE)[664].

Tractional retinal detachment occurs when glial fibrosis over the pars plana and peripheral retina contracts, causing both tangential and radial traction. This leads to peripheral retinal elevation, which in itself relieves further traction, explaining the lack of progression in the vast majority of cases. The traction is not exerted by peripheral vitreous, which is usually already detached, but from gliosis over the ora serrata[665]. The terms uveal effusion, choroidal effusion, ciliochoroidal effusion, ciliochoroidal detachment, and choroidal detachment have been used interchangeably in the literature. These labels all describe an abnormal collection of fluid that expands the suprachoroidal space, producing internal elevation of the choroid [623]. There are many causes of uveal effusion, often occurring in association with hypotony or inflammation. Examples include trauma, scleritis, pars planitis, and following surgery for cataract, glaucoma, and retinal detachment [666]. There is often co-existing, shifting subretinal fluid that may involve the macula. Chronic disease may lead to secondary retinal pigment epithelial (leopard spot) changes and permanently reduced visual acuity [666].

Central serous chorioretinopathy (CSR) is a disease of the retina characterized by serous detachment of the neurosensory retina secondary to one or more focal lesions of the retinal

pigment epithelium (RPE)[667]. CSR occurs most frequently in mid-life and more often in men than in women [668]. Major symptoms are blurred vision, usually in one eye only and perceived typically by the patient as a dark spot in the centre of the visual field with associated micropsia and metamorphopsia. CSR has been described in patients with endogenously high levels of corticosteroids as well as in patients with hypercortisolism due to the treatment of ocular or systemic diseases [669]. Ophthalmoscopic signs of CSR range from mono- or paucifocal RPE lesions with prominent elevation of the neurosensory retina by clear fluid - typical of cases of recent onset - to shallow detachments overlying large patches of irregularly depigmented RPE. The spectrum of lesions includes RPE detachments. Eyes with acute central serous chorioretinopathy (CSC) have focal leakage at the level of the retinal pigment epithelium (RPE) seen on fluorescein angiography (FA). The subsequent changes at the RPE allow the fluid to enter the subretinal space and constitute the sub-retinal fluid(SRF) which can be well documented with OCT[670]. Chronic CSR may be difficult to differentiate from occult choroidal neovascularisation secondary to CSR [667]. Serous retinal detachment is a common feature in VKH, toxoplasmosis, and in certain metastatic neoplasms. Bilateral SRD and multifocal hyperfluorescence beneath the detachment in the early phase of fluorescein angiography would support VKH as the most likely diagnosis [166, 671].

Aims and objectives.

The last main study on causes of visual loss in patients with uveitis was published in 1996 by Rothova et al.[300]. They found that 35% of patients were visually impaired, with bilateral legal blindness in 4% of patients, 4.5% had one blind eye with visual impairment of the other, and 1.5% had bilateral visual impairment. Unilateral blindness developed in 14% of patients, whereas 11% exhibited unilateral visual impairment. The most important cause of both blindness and visual impairment was cystoid macular oedema (29% and 41% respectively). Complications of uveitis were encountered in more than half of the patients and 23% underwent one or more surgical procedures. When the patients were subdivided according to anatomical site, those with panuveitis had the worst visual prognosis. The systemic diseases associated with poor visual prognosis were juvenile chronic arthritis and sarcoidosis. Ocular toxoplasmosis was the most frequent cause of unilateral visual loss.

In the last decade, the treatments for uveitis have changed considerably and many patients are much more successfully treated for macular oedema, particularly with intraocular steroids and additionally with immunosuppressive agents.

The outcome of cataract surgery in uveitis patients is very much improved, and more powerful topical treatments are available for adequate IOP control.

Ischemia is not common but does occur in certain types of uveitis and is currently not influenced by any of the medications. Vitreoretinal procedures are common for epiretinal membrane removal with varying degrees of visual recovery. Retinal thinning from atrophy occurs in certain types of uveitis e.g. Birdshot choroidopathy and effect of immunosuppression on this in the long term is unknown.

Despite advances made in the management of uveitis, patients still lose vision.

In this study we aimed:

- To evaluate the types of uveitis,
- To determine the cause of irreversible visual loss in uveitic eyes.
- To determine the impact of different surgeries on visual acuity.
- To assess the impact of different therapeuctics on visual acuity in eyes with ischemia.

While previous studies had less than 600 patients, our population is three times bigger. We looked at the visual outcome in patients with different types of uveitis, treatment and complications. In particular we looked at the visual outcome of patients who underwent surgical procedures.

The information gathered from this study will enable us to identify the current causes of visual loss and address them with targeted therapeutic strategies with the aim of preventing these where possible in the future.

Chapter 2. Patients and methods.

Ethics approval for the study was obtained from the R&D department at Moorfields Eye Hospital (*LIGS 1021*).

This was a retrospective study of patients attending the uveitis clinics of one consultant (*Prof. Sue Lightman*) at Moorfields Eye Hospital from June 2008 to June 2010. Case notes of patients due to attend two adults clinics and one paediatrics clinics were pulled out one day before the clinics. I reviewed those notes twice a week and extracted data over a two-year period.

I was aware of a selection and referral bias by using this strategy.

All patients had their visual acuity (VA) measured separately in each eye by using an illuminated Snellen chart at a distance of 6m. The best corrected visual acuity (BCVA) ± a pin hole was recorded. If VA could not be measured with the Snellen chart, finger counting, hand movements and light perception were assessed at a distance of 1 m.

A full history was taken by the clinician, including ocular history, past medical history, systems review, a sexual history where relevant and drugs history including allergies.

All patients underwent a full ophthalmological examination including slit-lamp examination, funduscopy using indirect ophthalmoscopy after pupil dilation and intraocular pressure (IOP) was measured using Goldman applanation tonometry. Ancillary tests such as optical coherence tomography (OCT) using Heidelberg Spectralis, Topcon 3D OCT or Zeiss Stratus machines depending on the period the patient was seen, fundus fluorescein angiography (FFA) (performed by injecting 5ml IV of sodium fluorescein 10%), B-Scan ultrasound, electrophysiological and laboratory tests were requested as appropriate to the history and the clinical examination.

Humphrey visual fields were performed for each eye separately when the IOP was raised.

In this study, uveitis was classified anatomically as per the SUN criteria.

(i) Anterior uveitis: the inflammation is confined to the anterior segment.
(ii) Intermediate uveitis: presence of anterior vitreous cells, snowballs or snowbank.
(iii) Posterior uveitis: the inflammation affects the choroid and/or the retina
(iv) Panuveitis: the inflammation is present in the anterior chamber, the vitreous, the retina and the choroid.

To be included in this study, patients had to have a minimum follow-up time of 6 months and have a non infective uveitis. Exceptionally, I included cases of Toxoplasmosis choroiditis. Although being an infective cause of uveitis, the immune mechanism is more damaging than the parasite itself.

Patients with bacterial, viral and fungal uveitis, scleritis, retinitis, corneal graft rejection, severe allergic keratoconjonctivitis, GVHD, and those who had another ocular co-morbidity not related to uveitis (such as diabetic retinopathy) and which could have an impact on visual acuity were excluded from this study.

Different diagnosis were made by the examining clinicians in accordance with the criteria described the Illustrations of different clinical entities included in this study were graciously provided by Prof. Lighman from her collection.

2.1 Data collection.

Data extracted from the case notes and recorded on a designed proforma (Annex) were age, sex, date of first presentation, date of onset where possible, best corrected visual acuity (BCVA) at presentation and on subsequent visits, intraocular pressure, diagnosis, systemic associated disease, treatment, complications and cause of visual loss. Complications or vision loss present at the first visit were considered to have occurred on that date, unless there was documentation in the form of a referral letter or outside medical records that indicated an earlier date. Complications were included only if there was clear documentation of clinically significant events in the case notes.

Data collected on the proforma were transferred to an excel spreadsheet on MEH HD drive with full database protection, and datasheets with patient's identifiable data were kept locked in a filing cabinet in the offices of Prof Lightman. Patients were anonymized on the database by being given a study number to comply with the regulations on data protection.

2.2 Main outcome measures.

Key outcome measures such as irreversible vision loss < 6/12, i.e. 6/18- 6/36 and vision loss to 6/60 or worse, and causes of visual loss were recorded.

For technical reasons the 6/15 Snellen vision cut-off as recommended by Jabs et al[124] was not used because the charts used to evaluate visual acuity do not have the 6/15 line.

The cause of visual impairment was recorded for each eye separately.

For patients who developed more than one complication, I chose the complication that caused the initial irreversible visual impairment.

Bilateral visual impairment and blindness were defined by BCVA in the better-seeing eye. If a patient was blind in one eye and visually impaired in the other, he/she was considered to have bilateral visual impairment. Unilateral visual impairment and blindness were based on BCVA in the worse eye.

I identified patients who had cataract surgery but did not improve visual acuity. In this group I recorded time of onset or first presentation with cataract formation, time of cataract surgery, visual acuity at presentation, type of uveitis, visual acuity post operative at 1 month, 3 month, 6 months, 1 year, 2 years, 3, 4 and 5 years, and cause of visual loss.

Although the key element of surveillance for patients who undergo glaucoma surgery is IOP measurements, in the scope of this study I mainly focussed on the impact of surgery on visual acuity. Hence, IOP measurements post glaucoma surgery is not included.

Patient who developed ischemia were also identified as described earlier. I looked at the impact of different treatments including laser on their visual acuity with time.

In cases of bilateral disease, I report the results seen in all affected eyes, and the results seen in the better eye (e.g. the eye with the better visual acuity) [672]

To enable data comparison, I used the SUN recommendations for reporting data from clinical series [124]. Visual acuity results are reported as rates falling below 6/12(i.e 6/18-6/36), or 6/60 or worse[672].

To allow statistical analysis, Snellen visual acuity was converted to Log MAR using the formula: log MAR = - $\log_{10}$(visual acuity fraction).

Referring to a study by Holladay[270], count fingers at a given distance can be converted to a Snellen equivalent by assuming that the fingers are approximately the size of the elements of a 200 feet letter. Therefore, a person who can count fingers at 20 feet would have approximately 20/200 vision. A person able to count fingers at 2 feet would have 2/200 vision or the equivalent of 20/2000. Hand motion at a given distance is ten times worse than count fingers, i.e., a person who can detect hand motion at 20 feet has approximately 20/2000 Snellen visual acuity equivalent. A person who has hand motion at 2 feet would have an equivalent Snellen of 20/20,000.

In this study, patients had count fingers or hand movements tested at 1m distance. Visual fields were not analysed.

Eyes that have halved the minimum angle resolution are reported to have improved visual acuity; eyes that have doubled the minimum angle resolution are reported to have worsened visual acuity[124].

When looking at associated systemic conditions, we deliberately did not consider HLA-B27 antigen to avoid a bias as all patients presenting with any type of uveitis were not systematically screened for this.

2.3 Statistical analysis.

The IBM SPSS statistics software version 19 was used for statistical analysis. Statistical analysis included descriptive statistics of the types of uveitis, age at onset and at final follow up visit, complications, and level of visual loss. Multiple comparisons were calculated using the one-way ANOVA. The Pearson correlation was used to assess correlation between variables when comparing two groups. The Pearson correlation was significant at the 0.01 level. Results are presented with 95% confidence interval (CIs). Nominal p values were calculated using t-test and the level of significance for changes of visual acuity or other parameters was significant at 0.05. P value was highly significant when < 0.01.

The incidence rate of visual loss is reported as the number of eyes with visual loss divided by the total follow-up of eyes exposed. It is expressed per unit time (e.g., 0.50/Eye-Year).

Chapter 3: Demographics of uveitis and visual loss.

3.1 Introduction

Uveitis may occur at any age, but most commonly afflicts people between 20 and 59 years of age [134, 228, 275, 278]. Numerous studies have been performed worldwide to determine the distribution, clinical patterns and aetiology of uveitis as this knowledge may assist in improving the management of the disease[134]. The aetiologies and disease types of endogenous uveitis differ depending on many factors including ethnicity, geographical region, and age. Statistics from Japan and European or American countries show distinct characteristic distribution patterns of uveitic diseases [280, 673-675].

Uveitis is not a single disease but includes ocular involvement related to various systemic disorders as well as primary ocular conditions. The association of uveitis with systemic disease is well known [228]. In 20-30% of cases a systemic disease is associated with the intraocular inflammation [228, 673].

The main complications leading to visual loss are CMO, cataract, glaucoma, retinal detachment, vitreous opacities, epiretinal membranes and other chronic macular damage. The extent of visual loss is influenced primarily by the location, severity, and duration of CMO [676]. Previous studies documented various prognosticators of poor visual outcome in uveitic macular oedema, including prolonged duration of the uveitis and of CMO itself, a large foveal avascular zone, the presence of an incomplete vitreous detachment, and an increased macular thickness on OCT [325, 341]. The advanced age of patients was reported to be an independent factor for early development and poor outcome of CMO in uveitis [341, 677].

In this chapter I describe the types of uveitis encountered, the proportion of eyes which developed visual loss and the causes of visual loss in different types of uveitis. Visual loss at presentation and their causes in different follow-up groups is another question I tried to find an answer to. I also looked at the impact of systemic diseases on visual acuity in different uveitis entities.

3.2 Results

3.2.1 *Demographics.*

A total number of 1594 patients (2543 eyes) fulfilled our inclusion criteria. Of these, 737 were males and 857 females.

The mean age at first presentation or onset was 41.8 years (range 3-92).

The mean follow up was 5.7 years (range 1/2 - 45 years).

Table 3.1 Patients by age group at presentation.

Age groups	3-16	17-24	25-34	35-44	45-53	54-63	64-95	Tot.
N.patients	126	122	299	369	291	224	163	1594
%	8	8	19	23	18	14	10	100

The majority of patients (74%) were in the age group 25-63 years, 8% were aged between 3 and 16 years. Ten percent of patients were aged > 64 years at first presentation.

Table 3.2 Mean age at onset/first presentation of different types of uveitis

Types of uveitis	Mean age (SD)
AU	42.4 (± 17.3)
IU	39.6 (± 16.8)
Pu	41.5 (± 15.3)
Panu	42.7 (± 18.4)

The difference in age at first presentation of patients with different uveitis types was statistically significant (p = 0.043), patients with IU were younger than those with AU or Pan and Pu.

Table 3.3 Types of uveitis, laterality and comparison between sexes.

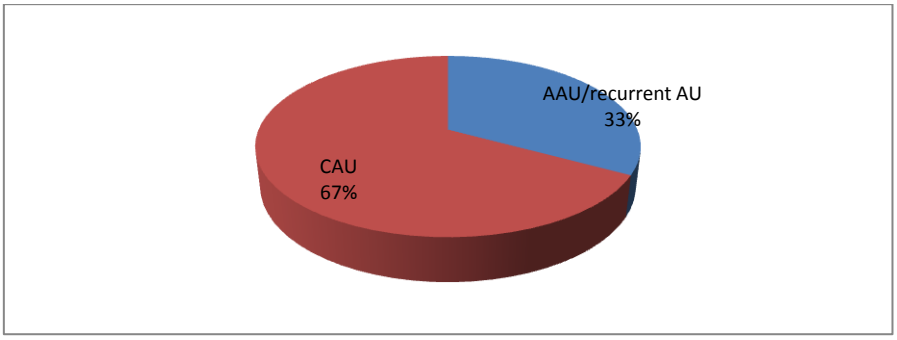
Uv. types↓	Unilat (%)	Bilat.(%)	Male (%)	Female(%)	Tot.eyes(%)
AU	332 (51.3)	718 (45.2)	323 (44)	366 (43)	1050 (41.3)
IU	104 (16)	562 (35.4)	165 (22.5)	220 (25.9)	666 (26.2)
Pu	139 (21.5)	150 (9.4)	150 (20.5)	139 (16.3)	439 (17.2)
Panu	72 (11.2)	158 (10)	95 (13)	126 (14.8)	388 (15.3)
Tot.(%)	647 (100)	1588 (100)	733 (100)	851 (100)	2543 (100)

AU accounted for 41% of all types of uveitis, followed by IU diagnosed in 26% of eyes. A further third of eyes developed PU in 17% and Panu in 15%.

Amongst uveitis that presented as unilateral cases, half were AU, followed by PU, accounting for 22%. When looking at cases with bilateral involvement, AU accountd for 45%, followed by IU with 35.4%.

Both genders developed different types of uveitis in the same proportions.

Figure 3.1 Types of anterior uveitis by chronicity.



Sixty seven percent of all anterior uveitis were chronic, while AAU and recurrent accounted for 33%.

Table 3.4 Patients by uveitis types and associated systemic diseases.

Patients/uv.type→	AU:689	IU:385	PU: 293	Panu: 227	Tot.:1594
	---	---	---	---	---
Assoc.disease↓	n. (%)	n. (%)	n. (%)	n. (%)	n. (%)
Sarcoidosis	81(11.8)	40(10.4)	9(3.0)	34 (14.9.)	164(10.3)
Behçet's disease.	7(1.0)	9(2.3)	25(8.5)	18 (8)	59(3.7)
JIA	15(2.2)	4(1.0)	-	6 (2.6)	25(1.6)
AS	39(5.6)	1(0.3)	1(0.3)	2 (0.9)	43(2.7)
VKH	-	1(0.3)	-	10 (4.4)	11(0.7)
MS	-	11(2.8)	-	2 (0.9)	13(0.8)
Lupus	1(0.1)	5(1.3)	5(1.7)	-	11(0.7)
Toxo.	-	-	68(23.2)	-	68 (4.2)
Miscellanous	11(1.6)	9(2.3)	26(9)	15 (6.6)	61(3.8)
Total(%)	154(22.3)	80(20.7)	134 (45.7)	87 (38.3)	455(28.5)

At least one associated systemic disease was found in 455 patients, representing 29% of our population.

A systemic condition was associated with anterior uveitis in 22%, with intermediate uveitis in 21%. In 46% and 39%of patients who developed posterior uveitis and panuveitis respectively, a systemic disease was present.

Sarcoidosis was the most common systemic disease associated with all types of uveitis, accounting for 10%. Of these, half developed anterior uveitis.

Behçet's disease was found in 4% of patients. Of these, 42.3% developed PU and 30.5% panuveitis.

Toxoplasmosis was the commonest systemic disease associated with posterior uveitis where it accounted for 23.5%.

Uveitis was associated with MS in 1%, the majority (87%) of whom had intermediate uveitis. Ninety one percent of all patients with ankylosing spondylitis associated uveitis developed anterior uveitis. Lupus was found in 11 patients, half of these patients developed retinal vasculitis.

Table 3.5 Miscellaneous systemic diseases.

Disease	N.patients
Crohn's disease	3
Ulcerative colitis	8
Polymyalgia rheumatic	7
Interstitial nephritis	3
Reiter's disease	4
Rheumatoid arthritis	10
TB	18
Waldenstrom macroglobulinemia	1
Wegener's granulomatosis	3
Intraocular lymphoma	2

TB was diagnosed or presumed in 18 patients. Rheumatoid arthritis was associated with uveitis in 10 patients, ulcerative colitis and polymyalgia rheumatica in 8 and 7 patients respectively. Three patients developed uveitis associated with interstitial nephritis. One patient had Waldenstrom macroglobulinemia associated with uveitis. Three patients had Wegener's granulomatosis and 2 other patients had the diagnosis of intraocular lymphoma.

Table 3.6 Types of uveitis associated with diabetes.

N.patients	*DM	%
AU (689)	28	4.1
IU (385)	19	5
PU(293)	11	3.8
Panu(227)	9	4.0
Total(1594)	67	4.2

**DM= Diabetes mellitus*

Overall, diabetes was associated with uveitis in 4.2%. It was found to be associated with different types of uveitis in the same proportions.

Table 3.7 Eyes with BCVA 6/18-6/36 and BCVA ≤ 6/60 in different uveitis types at presentation.

BCVA	AU(n=1050) n.(%)	IU(n=666) n.(%)	PU(n=440) n. (%)	Panu(n=387) n. (%)
6/18- 6/36	118 (11.2)	136 (20.4)	85 (19.3)	88 (22.9)
≤ 6/60	80 (7.6)	52 (7.8)	89 (20.2)	83 (21.6)

Eleven percent of eyes with AU presented with BCVA 6/18- 6/36, and 8% had BCVA 6/60 or worse similarly with eyes with IU. In the latter 20% presented with BCVA 6/18-6/36. Eyes with posterior uveitis and panuveitis presented with severe visual loss in 20 and 22% respectively.

Table 3.8 Laterality of visual loss by uveitis types at presentation.

Laterality Uveitis types	Bilat.≤6/60 n.patients (%)	Bilat.6/18-6/36 n.patients (%)	Unilat. 6/18-6/36 n.patients (%)	Unilat ≤6/60 n.patients (%)	6/18-6/36 and ≤6/60. n.patients (%)
AU (n=689)	15 (2.2)	12 (1.7)	63 (16.4)	40 (5.8)	10 (1.5)
IU (n=385)	18 (4.7)	10 (2.6)	69 (17.9)	16 (4.1)	9 (2.3)
PU (293)	10 (3.4)	7 (2.4)	60 (20.5)	55 (18.8)	15 (5.1)
Panu (227)	16 (7.1)	13 (5.7)	47 (20.7)	40 (17.6)	13 (5.7)
Total (n=1594)	59 (3.7)	42 (2.6)	239 (15)	151 (9.5)	47 (2.9)

From the whole population, 257(16.1%) developed severe visual loss or blindness in at least one eye. Of these, 4% presented with bilateral severe visual loss or blindness. The proportion of patients with panuveitis was higher than those with other uveitis types in the latter group. Ten percent of patients had unilateral severe vision loss, when a further 3% had severe visual loss in one eye and BCVA 6/18-6/36 in the other. Fifteen percent of patients had unilateral vision loss to 6/18-6/36 and 3% had this level of visual loss bilaterally.

Table 3.9 Eyes with BCVA 6/18-6/36 by uveitis types in different follow-up groups (Time from presentation to data collection in years).

Follow up→	1/2 - 1 yr		>1yr- 3 yrs		>3yrs – 5 yrs		>5 yrs- 10 yrs		⍰ 10 years	
n.eyes uveitis type↓	n.	v.loss(%)	n.	v.loss (%)	n.	v.loss (%)	n.	v.loss (%)	n.	v.loss (%)
AU(n.=1050)	381	31 (8.1)	154	16 (10.4)	120	12 (10)	219	25 (11.4)	176	12(6.8)
IU(n.=666)	214	19 (8.9)	100	15 (15)	93	15 (16.1)	139	14 (10.3)	120	31(25.8)
Pu(n.=440)	143	14 (9.8)	66	9 (13.6)	52	7 (13.3)	94	14 (14.9)	85	12 (14.1)
Panu(n.=387)	119	22 (18.5)	66	8 (12.1)	33	11 (33.3)	89	19 (21.3)	80	20 (25)

The proportion of eyes with AU which developed BCVA 6/18-6/36 did not change much in different follow-up groups. Only 7% of eyes with AU followed up for more than 10 years were visually impaired.

Twenty six percent of eyes with IU followed up for more than 10 years were visually impaired, 3 times fold the proportion of eyes followed up for 1 year or less.

Visual impairment in eyes with posterior uveitis did not increase with time, while the number of eyes with panuveitis with BCVA 6/18-6/36 reached a peak in the group of eyes followed up for 3-5 years before a sharp decline and plateauing.

The incidence rate of visual loss to < 6/12 was 0.02/EY for AU, 0.04/EY and 0.08/EY for IU and Pan /Pu respectively.

Table 3.10 Eyes with BCVA ≤ 6/60 by uveitis types in different follow-up groups.(Time from presentation to data collection in years)

Follow up→	1/2 - 1 yr		>1yr- 3 yrs		>3yrs - 5 yrs		>5yrs - 10 yrs		>10years	
Uveitis types↓	n.	v.loss(%)	n.	v.loss(%)	n.	v.loss(%)	n.	v.loss(%)	n.	v.loss (%)
AU(n=1050)	381	12 (3.1)	154	8 (5.2)	120	10(0.8)	219	14(6.4)	176	24(13.6)
IU(n=666)	214	11(5.1)	100	5(5)	93	8(8.6)	139	16(11.5)	120	16(13.3)
Pu (n=440)	143	25(17.5)	66	12 (18.2)	52	14(26.9)	94	34(36.2)	85	20 (23.5)
Panu(n=387)	119	18 (15.1)	66	9 (13.6)	33	6 (18.2)	89	17 (19.1)	80	24 (30)

There is a constant increase in the proportion of eyes with severe visual loss with time.

The incidence rate of visual loss of 6/60 or worse was 0.01/EY for AU, 0.02/EY for IU and 0.13/EY for Pan/Pu.

Table 3.11 Causes of BCVA 6/18-6/36 in different follow- up groups.(Time from presentation to data collection in years)

FU groups→ Complications↓	1/2 -1year n.eyes=88(%)	>1 - 3 years n.eyes= 49(%)	>3 - 5 years n.eyes= 42(%)	>5 -10 years n.eyes= 75(%)	> 10 years n.eyes=75(%)	Tot. (%) n.eyes=329
CMO	54(61.3)	13(26.5)	15((36)	6(8)	6(8)	94(28.6)
Chr.mac.damage	11(12.5)	21(43)	13((31)	44(58.8)	46(61.4)	135(41)
Glaucoma	8(9)	6(12.2)	9(21.4)	19(25.3)	8(10.7)	50(15)
Hypotony	1(1)	-	1(2.3)	1(1.3)	-	3(0.9)
Macular ischemia	2(2.2)	1(2.0)	-	1(1.3)	4(5.3)	8(2.4)
Op. Atrophy	-	-	-	1(1.3)	4(5.3)	5(2)
Retinal detachment	-	3(6.1)	1(2.3)	-	4(5.3)	8(2.4)
Cataract	6(7)	4(8.2)	3(7)	3(4)	1(1.3)	17(5)
Miscellaneous	6(7)	1(2.0)	-	-	2(2.7)	9 (2.7)
Total (%)	88(100)	49(100)	42(100)	75(100)	75(100)	329(100)

CMO was the cause of 2/3 of vision loss to 6/18-6/36 in eyes followed up to one year. The main cause of visual loss to 6/18-6/36 in eyes followed up for 10 years or more was chronic macular damage. At ten years follow-up, the incidence of glaucoma had tripled.

Table 3.12 Causes of BCVA ≤6/60 in different follow up groups.(Time from presentation to data collection in years)

Follow up groups→ Complications↓	1/2 -1 year n. eyes=68(%)	>1-3 years n. eyes=41(%)	>3-5 years n.eyes=40(%)	>5- 10 years n.eyes=82(%)	>10 years n.eyes=94(%)	Total (%) n.eyes=324
CMO	19(28.8)	4(10)	6(15)	3(3.7)	1(1.1)	33(10.5)
Chr.mac damage	21(31.8)	12(30)	14(35)	25(30.9)	46(52.9)	118(37.6)
Glaucoma	8(12.1)	10(25)	8(20)	19(23.5)	14(16)	59(18.8)
Hypotony	-	2(5)	-	3(3.7)	4(4.6)	9(2.9)
Mac. Ischemia	3(4.5)	6(15)	2(5)	2(2.5)	6(6.9)	19(6)
Op. Atrophy	2(3)	2(5)	2(5)	9(11.1)	2(2.3)	17(5.4)
Retinal detachment	8(12.1)	3(7.5)	3(7.5)	2(2.5)	3(3.4)	19(6)
Phthisis	-	-	3(7.5)	12(14.8)	8(9.2)	23(7.3)
Cataract	3(4.5)	1(2.5)	1(2.5)	3(3.7)	3(3.4)	11(3.5)
Miscellaneous	2(3)	-	1(2.5)	3(4)	-	6(1.9)
Total	66(100)	40(100)	40(100)	81(100)	87(100)	314(100)

The main cause of severe visual loss was macular damage throughout. Ninety one percent of phthisis developed from 5 years. Seventy four percent of RD developed within the first five years.

The one-way ANOVA shows a stastistically significant correlation between time and glaucoma (p= 0.034, 0.18-9.1 95% CI), time and phthisis (p= 0.002, 1.9-15.6 95%CI) and time-chronic macular damage (p< 0.001, 2.8-10.3 95% CI). The incidence of hypotony, macular ischemia and optic atrophy was not affected by time.

There was no correlation between age at onset of the intraocular inflammation and complications developed (p= 0.68).

Table 3.13 Complications in different uveitis types.

Uveitis types→ Complications↓	AU n.eyes=164(%)	IU n.eyes=144(%)	Pu n.eyes=153(%)	Panu n.eyes=192(%)	Total n.eyes=653(%)
CMO	26 (16)	55 (38.2)	12(7.8)	35(18.2)	128(19.6))
Chr. mac damage	40 (24.4)	53 (36.8)	90(58.8)	89(46.3)	272(41.6)
Glaucoma	52 (31.7)	15 (10.4)	12 (7.8)	23(12)	102(15.6)
Op.atrophy	4 (2.4)	2 (1.4)	6 (3.9)	6(3.1)	18 (2.7)
Mac.ischemia	-	-	27 (17.6)	1(0.5)	28(4.3)
Phthisis	10 (6.0)	-	-	13(6.7)	23(3.5)
Cataract	14 (8.5)	9 (6.3)	-	5(2.6)	28(4.3)
Retinal detachment	4 (2.4)	9 (6.3)	3 (1.9)	11(5.7)	27(4.1)
Hypotony	6 (3.7)	-	-	6(3.1)	12(1.8)
Miscellaneous	8 (5)	1 (0.7)	3(1.9)	3(1.5)	15(2.3)
Total (%)	164 (100)	144(100)	153 (100)	192(100)	653(100)

Glaucoma developed in 32% of eyes with AU, and CMO in 38% of eyes with IU. Chronic macular damage was the major cause of visual loss in posterior uveitis and panuveitis, accounting for 59% and 46% respectively. Phthisis bulbi occurred mainly in panuveitis and anterior uveitis. Macular ischemia developed essentially only in posterior uveitis. Of the total number of eyes which developed retinal detachment, 52% had panuveitis. Hypotony developed in 4% of eyes with AU and 3% of eyes with panuveitis. Miscellaneous complications developed in 15 eyes. These included corneal decompensation and opacities in 6 eyes, vitreous haemorrhage in 1 eye, macular dysfunction evidenced by electrophysiological tests, and cyclitic membranes.

Table 3.14 Eyes with BCVA 6/18-6/36 at presentation in patients with a systemic disease associated.

Uveitis types→	AU	IU	Pu	Panu	Tot.
Assoc. disease↓	n.eyes=28(%)	n.eyes=12(%)	n.eyes=39(%)	n.eyes=34(%)	n.eyes=88(%)
Sarcoidosis	12(42.9)	2(16.6)	2(5.1)	11(32.3)	27(23.9)
Behçet's disease	-	2(16.6)	6 (15.4)	11(32.3)	19(16.8)
JIA	6(21.4)	-	-		6(5.3)
AS	3(10.7)	-	-	-	3(2.6)
VKH	-	-	-	5(14.7)	5(4.4)
MS	1(3.6)	3(25)	-	-	4(3.5)
SLE	-	-	2(5.1)		1(1.8)
Toxo.	-	-	17(43.6)		17(15)
Diabetes	3(10.7)	3(25)	8(20.5)	6(17.6)	20(17.7)
Miscellaneous	3(10.7)	2(16.6)	4(10.2)	1(2.9)	6(5.3)
Tot. (%)	28(100)	12(100)	39(100)	34(100)	113(100)

Sarcoidosis was the main systemic disease found in patients who presented with vision loss 6/18-6/36, accounting for 24%, followed by BD and diabetes with 17% each. Toxoplasmosis accountd for 15%

When looking at systemic diseases in different uveitis types which presented with vision loss, sarcoidosis was predominant in AU with 43%, and in 32% of eyes with panuveitis. In 17% of eyes with IU and visual loss of 6/18 to 6/36 at presentation, sarcoidosis was associated.

Table 3.15 Eyes with BCVA ≤ 6/60 at presentation in patients with a systemic disease associated.

Uveitis types→	AU	IU	Pu	Panu	Total
Systemic disease↓	n.eyes=17(%)	n.eyes=12(%)	n.eyes=39(%)	n.eyes=26(%)	n.eyes=94(%)
Sarcoidosis	4 (23.5)	7(58.4)	1(2.6)	8(30.8)	20(21.2)
Behçet's disease	-	-	16(41)	8(30.8)	24(25.5)
JIA	7(41.2)	1(8.3)	-	5(19.2)	13(13.8)
AS	1(5.9)	-	1(2.6)		2(2.1)
VKH	-	-	-	2(7.7)	2(2.1)
MS	-	1(8.3)	-	-	1(1.0)
SLE	-	-	3(7.7)	-	3(3.2)
Toxo.	-	-	13(33.3)	-	13(13.8)
Diabetes	4(23.5)	3(25)	1(2.6)	2(7.7)	10(10.6)
Miscellaneous	1(5.9)	-	4(10.2)	1(3.8)	6(6.4)
Total	17(100)	12(100)	39(100)	26(100)	94(100)

BD was the main systemic disease found in patients who presented with severe visual loss. It accounted for 25%, followed by sarcoidosis with 21%. Toxoplasmosis and JIA were present in 14% of eyes with visual loss of 6/60 or worse at presentation. Miscellaneous diseases including ulcerative colitis, polymyalgia rheumatic, Crohn's disease, rheumatoid arthritis, Gout and TB were found in 6% of cases with severe visual loss.

Thirteen percent (344) of affected eyes improved visual acuity over follow up period, while in 9% (228 eyes), visual acuity worsened.

The incidence rates of visual loss to 6/18-6/36 and 6/60 or worse in patients with sarcoidosis were 0.024/EY and 0.020/EY respectively.

Incidence rates of visual loss to 6/18 - 6/36 and 6/60 or worse were respectively 0.03/EY and 0.05/EY in patients with BD.

For patients with JIA related uveitis, incidence rates of vision loss were 0.01/EY for 6/18-6/36, and 0.04/EY for vision of 6/60 or worse.

Table 3.16 Patients with chronic complications and systemic disease.

Complications→ Systemic disease↓	CMO n.patients=19	Glaucoma n.patients=34	Mac.ischemia n.patients=7	Op. atrophy n.patients=11	Hypotony n.patients=7
AS	-	2(6)	-	-	1(14.3)
Behçet's disease	3(16)	4(11.8)	3(43)	4(36.4)	-
Diabetes	4(21)	6(17.6)	-	1(9)	1(14.3)
JIA	2(10.5)	6(17.6)	-	-	2(28.6)
MS	-	-	-	2(18.2)	-
Sarcoidosis	5(26.3)	14(41)	-	4(36.4)	3(42.8)
SLE	-	1(3)	*3(43)*	-	-
Toxo	1(5.2)	-	-	-	-
Miscellaneous	4(21)	1(3)	1(14).	-	-
Total	19(100)	34(100)	7(100)	11(100)	7(100)

Nineteen patients with chronic CMO had an underlying systemic disease. Of these, 26% had sarcoidosis, and 21% had diabetes. BD and JIA were present in 16% and 10.5% respectively.

Thirty four patients had glaucoma associated with systemic disease. Sarcoidosis was the commonest disease, accounting for 41%. JIA and diabetes accounted equally for 18% and BD accounted for 12%.

The two main systemic conditions associated with macular ischemia were BD and SLE.

Eleven patients had a systemic disease associated with optic atrophy. BD and sarcoidosis accounted for 36.4% each, and MS was found in 18.2%.

The commonest disease associated with hypotony was sarcoidosis, accounting for 43%, followed by JIA with 29%.

3.2.2 *Sarcoidosis-related uveitis.*

Out of the whole population of uveitis patients, 161(11%) had sarcoidosis associated. Of these, 103 females and 58 males (sex ratio 2:1).

The mean age at first assessment was 45.06 years (STD ± 14.7), range 5-91. The difference of age at first presentation for males was 42.4 years (SD 14.8) and 46.5 years (SD 14.5) for females. The difference between genders was not statistically significant (p= 0.08). The mean follow up was 6.3 years, range 0.6- 45 years.

In 83.8% of patients, the inflammation was bilateral.

The types of uveitis developed were as followed: 144 AU (48%), 82 IU (27.3%), 74 Pan/pu (24.6%).

Table 3.17 Eyes with BCVA 6/18-6/36 and ≤ 6/60 at presentation in sarcoidosis associated uveitis**.**

Types of uveitis	6/18- 6/36 n.eyes (%)	≤ 6/60 n.eyes (%)
AU n.eyes= 144	16 (11.1)	8 (5.6)
IU n.eyes=82	13 (15.9)	4 (4.9)
PU n.eyes=15	-	1 (6.6)
Pan n.eyes= 60	13 (21.7)	8 (13.3)

Twenty two percent of eyes with panuveitis associated with sarcoidosis presented with vision loss to 6/18-6/36, while 13% had severe visual loss at first visit. Sixteen percent of eyes with IU associated with sarcoidosis had 6/18-6/36 at presentation, 5% had visual loss to 6/60 or worse, the same proportion for eyes with AU.

Table 3.18 Causes of BCVA 6/18-6/36 in sarcoidosis-related uveitis.

Uveitis types→ Complications↓	AU	(%)	IU	(%)	Panu	(%)	Tot.	(%)
CMO	2	(11.7)	1	(16.7)	3	(21.4)	6	(16.2)
Chr.m. damage	4	(23.5)	2	(33.3)	7	(50)	13	(35.1)
Glaucoma.	10	(58.8)	1	(16.7)	1	(7.1)	12	(32.4)
Hypotony	-	-	-	-	1	(7.1)	1	(2.7)
Opt. atrophy.	-	-	2	(33.3)			2	(5.4)
Cataract	1	(6)	-		2	(14.3)	3	(8.1)
Total	17	(100)	6	(100)	14	(100)	37	(100)

Chronic macular damage was the major cause leading to visual loss to 6/18- 6/36 in eyes with sarcoidosis related uveitis, accounting for 35.1%, followed by glaucoma and CMO found in 32.4% and 16.2% respectively.

When looking at different uveitis types separately, glaucoma accounted for 58.8% of all causes of BCVA 6/18 - 6/36 in eyes with anterior uveitis, while it caused visual loss in 16.7% of eyes with intermediate uveitis and 7% of panuveitis. No eyes with posterior uveitis associated with sarcoidosis developed vision loss of 6/18-6/36.

Table 3.19 Causes of severe visual loss in sarcoidosis related uveitis.

Uveitis types→ Complications↓	AU (%)	IU (%)	Pu (%)	Panu (%)	Total (%)
CMO	-	1 (16.7)	1 (25)	1 (12.5)	3 (12.5)
Chr. mac .damage	-	3 (50)	2 (50)	1 (12.5)	6 (25)
Glaucoma	5 (83.3)	-	-	3 (37.5)	8 (33.3)
Hypotony	-	1 (16.7)	-	-	1 (4.1)
Op.atrophy	-	-	1 (25)	-	1 (4.1)
Retinal detachment	-	-	-	1 (12.5)	1 (4.1)
Mac. Ischemia	-	1 (16.7)	-	-	1 (4.1)
Phthisis	-	-		1 (12.5)	1 (4.1)
Cataract	1 (16.7)		-	1 (12.5)	2 (8.3)
Total	6 (100)	6 (100)	4 (100)	8(100)	24 (100)

Glaucoma was the main complication leading to severe vision loss in sarcoidosis related uveitis, accounting for 33.3%. In eyes that developed AU, it was the leading cause with 83%. Chronic macular damage caused severe visual loss in 50% of eyes with IU.

Incidence rates for visual loss in sarcoidosis associated uveitis were 0.03/EY and 0.02/EY for visual impairment and severe visual loss or blindness respectively.

3.2.3 *Behçet's disease.*

Sixty three patients (4.3%) of the uveitis population had the diagnosis of Behçet's disease. Of these, 37 were males and 26 females.

The mean age at first presentation was 38.0 years (range17- 58). There was no difference between genders (p=0.60).

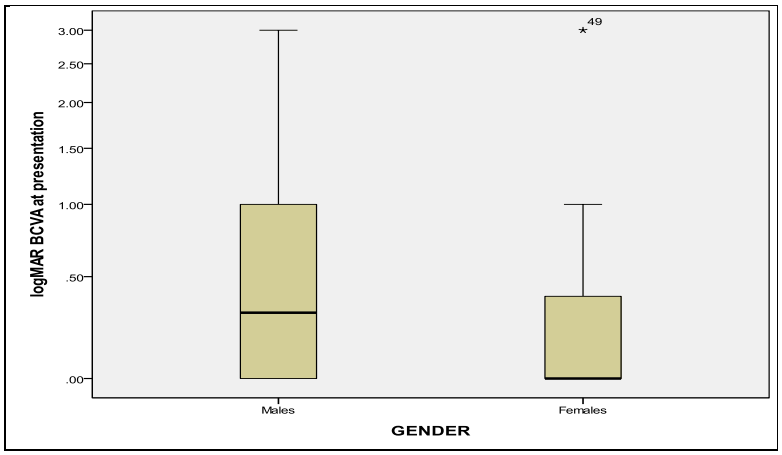
The mean follow-up was 7.3 years (range1/2-38 years).

Table 3.20 Types of uveitis in Behçet's disease.

Uveitis types	N. eyes	(%)
AU	10	(9.5)
IU	13	(12.4)
Pu	46	(43.8)
Panu	36	(34.3)
Total	105	(100)

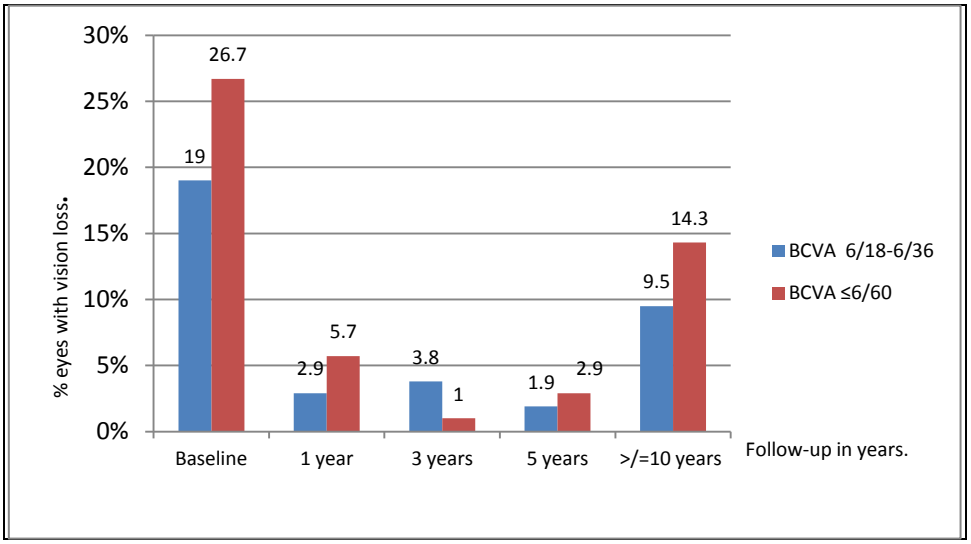
A total of 105 eyes were affected. Of these, 44% developed posterior uveitis and 34% panuveitis. Anterior and intermediate uveitis accounted respectively for 9.5% and 12.4% of eyes.

Figure 3.2 Visual acuity at presentation in males and females patients with BD.



The mean log MAR BCVA at presentation was 0.67(SD 0.87) for males, and 0.29 (SD 0.64) for females. The difference was statistically significant (p= 0.049). Overall, 45% of affected eyes presented with vision loss. Of these, 19% had BCVA 6/18-6/36 and 26% severe visual loss.

Figure 3.3 Visual loss at baseline and in different follow-up groups in BD.



At presentation, 19% of affected eyes had BCVA 6/18-6/36, 27% of eyes had severe visual loss or blindness. At 1 year follow-up, the number of eyes with vision loss was dramatically reduced to 3% for BCVA 6/18- 6/36 and 6% for BCVA≤ 6/60. Then these proportions increased gradually to reach 9.5% and 14.3% for visual impairment and severe vision loss respectively. At presentation, 4 patients (6.3%) were legally blind. This proportion increased to 7.9% (5 patients) over time. Fifteen eyes improved visual acuity, while 7 eyes had visual acuity worsened.

Table 3.21 Causes of visual loss 6/18-6/36 in BD associated uveitis.

Complications	N.eyes	%
Cataract	3	15.8
CMO	2	10.5
Glaucoma	1	5.3
Mac. Ischemia	3	15.8
Chronic m. damage	10	52.6
Total	19	100

Chronic macular damage was the main cause of BCVA 6/18-6/36 accounting for 52.6%, followed by macular ischemia (15.8%). CMO caused BCVA 6/18-6/36 in 2 eyes (10.5%).

Table 3.22 Causes of BCVA ≤ 6/60 in eyes with BD associated uveitis.

Complications	N.eyes	%
Cataract	1	4.2
CMO	2	8.3
Glaucoma	5	20.8
Mac ischemia	4	16.7
Op. Atrophy	9	37.5
Chronic m damage	1	4.2
Phthisis	2	8.3
Total	24	100

One third (37.5%) of eyes with BCVA≤ 6/60 had optic atrophy. Glaucoma was the second cause of severe visual loss, accounting for 21%, followed by macular ischemia with 17%. Thirteen eyes (12.3%) had improved visual acuity, and 10 eyes (9.5%) had worsened visual acuity over follow-up time.

3.2.4 ***JIA- related uveitis.***

Twenty five patients (48 eyes) had JIA related uveitis. Ten were males, 15 females (ratio 1.5 in favour of females).

The mean age at diagnosis was 12.1 years (range 3-49 years). The mean follow-up was 14.5 years (range 0.6-41 years).

Table 3.23 Types of uveitis developed in JIA.

Uveitis types	N.	%
AU	29	60.4
IU	7	14.6
Pan	12	25
Total	48	100

Two-third of eyes developed AU. Panuveitis accounted for 25%, and a further 15% of eyes developed IU.

At presentation 10 eyes (20.8%) had BCVA 6/18-6/36, 15 eyes (31.3%) had BCVA ≤ 6/60. The incidence rate for visual loss to 6/18-6/36= 0.02/EY, incidence rate for BCVA≥ 6/60 = 0.04/EY.

Glaucoma accounted for 43% of causes of severe visual loss, 3 eyes (21.4%) developed chronic CMO. Two eyes (14.3%) were phthisical, 2 (14.3%) retinal detachment and 1 eye (7%) had non operated cataract.

Incidence rates for cataract development and for glaucoma were 0.05 /EY and 0.03/EY respectively.Twenty-six eyes underwent cataract surgery. Of these, 20 (77%) were aphakic and 23% pseudophakic. Of the aphakic eyes, 45% had severe visual loss or blindness, 1 eye had BCVA 6/18-6/36. Of the pseudophakic eyes, 33.3% developed severe vision loss or blindness, 1 eye had BCVA 6/18-6/36.

Overall 8 eyes had improved visual acuity, 4 eyes had worsened visual acuity over follow-up.

3.2.5 *Uveitis in Multiple sclerosis.*

Thirteen patients (0.8% of the whole population) with MS were identified (24 eyes); 8 were females and 5 Males (ratio 1.6).

Twenty eyes (83.3%) developed intermediate uveitis, 4 eyes (16.6%) panuveitis.

In the whole group of patients who developed IU (385), 11 patients (2.9%) had MS.

The mean age at first presentation was 46 years (range 26-78); the mean follow-up was 4.7 years (range 0.6-12 years).

Nine patients (69.2%) had the diagnosis of MS before uveitis, 4 patients presented with uveitis first.

The mean age at diagnosis of MS was 44.4 years (limits 27-78years). The mean time interval between the diagnosis of MS and uveitis was 8.1 years (limits 1-15 years). For patients who developed uveitis first, time to diagnose MS varied from 6 months to one year.

Five eyes (20.8%) had BCVA 6/18-6/36 at first visit, one eye presented with severe visual loss.

With time, 4 eyes improved visual acuity to normal.

Causes of visual loss were as followed: 1 eye had chronic macular damage, 1 eye developed optic atrophy.

3.2.6 *Vogt Koyanagi Harada disease (VKH).*

Nineteen patients (37 eyes) with VKH were identified. Five were males and 14 females. The mean age at first presentation was 28 years ± 14.7 for males, 36 years ± 14.4 for females. The difference was not statistically significant.

Ninety-two percent of eyes had panuveitis, 2 eyes developed IU.

At presentation, 11 eyes (30%) were visually impaired. Seven eyes (19%) had BCVA 6/18-6/36, 4 eyes (11%) had severe visual loss.

With time, 4 eyes (33.4%) improved visual acuity.

The causes of irreversible visual loss were as followed: 5 eyes had BCVA 6/18-6/36 due to CMO in 4 eyes and chronic macular damage in 1 eye. Two eyes had BCVA ≤6/60 due to glaucoma.

Multivariate tests showed that visual acuity at presentation is a predictive factor for visual outcome ($p = 0.003$)

3.2.7 *Diabetes and uveitis.*

Fifty-six patients had diabetes associated with uveitis. The mean ages at presentation were 51.8 years ± 18.2 for males and 56 ± 10.2 for females. ($p= 0.057$)

Table 3.24 Types of uveitis in patients with diabetes.

Uveitis types	AU (n=(1050) n.eyes (%)	IU (n=666) n.eyes (%)	Pan (n=827) n. eyes (%)
	33 (3.1)	22 (3.3)	36 (4.3)

Three percent of eyes with AU and IU developed in patients with diabetes. Four percent of eyes with panuveitis had diabetes associated.

The incidence rate for vision loss to 6/18-6/36 was 0.034/EY.

Table 3.25 Causes of visual loss in eyes with diabetes associtiated uveitis.

Complications	BCVA 6/18-6/36 n. eyes (%)	BCVA ≤6/60 n.eyes (%)
CMO	5 (35.7)	-
Glaucoma	2 (14.4)	4 (30.8)
Hypotony	1 (7.1)	-
Macular ischemia	1 (7.1)	-
Chronic mac damage	5 (35.7)	7 (53.8)
Phthisis	-	2 (15.5)
Total	14 (100)	13 (100)

The main causes of BCVA 6/18-6/36 were CMO and chronic macular damage. In the group of eyes which developed severe visual loss or blindness, chronic macular damage was the leading cause with 53.8% followed by glaucoma accounting for 30.8%

3.2.8 Birdshot choroidopathy.

Twenty four patients (48 eyes) representing 1.5% of the whole population had the diagnosis of BSCR. Six patients were males, and 18 females (ratio 3:1).

The mean age at first presentation was 57.2 years (limits 41-74 years).

The mean follow up time was 5.9 years (limits 0.6-18 years).

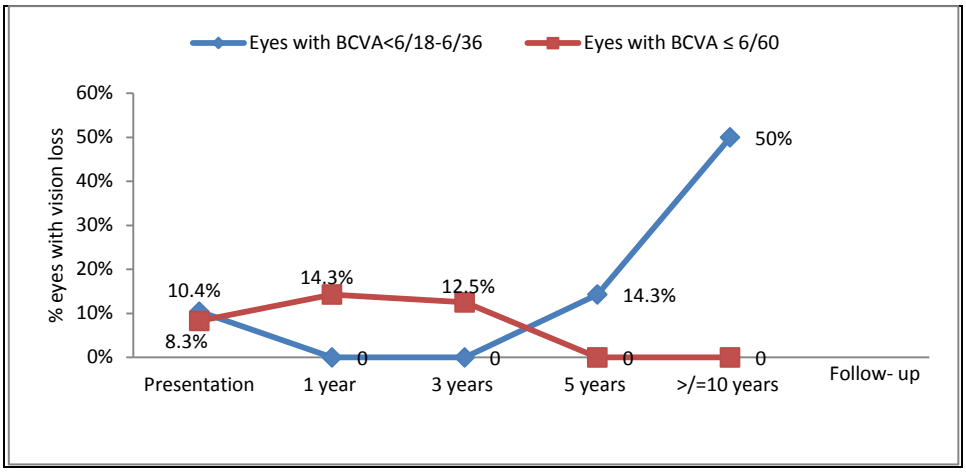
At presentation, 8 eyes (33.3%) had BCVA 6/18-6/36. Five eyes (20.8%) had vision loss of 6/60 or worse.

Visual loss between 6/18-6/36 was due to chronic CMO in 4 eyes (50%), chronic macular damage in 2 eyes (25%), and cataract in a further 25%.

Three eyes developed severe visual loss. In 2 eyes, vision loss was caused by CMO and by chronic macular damage in 1 eye.

Over the follow up period, 6 eyes had gained 3 Snellen lines or more, 3 eyes had lost 3 Snellen lines or more.

Figure 3.4 Visual loss with time in eyes with BSCR.



At presentation, 10.4% of affected eyes had BCVA 6/18-6/36. At one year follow-up and up to 3 years, there was no eye with BCVA 6/18-6/36. After 3 years, there was a sharp rise in the number of eyes with BCVA 6/18-6/36, reaching 14.3% at 5 years and 50% at 10 years or more. During the first year of follow up, the number of eyes with severe visual loss increased from 8.3% at presentation to 14.3% before starting a gradual improvement to reach 12.5% at 3 years. From 5 years follow-up, no eye had severe visual loss.

Incidence rates on follow-up for visual loss were 0.05/EY and 0.03/EY for BCVA 6/18-6/36 and BCVA 6/60 or worse respectively.

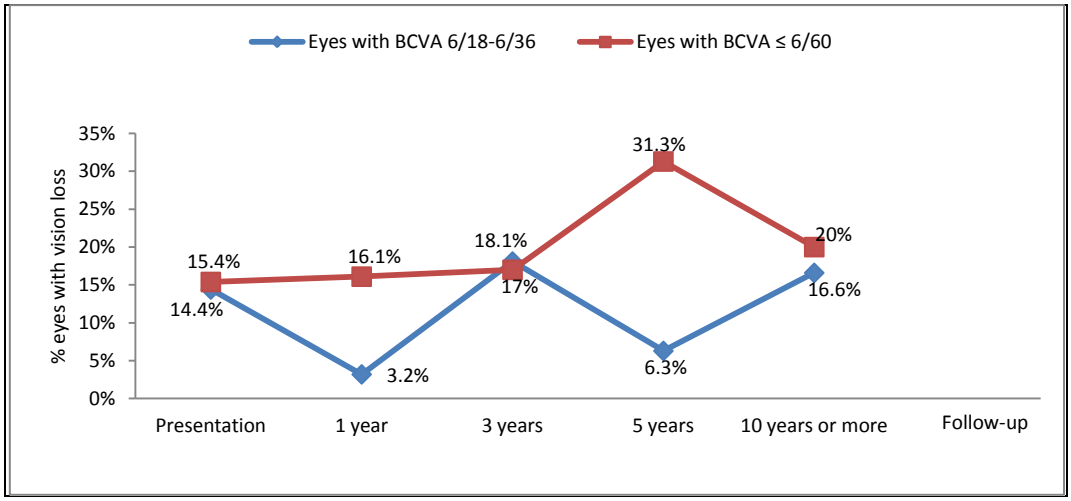
3.2.9 *Multifocal choroidopathy (MFC).*

Fifty two patients with MFC were identified (104 eyes), of whom 20 were males and 32 females. The mean age at first presentation was 46.8 years (range 11-79). The mean age for males was 43 years (SD± 17.2), and 49 years (SD± 15.8) for females. The difference was not statistically significant (p= 0.71).

The mean follow up time was 6.1 years (range 0.6- 20).

At presentation, 15 eyes (14.4%) had BCVA 6/18-6/36, 16 eyes (15.4%) had BCVA 6/60 or worse. Bilateral vision loss to 6/18-6/36 was present in 3.8% of patients and the same proportion presented with BCVA 6/60 or worse.

Figure 3.5 Visual loss over time in eyes with MFC.



Visual acuity of eyes which presented with BCVA 6/18-6/36 was erratic over time. During the first year, there was a dramatic improvement with a drop in the number of eyes visually impaired to only 3.2% at 1 year follw-up. After 1year, VA worsened. The number of eyes with vision loss reached 18% at 3 years follow-up before another drop to 6.3% at 5 years. The proportion of eyes with BCVA 6/18-6/36 at 10 years follow up or more was almost equal to the proportion at presentation. As for eyes with severe visual loss or blindness at presentation, there was an increase in number over time, with a peak at five years follow-up. Overall, there were more eyes with severe visual loss or blindness in the group of eyes followed-up for 10 years or more.

The incidence rates of visual loss to 6/18-6/36 and 6/60 or worse were 0.03/EY and 0.06/EY respectively.

Table 3.26 Causes of visual loss in eyes with MFC.

Vision loss →	6/18-6/36	≤ 6/60
Complications↓	n.eyes= 9 (%)	n.eyes= 20 (%)
Chronic mac. damage/scars	6 (67)	15 (75)
CNVM	2 (22)	4 (20)
CMO	1 (11)	1 (5)
Total (%)	9 (100)	20 (100)

With time, 9 eyes with MFC developed visual loss to 6/18-6/36. Chronic macular damage accounted for 67%. CNVM and CMO accounted for 22% and 11% respectively.

Twenty eyes developed severe visual loss due to chronic macular damage in 75%, CNVM and CMO in 20% and 5% respectively.

Thirteen eyes (12.5%) with MFC improved visual acuity with time, 16 eyes (15.4%) had visual acuity worsened.

Incidence rates on follow-up for BCVA 6/18-6/36 and ≤ 6/60 were 0.03/EY and 0.06/EY respectively.

3.2.10 *Punctate inner choroidopathy (PIC).*

Seventeen patients (28 eyes) with PIC were identified. Fifteen (88%) were females, 2 were males.

The mean age at first presentation was 33.8 years (range16-58).

The mean follow up was 4.7 years (range 0.6-11)

Eight eyes (29%) with PIC presented with BCVA 6/18-6/36, 4 eyes (14.3%) with BCVA ≤6/60.

Three eyes developed visual loss to 6/18-6/36. This was due to CNVM in 2 eyes and chronic macular damage in 1 eye. Five eyes developed severe visual loss due to CNVM.

Seven eyes (25%) had improved visual acuity, 10.7% had worsened visual acuity at the end of the follow-up period.

Incidence rates for vision loss were 0.02/EY for BCVA 6/18-6/36 and 0.07/EY for BCVA ≤ 6/60.

3.2.11 *Acute multifocal placoid pigment epitheliopathy (AMPPE).*

Eleven patients (22 eyes) had the diagnosis of AMPPE. Ten were males and one female. The mean age at first presentation was 27.1 years (range 16-42).

The mean follow up was 4.3 years (limits 0.6-12).

At presentation, 5 eyes (22.7%) had BCVA 6/18-6/36, 3 eyes (13.6%) had BCVA 6/60 or worse.

One eye developed visual loss to 6/18-6/36 due to chronic macular damage and 1 eye due to SRF.

Three eyes developed severe visual loss due to chronic macular damage in 1 eye, to CNVM in 1 eye, and SRF in 1 eye.

Visual acuity improved in 7 eyes (32%) and worsened in 3 eyes (14%). Multivariate analysis show a strong correlation between visual acuity at presentation and final visual acuity ($p = 0.04$). Age at diagnosis and follow-up do not influence visual outcome.

Incidence rates for vision loss were 0.04/EY and 0.06/EY for BCVA 6/18-6/36 and ≤ 6/60 respectively.

3.2.12 *Fuchs' heterochromia uveitis (FHU).*

In this series, 47 patients (50 eyes) had Fuchs' heterochromia iridocylitis. Of these, 20 were females and 27 males. The mean age at first presentation was 39.6 years (range 15-76).

The mean follow-up was 7 years (range 0.5-27).

Three patients (6.4%) had the condition bilaterally.

Five eyes (10%) presented with IOP> 21mmHg.

At presentation, 11 eyes (22%) had BCVA 6/18-6/36. Two eyes (4%) had BCVA 6/60 or worse.

With time, only 3 eyes developed visual loss between 6/18 and 6/36. No eyes had developed severe visual loss.

Twelve eyes (24%) underwent cataract surgery, and 4 eyes (7.7%) developed glaucoma. Of the eyes which developed glaucoma, 3 underwent glaucoma surgery.

In one eye vision loss was due to glaucoma, and chronic macular damage caused visual impairment in 2 eyes.

3.2.13 *Sympathetic ophthalmia.*

Twenty patients (20 eyes) developed SO. Thirteen of these were males, 7 females.The mean age of patient at first presentation was 41 years (range 4- 85).

Four eyes (20%) presented with AU, while in 16 eyes (80%), SO manifested as panuveitis.

At presentation, 5 eyes (25%) had BCVA 6/18-6/36, 3 eyes (15%) had BCVA 6/60 or worse.

At the end of the follow-up period, 47.4% of eyes maintained visual acuity of 6/12 or better. Four eyes developed vision loss to 6/18-6/36 while 5 eyes developed severe vision loss or blindness. Two eyes had improved visual acuity, 5 eyes had worsed visual acuity, while in 13 eyes visual acuity remained unchanged over time.

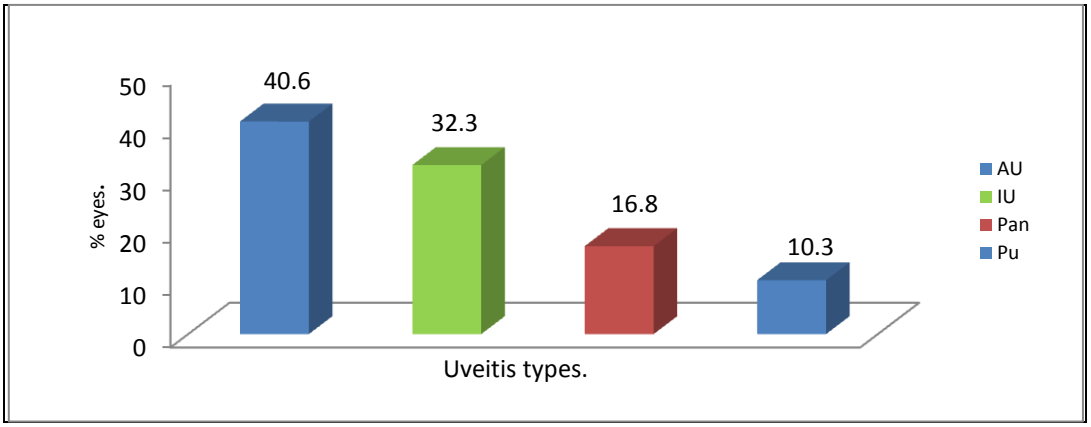
Incidence rates for visual loss were 0.01/EY and 0.02/EY for BCVA 6/18-6/36 and ≤ 6/60 respectively. Causes of visual loss to 6/18-6/36 were as followed: CMO 2 eyes, hypotony 1 eye and RD 1 eye. Severe visual loss was due to hypotony in 1 eye, RD in 1 eye and chronic macular damage in 3 eyes.

3.2.14 *Uveitis in patients aged ≤ 16 years.*

Ninety five patients aged ≤ 16 were identified (157 eyes). Of these, 51 were males and 44 females.

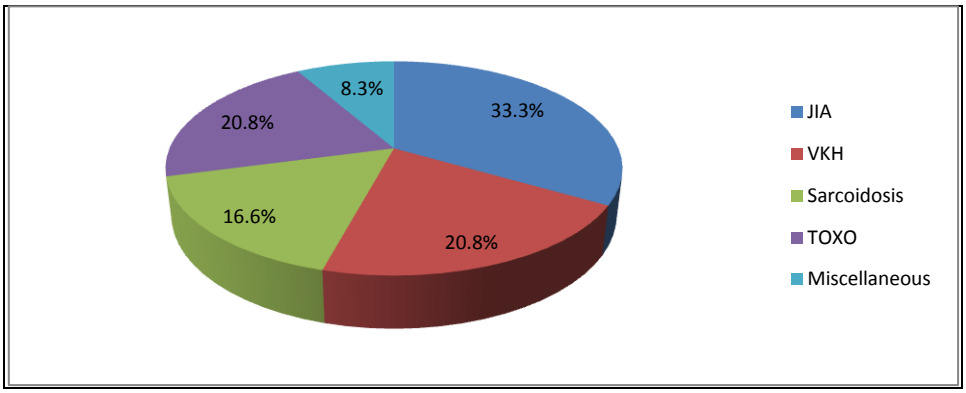
The mean age at presentation was 10.1 years (range 3-16).The mean follow up was 1.9 (range 0.6-11).

Figure 3.6 Types of uveitis in 95 patients aged ≤ 16 years.



Anterior uveitis was the most common entity in the paediatric group (63 eyes) representing 40.6% of all uveitic eyes in children. Fifty eyes (32%) developed IU 26 eyes developed panuveitis and 16 eyes posterior uveitis, representing respectively 16.8% and 10.3%.

Figure 3.7 Systemic diseases associated with uveitis in children.



We found 24 patients (25.2%) who had a systemic condition associated with uveitis. Of these, 33.3% had JIA. Toxoplasmosis and VKH accounted for 20.8% each. Sarcoidosis accounted for 16.6%, 2 patients had the diagnosis of tubulointerstitial nephritis.

Table 3.27 Associated systemic disease by uveitis types in patients aged ≤16.

Uveitis types.→ Systemic disease↓	AU n.patients=37 (%)	IU n.patients=27 (%)	Pan n.patients =18(%)	PU n.patients=13 (%)	Total n. patients= 95(%)
JIA	5 (13.5)	2 (7.4)	1 (5.6)	-	8 (8.4)
VKH	1 (2.7)	-	3 (16.6)	-	4 (4.2)
Sarcoidosis		3 (11.1)	2 (11.1)	-	5 (5.3)
Toxo.	-		-	5 (38.4)	5 (5.3)
Miscellaneous	1 (2.7)	1 (3.7)	-	-	2 (2.1)
Total (%)	7 (18.9)	6 (22.2)	6 (33.3)	5 (38.4)	24 (100)

Of the 37 patients with AU, 19% had a systemic associated disease. JIA was topping the list with 14%. In twenty two percent of patients with intermediate uveitis, a systemic disease was found, and sarcoidosis accounted for 11%, followed by JIA with 7.4%. Thirty three percent of patients with panuveitis had a systemic disease associated, VKH being the most common. Toxoplasmosis was the main condition found in posterior uveitis. Of the two patients with tubulointerstitial nephritis, one developed AU and another intermediate uveitis.

Table 3.28 Eyes with BCVA 6/18-6/36 in children at presentation by uveitis types.

Uveitis types	n.eyes with visual loss	%
AU(n=63)	2	3.2
IU(n=50)	9	18
Pan(n=26)	6	23
PU(n=16)	2	12.5
Total(n=155)	17	11

Twenty three percent of eyes with panuveitis presented with visual loss of 6/18-6/36 and 18% of eyes with intermediate uveitis had vision of 6/18-6/36 at first visit.

Of the 27 children who developed IU, 16 were males and 11 females. Nine children (33.3%) presented aged </= 7, 18 children (66.7%) were aged >7 when diagnosed with IU.

There was no difference in BCVA at presentation between these two age subgroups (p=0.44).

Table 3.29 Eyes with BCVA ≤ 6/60 in children at presentation by uveitis types.

Uveitis types↓	N.eyes	%
AU (n= 63)	3	4.8
IU (n= 50)	3	6
Pan(n= 26)	7	27
Pu (n=16)	3	19
Total (n=155)	16	10.3

Ten percent of eyes had BCVA 6/60 or worse at presentation. When looking at different uveitis types, 27% of eyes with panuveitis and 19% of eyes with posterior uveitis presented with severe visual loss.

Table 3.30 BCVA in different follow-up groups in children.(Time from presentation to data collection in years.)

Time line→	Baseline	1/2 -1year	>1yr- 3years	>3yrs- 5yrs	>5yrs- 10yrs
n.eyes (%)	157(100%)	94 (59.8%)	35(22.3%)	15 (9.6%)	13 (8.3%)
6/12 or better	127 (80.9)	83 (88.3)	27 (77)	11 (73.3)	8 (61.5)
6/18-6/36	20 (12.7)	8 (8.5)	6 (17)	1 (6.6)	-
≤ 6/60	10 (6.4)	3 (3.2)	2 (6)	3 (20)	5 (38.5)

At presentation, 81% of eyes had BCVA of 6/12 or better. Thirteen percent and 6% of eyes had BCVA 6/18-6/36 and ≤ 6/60 respectively. The proportion of eyes with visual impairment decreased with time. When it comes to eyes with severe visual loss, after an improvement at 1 year follow-up, the proportions increased with time. In the group of eyes followed up for 10 years or more, we found no eye with visual impairment. One third of eyes in this group developed vision loss to 6/60 or worse.

The incidence rate for BCVA 6/18-6/36 was 0.10/EY, the incidence rate for severe visual loss was 0.05/EY.

Table 3.31 Causes of BCVA 6/18-6/36 in children in different uveitis types.

Uveitis types→ complications↓	AU (%)	IU (%)	Pu (%)	Panu (%)	Total (%)
CMO	-	6 (86)	-	5(83.3)	11 (73.3)
Cataract	-	1 (14)	-	-	1 (6.7)
Chronic mac.damage	-	-	2 (100)	1 (16.7)	3 (20)
Total (%)	-	7(100)	2 (100)	6(100)	15 (100)

More than 2/3 of visual loss to 6/18-6/36 was caused by CMO. Seven eyes with IU, 2 eyes with posterior uveitis, and 6 eyes with panuveitis developed visual impairment. No eye with anterior uveitis had visual loss of 6/18-6/36.

Table 3.32 Causes of BCVA ≤6/60 in children in different uveitis types.

Uveitis types→ Complications↓	AU (%)	IU (%)	Pu (%)	Panu(%)	Total (%)
CMO	-	-		1(12.5)	1 (7.7)
Chr.mac damage.	2 (50)	-	1	4(50)	7 (53.8)
Hypotony		-	-	1(12.5)	1 (7.7)
Phthisis	1 (25)	-	-	-	1 (7.7)
Retinal detachment	1 (25)	-	-	2(25)	3 (23.1)
Total (%)	4 (100)	-	1 (100)	8(100)	13 (100)

Chronic macular damage was the main cause of severe visual loss, accounting for 54%.

No eye with IU developed severe vision loss.

Of the children who developed IU aged </=7, none developed visual impairment at the end of the follow-up period. Only 22.2% of those aged > 7 at onset of IU developed visual impairment at the end of the follow- up period.

3.2.15 *Uveitis in patients aged ≥ 60.*

We identified 228 patients (392 eyes) aged ≥ 60, representing 14.3% of the whole uveitis population. Of these, 90 were males and 138 females.

The mean age at first presentation was 68.1 years (range 60-92).

The types of uveitis developed were as followed: 176 eyes (45%) AU, 83 eyes (21%) IU, 45 eyes (11.5%) with posterior uveitis and 88 eyes(22.4%) with panuveitis.

A systemic disease was identified in 158 patients (69.3%). Sarcoidosis accounted for 13.2%, diabetes mellitus for 8.3% and SLE for 1.3%. Two patients had AS, 1JIA, 1 MS, 1 toxoplasmosis. Miscellaneous diseases included 2 ulcerative colitis, 2 Waldestrom macroglobulinaemia, 1 HTLV1-Tcell lymphoma, 1 Non-Hodgkin lymphoma, 2 Sjögren disease, 1 PMR and 2 Interstitial nephritis.

Table 3.33 Causes of BCVA 6/18-6/36 in patients aged ≥ 60.

Types of uveitis→ Complications↓	AU (%)	IU (%)	Pu (%)	Panu (%)	Total (%)
CMO	14 (54)	9 (56.2)	1(33)	2 (25)	26 (49)
Chronic mac. Damage	5 (19.2)	7 (43.8)	2 (67)	4 (50)	18 (34)
Glaucoma	4 (15.3)	-	-	2 (25)	6 (11.3)
Cataract	3 (11.5)	-	-	-	3 (5.7)
Total	26 (100)	16 (100)	3 (100)	8(100)	53 (100)

CMO accounted for 49% of all causes of BCVA 6/18-6/36 in patients aged 60 or more, followed by chronic macular damage accounting for 34% and glaucoma 11%. When looking at different uveitis types, CMO was the leading cause of BCVA 6/18-6/36 in AU and IU with 54% and 56% respectively. Chronic macular damage occurred more in eyes with IU (44%).

Table 3.34 Causes of BCVA ≤ 6/60 in patients aged ≥ 60.

Types of uveitis → Complications↓	AU (%)	IU (%)	Pu (%)	Panu (%)	Total (%)
CMO	-	4 (36.4)	1 (8.3)	2 (13.3)	7 (13.2)
Chronic mac damage	7 (46.7)	4 (36.4)	7 (58.3)	4 (26.6)	22 (41.5)
Glaucoma	8 (53.3)	3 (27.2)	1 (8.3)	4 (26.6)	16 (30.2)
Mac ischemia	-	-	2 (16.7)	-	2 (3.8)
Retinal detachment	-	-	1 (8.3)	3 (20)	4 (7.6)
Phthisis	-	-	-	2 (13.3)	2 (3.8)
Total	15 (100)	11 (100)	12 (100)	15(100)	53 (100)

Chronic macular damage was the main cause of severe visual loss accounting for 41.5%, followed by glaucoma with 30% and CMO with 13%. In eyes with AU, glaucoma accounted for 53% of severe visual loss. Severe visual loss in eyes with IU was caused by CMO and chronic macular damage in the

ssame proportions (36.4%). In 58% of eyes with PU, chronic macular damage was the main cause of severe visual loss, whereas the latter accounted for 26.6%, the same proportion with glaucoma in eyes with panuveitis.

3.2.16 *Treatment of uveitis.*

Table 3.35 Number of eyes treated with different regimen in different uveitis types.

Treatment→ Uveitis type↓	Oral steroids n.eyes	Steroid sparing n.eyes	Biologic agents n.eyes	OFI n.eyes	IVTA n.eyes	Total n.eyes
AU n=1050(%)	76 (7.2)	22 (2.1)	2 (0.2)	4 (0.4)	4 (0.4)	108 (10.3)
IU n= 666 (%)	196 (29.4)	72 (10.8)	13 (1.9)	20 (3.0)	33 (5)	334 (50.1)
PU n=440(%)	263 (59.7)	69(15.7)	5 (1.1)	4 (0.9)	5 (1.1)	346 (78.6)
Panu n=387(%)	255(65.9)	76(19.6)	3 (0.8)	13(3.4)	13(3.4)	360 (93)
Total n=2543 (%)	790 (31)	239 (9.4)	23 (0.9)	41(1.6)	55 (2.2)	1148 (45.1)

Fifty five percent of affected eyes were managed with topical treatment only. Oral steroids were used to treat 31% of eyes. For 9.4% of eyes, a steroid sparing agent drug was used, and biologic agents were used to control the inflammation in only 1% of eyes. Orbital floor and IVTA injections were used to treat 4% of eyes.

Ninety percent of eyes with AU were managed with topical treatment alone. In 7.2% of AU, oral steroids were used. In most of these eyes which required a systemic treatment, an underlying systemic disease was present.

Fifty percent of eyes with IU were treated with topical steroids alone. Twenty nine percent were managed with systemic steroids, and in 10.8% a steroid sparing agent was added. Biologic agents were used on 2% of eyes with IU, and OFI and IVTA were used in 3 and 5% respectively. The proportion of eyes treated with OFI and IVTA was higher in IU when compared with other uveitis types.

Sixty percent and 66% of eyes with posterior and panuveitis respectively were treated with oral steroids. Sixteen percent of eyes with posterior uveitis and 20% of eyes with panuveitis were treated with a steroid sparing agent.

Chapter 4. Surgery in uveitis.

4.1 Introduction.

The sequelae of uveitis that may cause visual impairment are well known and include cataract, glaucoma, band keratopathy, vitreous opacities, retinal scars and ERMs, retinal detachment, retinal vascular abnormalities, CMO and optic atrophy. Several of these are surgically treatable, such as cataract, glaucoma, vitreous opacities, ERMs and retinal detachment [678].
The risk factor for development of early cataract requiring surgery in children with JIA-associated uveitis is the presence of posterior synechia at the time of diagnosis of uveitis [679].

Optimal treatment of cataract in the setting of uveitis requires optimal management of uveitis, including appropriate diagnostic workup and scrupulous attention to preoperative preparation, intraoperative technique, and postoperative management. Recent long-term outcome studies in cohorts of uveitis patients undergoing cataract surgery suggest very good outcomes in the majority of patients[403]. Using stringent perioperative and postoperative control of inflammation, patients with uveitis usually maintain high visual acuity over long-term follow-up[680]. Poor visual outcome after surgery is most commonly the result of preoperative vision-limiting conditions [411, 413].

Secondary glaucoma is a difficult and frequent complication of uveitis[681]. Patients with uveitic glaucoma can have good outcomes after trabeculectomy with antiproliferative agents [682, 683]. Deep sclerectomy with implant in uveitic glaucoma appear to be effective in controlling the IOP at short-term follow-up with no serious postoperative side-effects [684]. In children, reports on the use of trabeculectomy, goniosurgery, glaucoma drainage devices, and cyclodestructive procedures show higher failure rates than when used for primary open angle glaucoma in adults [685]. However, with good immunomodulatory control of their inflammation and appropriate follow-up, Ahmed valve implantation can be an effective and safe procedure for treating pediatric uveitic glaucoma[685]. With the advent of modern vitreoretinal surgical techniques, the spectrum for surgical interventions in various forms of uveitis has been notably expanded. Removal of optically relevant vitreous opacities, improvement of secondary macular edema, delamination of epiretinal membranes, and release of traction in the presence of abnormal vitreoretinal

adhesions represent indications for vitreoretinal procedures in uveitis patients [686]. ERM surgery appears to improve patients' subjective perception of visual function [687].

The major question addressed in this section is to establish whether uveitis patients who underwent cataract, glaucoma and vitreoretinal surgeries had their visual acuity improved. If vision did not improved, was this due to the surgery itself?

4.2 Results.

4.2.1 *Demographics.*

From the whole uveitis population, 463 patients (696 eyes) representing 29% of patients underwent surgery. Of these 197 were males and 266 females.

Table 4.1 Number of eyes that underwent surgery by uveitis types.

Types of uveitis	Tot. N. Eyes	Surgery/n.eyes	% eyes having surgery
AU	1050	270	25.7
IU	666	191	28.7
Pu.	440	62	14
Panu	387	171	44.2
Total.	2543	696	27.4

Twenty seven percent of all uveitic eyes were operated on. A quarter of eyes with AU and those with inermediate uveitis underwent surgery, while the proportion of eyes with panuveitis which underwent surgery was the highest (44%). Only 14% of eyes with posterior uveitis required surgery at some point.

Table 4.2 Systemic diseases associated with uveitis in patients who underwent surgery.

Systemic d.	Tot. Patients	n. *Sx	%
Sarcoidosis	170	41	24.1
Behçet's	60	7	11.6
Diabetes	67	28	41.7
JIA	27	16	59.2
VKH	19	5	26.3
MS	13	3	23.0
Toxo	68	4	5.8
Miscellaneous	40	27	67.5
Total	464	131	28.2

*Sx= surgery

Twenty eight percent of patients who underwent surgery had an underlying systemic condition. More than half the number of patients with JIA had surgery. Forty two percent of patients with diabetes had surgery, while 26% and 24% of those with VKH and sarcoidosis repectively underwent surgery.

Table 4.3 Surgery in different uveitis types.

Types of surgery Uveitis types.	Cataract surgery n. eyes	Glaucoma surgery n. eyes	VR surgery n.eyes
AU: 1050(%)	246 (23.4)	44 (4.2)	16 (1.5)
IU : 666(%)	157 (23.6)	20 (3.0)	23 (3.4)
Pu : 440(%)	37 (8.4)	7 (1.6)	14 (3.1)
Panu :387(%)	175 (45.2)	16 (4.1)	23 (6)
Total 2543	615 (24.1)	87 (3.4)	76 (3)

A quarter of all uveitis eyes underwent cataract surgery. Only 3% underwent glaucoma and vitreoreetinal surgeries.

The same proportion (23%) of eyes with AU and IU underwent cataract surgery. Only 8% of eyes with posterior uveitis had cataract surgery, and 45% of eyes with panuveitis underwent cataract extraction. Glaucoma surgery was performed on 4% of eyes with AU and panuveitis, on 3% and 1.6% of eyes with IU and posterior uveitis respectively. Six percent of eyes with panuveitis underwent vitreoretinal surgery. This proportion was the double of that of eyes with IU and posterior uveitis, and the quadruple of eyes with AU on which vitreoretinal procedures were performed.

4.2.2 *Cataract surgery*

Table 4.4 Types of cataract surgery in different uveitis types.

Surgery→ Uveitis type↓	Phaco. n.eyes	ECCE n.eyes	ICCE n.eyes	Lensectomy n. eyes
AU n=246(%)	214 (87)	3 (1.2)	19 (7.7)	10 (4.1)
IU n=157(%)	153 (97.4)	2 (1.3)	-	2 (1.3)
Pu. n=37(%)	37 (100)	-	-	-
Panu n=175(%)	141(80.5)	5 (2.9)	5(2.9)	24(13.7)
Total n=615(%)	545 (88.6)	10 (1.6)	43 (7)	17 (2.8)

Phaco.=Phacoemulsification;ECCE.=Extracapsular cataract extraction ; ICCE.=Intracapsular cataracact extraction

Phacoemulsification with intraocular lens implantation was the most common type of cataract surgery performed on uveitic eyes.

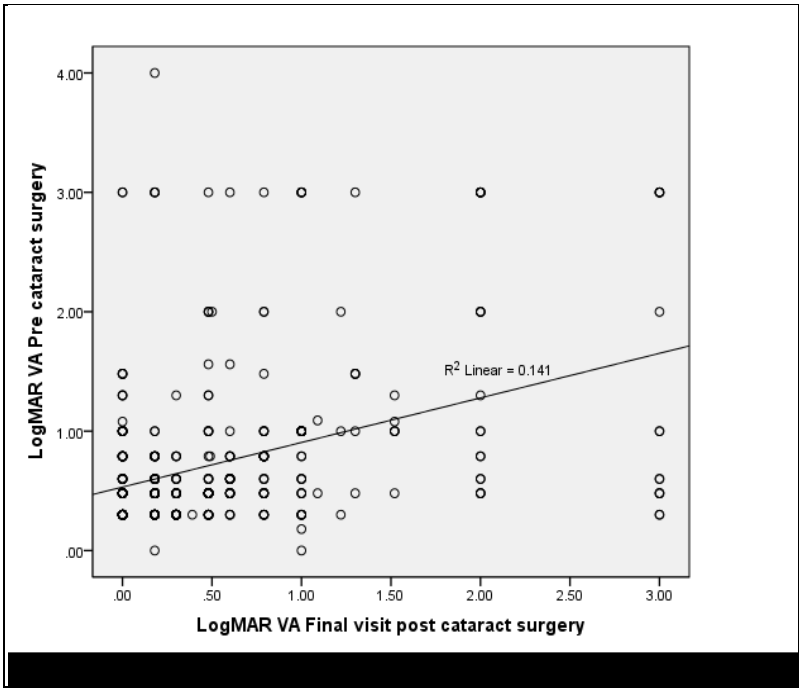
Ten eyes (1.6%) underwent ECCE, 43 eyes (7%) were aphakic following ICCE, 17eyes (2.8%) underwent lensectomy. The proportion of eyes on which the latter procedure was performed was higher in eyes with panuveitis than in other uveitis types.

Table 4.5 Mean logMAR BCVA pre-cataract surgery.

Uveitis types	Log MAR BCVA
AU	0.92 (SD± 0.78)
IU	0.75 (SD± 0.62)
Pu	0.79 (SD±0.63)
Panu	0.99 (SD±0.73)

Eyes with panuveitis had the worse visual acuity pre cataract surgery.

Figure 4.1 Correlation between pre-cataract surgery visual acuity and post-cataract surgery.



Although there was a positive correlation between visual acuity precataract surgery and post cataract surgery, this correlation was not statistically significant.(Pearson correlation =0.375).

The overall mean preoperative logMAR BCVA was 0.88 ± 0.76 (0.74 – 0.93 95% CI). The mean logMAR BCVA after cataract surgery improved to 0.34 ± 0.64 (0.26 – 0.39 95% CI; $p < 0.001$). Most eyes achieved best vision at first post op follow-up visit (1 week).

Table 4.6 Eyes with BCVA 6/18-6/36 and ≤ 6/60 post cataract surgery in different uveitis types.

Uveitis types	BCVA 6/18-6/36 n.eyes (%)	BCVA ≤ 6/60 n.eyes (%)
AU n.eyes=246	23 (9.3)	29 (11.8)
IU n.eyes=157	34 (21.6)	15 (9.5)
Pu n.eyes= 37	10 (27)	16 (43)
Panu n.eyes=175	38(21.7)	41 (23.4)
Total n.eyes = 615	105 (17.1)	70 (11.4)

Of the 615 eyes, 66.5% attained BCVA 6/12 or better at final follow- up visit post cataract surgery. Seventeen percent of eyes developed visual loss to 6/18-6/36. Overall, 11% of eyes had severe visual loss after cataract surgery. Eyes with AU had vision loss to 6/18-6/36 and 6/60 or worse in 9.3% and 11.8% respectively. A fifth of eyes with IU developed vision loss of 6/18-6/36 and 10% had severe visual loss after cataract surgery. Twenty seven percent and 22% of eyes with posterior uveitis and panuveitis respectively developed visual loss of 6/18-6/36, while the highest proportion of eyes with severe visual loss after cataract surgery was found in posterior uveitis (43%).

Table 4.7 Types of cataract surgery and vision loss.

Types of surgery	BCVA 6/18-6/36 n.eyes (%)	BCVA≤ 6/60 n.eyes (%)	Total n.eyes (%)
Phaco n.eyes = 545	92 (16.9)	68 (12.5)	160 (29.4)
Lensectomy n. eyes= 17	3 (17.6)	4 (23.5)	7 (41.1)
ECCE n.eyes = 10	3 (30)	5 (50)	8 (80)
ICCE n.eyes = 43	7 (16.3)	24 (55.8)	31 (72.1)

Seventeen percent of eyes that underwent phacoemulsification with IOL insertion developed vision loss to 6/18-6/36

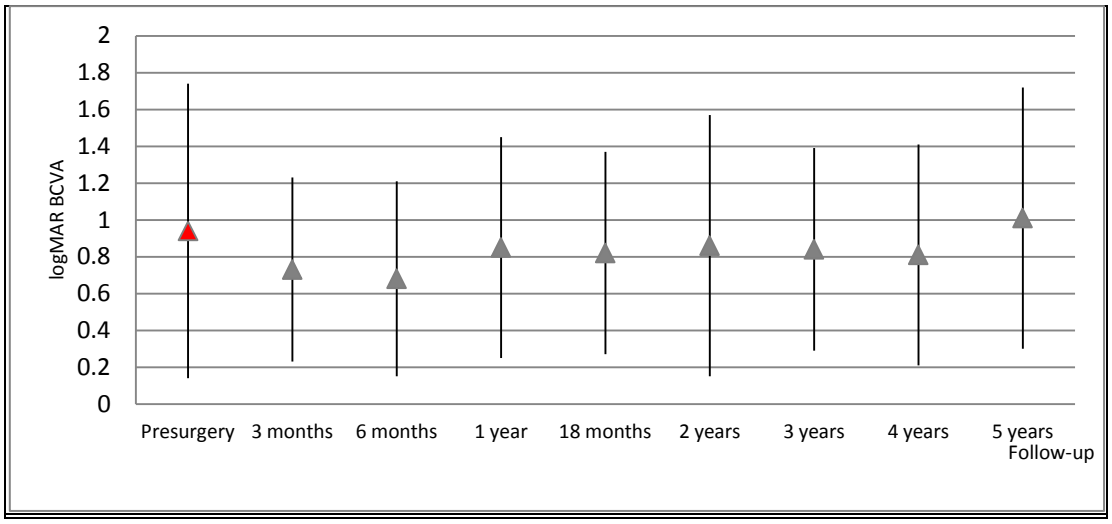
Eyes which had lensectomy and ECCE developed BCVA 6/18-6/36 in 18% and 30% respectively. Sixteen percent of aphakic eyes following ICCE had vision loss to 6/18-6/36.

In 13% of eyes that underwent phacoemulsification, severe vision loss occurred. Eyes in which lensectomy was performed had BCVA 6/60 or worse in 24%, while half and more than half the number of eyes that had ECCE and ICCE had severe vision loss.

Univariate analysis of variance for factors predicting visual loss post cataract surgery show that gender and age at first diagnosis were not predictive of visual loss. However, associated systemic disease, presurgery macular damage and type of surgery influenced visual outcome. p values= 0.003 for associated systemic disease, 0.027 for macular damage and <0.001 for type of surgery.

In multivariate analysis, systemic disease did not appear to be an independent factor influencing visual outcome post cataract surgery (p= 0.22). Pre cataract surgery VA and type of surgery influenced visual outcome.(p= 0.030 and p< 0.001 respectively).

Figure 4.2 Progression of visual acuity post cataract surgery in eyes with visual loss.



Eyes which were visually impaired at final follow-up visit after cataract surgery had a slight improvement of visual acuity up to 6 months postop. After 6 months, visual acuity declined.

Table 4.8 Causes of visual loss to 6/18-6/36 and ≤6/60 post cataract surgery.

Complications	BCVA 6/18-6/36 n. eyes (%)	BCVA 6/60 or worse n.eyes (%)
CMO	20 (19.0)	17 (16.8)
Glaucoma	21 (20)	36 (35.6)
Mac. Damage	45 (42.9)	31 (30.6)
Op. atrophy.	3 (2.9)	4 (4)
Hypotony	2 (1.9)	3 (3)
Retinal detachment	10 (9.5)	4 (4)
Phthisis	-	4 (4)
Miscellaneous	4 (3.8)	2 (2)
Total	105 (100)	101 (100)

BCVA 6/18-6/36 was due to chronic macular damage in 43% of eyes, to glaucoma and chronic CMO in 20% and 19% respectively. Most of these complications were present prior to cataract surgery. In a further 18% of eyes, visual loss resulted from retinal detachment (9.5%), optic atrophy (2.9%), hypotony (1.9), corneal decompensation and PCO (3.8%).

Glaucoma was the main cause of severe visual loss post cataract surgery accounting for 37%. Macular damage accounted for 31%, followed by refractory uveitic CMO which accounted for 17%. Optic atrophy and hypotony caused severe visual loss in 4% and 3 % respectively, and a further 10 % of eyes developed retinal detachment (4 eyes), phthisis (4 eyes), cyclitic membrane (2 eyes).

Table 4.9 BCVA 6/18-6/36 after cataract surgery and visual acuity at presentation.

BCVA at first visit	BCVA post cataract surgery	N.eyes (%)
6/12 or better	6/18-6/36	35 (33.3)
6/18-6/36	6/18-6/36	48 (45.7)
≤6/60	6/18-6/36	22 (21)
Total	-	105 (100)

Vision loss to 6/18-6/36 developed in 105 eyes after cataract surgery. Of these, 33% had normal visual acuity at presentation, 46% had BCVA 6/18-6/36 at presentation and 21% had severe visual loss at first visit.

Table 4.10 BCVA ≤6/60 after cataract surgery and visual acuity at presentation.

BCVA at first visit	BCVA post cataract surgery	N.eyes (%)
6/12 or better	≤6/60	14 (13.9)
6/18-6/36	≤6/60	23 (22.8)
≤6/60	≤6/60	64 (63.3)
Total	-	101 (100)

Severe visual loss after cataract surgery occurred in 101 eyes. Of these eyes, only 14% had BCVA 6/12 or better at presentation, 23% and 63% had BCVA 6/18-6/36 and 6/60 or worse respectively.

Cataract surgery in JIA-associated uveitis.

Of the 24 patients with JIA associated uveitis, 14 (58.3%), 21 eyes representing 80.8% of affected eyes underwent cataract surgery. Five eyes(23.8%) underwent phacoemulsification, 4 eyes(19.0%) underwent lensectomy. ICCE was performed on 12 eyes (57.1%).

Table 4.11 Visual acuity in pre cataract surgery and post cataract surgery in JIA uveitis.

BCVA	Pre cataract surgery n.eyes (%)	Post cataract surgery n.eyes (%)
6/18-6/36	13 (61.9)	6(28.6)
≤6/60	8(38.1)	8(38.1)

Sixty two percent of eyes operated on had BCVA 6/18-6/36 pre- cataract surgery, 38% were severely visually impaired. At final post op follow up visit, 33.3% of eyes attained BCVA 6/12 or better. Twenty nine percent of eyes developed visual impairment, and 38% had BCVA 6/60 or worse.

Table 4.12 Complications and visual loss post cataract surgery in JIA uveitis.

Vision loss→ Complications↓	BCVA 6/18-6/36	BCVA ≤ 6/60
CMO	1	2
Glaucoma	2	4
Band keratopathy	2	-
Hypotony	1	-
Macular damage	-	1
Phthisis	-	1

Glaucoma was the main cause of severe visual loss post cataract surgery in eyes with JIA-associated uveitis. CMO leading to severe vision loss developed in 2 eyes. Of eyes with severe visual loss one had chronic macular damage and one eye was phthisical.

Table 4.13 Causes of visual loss in pseudophakic eyes and aphakic eyes with JIA-associated uveitis.

Complications	Aphakic eyes n.eyes= 16	Pseudophakic eyes n.eyes= 5
CMO	1	2
Glaucoma	5	1
Hypotony	2	-
Mac. Damage	-	1
Band keratopathy	-	1
Phthisis	1	-

Glaucoma was the main cause of visual loss and developed more frequently in aphakic eyes. Of the 3 eyes which developed CMO, 1 was aphakic and 2 were pseudophakic. Two aphakic eyes developed hypotony. One aphakic eye developed chronic macular damage and another aphakic eye became phthisical at the final postop follow-up visit.

4.2.3 *Glaucoma surgery.*

Sixty eight patients (96 eyes) underwent glaucoma surgery. Of these, 34 were males and 34 females.

Table 4.14 Types of uveitis and glaucoma surgery.

Uveitis types	N.eyes	(%)
AU	46	(47.9)
IU	22	(22.9)
Pu	8	(8.3)
Pan	20	(20.8)
Total	96	(100)

Forty eight percent of eyes which underwent glaucoma surgery had AU. Intermediate uveitis and panuveitis accounted for 22.9% and 20.8% respectively. Eight percent had posterior uveitis.

Table 4.15 Systemic disease and glaucoma surgery.

Systemic disease	N.patients	(%)
Ankylosing spondylitis	4	(14.8)
Behçet's disease	3	(11.1)
Diabetes	3	(11.1)
JIA	8	(29.6)
Sarcoidosis	6	(22.2)
VKH	1	(3.8)
Miscellaneous	2	(7.4)
Total	27	(100)

Twenty seven patients representing 39.7% of patients who underwent glaucoma surgery had a systemic disease. One third of these had JIA. Sarcoidosis the second most important systemic disease accounting for 22%, followed by AS with 14.5%.

Table 4.16 Types of glaucoma surgery.

Types of surgery	N.eyes	(%)
Trabeculectomy	67	(69.8)
Tubes	20	(20.8)
Trabeculectomy+tubes	5	(5.2)
*PI + Trabeculectomy	4	(4.2)
Total	96	(100)

*PI= Peripheral iridotomy

Trabeculectomy with Mitomycin C was performed on 69.8% of eyes, tube insertion alone on 20.8%. Five eyes had trabeculectomy first and tube insertion subsequently. On 4 eyes, PI was performed before trabeculectomy.

The mean IOP preglaucoma surgery was 18 mmHg ± 10.5.

Forty nine eyes (50%) had also cataract surgery.

The mean logMAR BCVA preglaucoma surgery was 0.57± 0.88 (0.30 – 0.73 95% CI).

The mean logMAR BCVA after glaucoma surgery was 0.52 ± 0.72 (0.29 – 0.65 95% CI),

$p< 0.001$.

At final follow up visit after glaucoma surgery, 19 eyes (19.8%) had BCVA 6/18-6/36, and 22 eyes (23%) had BCVA ≤6/60. No patient had lost vision from glaucoma surgery.

4.2.4 *Vitreo-retinal surgery.*

Sixty four patients (76 eyes) underwent vitreo retinal surgery. Of these, 26 were males, 38 females.

The mean follow up post surgery was 3.8 years (SD ± 3).

Table 4.17 Types of VR surgery in different uveitis types.

VR surgery	AU n.eyes	IU n.eyes	Pu n.eyes)	Pan n.eyes	Total n.eyes)
Vitrectomy n.eyes (%)	6 (18.2)	7 (21.2)	3(8.8)	18(52.9)	34 (100)
ERM peel n.eyes (%)	1 (3.7)	11 (40.7)	7(29.1)	5(20.8)	24 (100)
RD surgery n.eyes (%)	9 (60)	3 (20)	1(6.2)	3(18.7)	16 (100)
Mac.surgery n.eyes (%)	-	-	5(83.3)	1(16.7)	6(100)
Total (%)	16 (20)	21 (26.2)	16 (20)	27(33.8)	80 (100)

Half the number of eyes which underwent vitrectomy had panuveitis. Eighteen percent and 21% had AU and IU respectively. Only 8.8 had posterior uveitis. Forty percent of eyes which underwent epiretinal membrane peel had intermediate uveitis, 29% and 21% had posterior uveitis and panuveitis respectively. Two thirds of eyes on which retinal detachment surgery was performed had AU, and most eyes which underwent macular surgery had PU.

Table 4.18 Eyes with BCVA 6/18-6/36 and ≤ 6/60 before and after VR surgery.

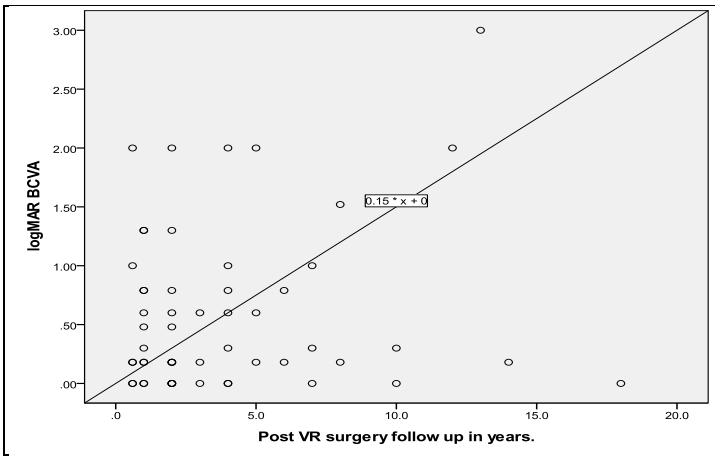
Vision loss→ Time	BCVA 6/18-6/36 n.eyes (%)	BCVA ≤ 6/60 n.eyes (%)
Pre VR surgery	25 (32.9)	40 (52.6)
Post VR surgery	21 (27.6)	30 (39.5)

Before surgery, 32.9% of eyes had BCVA 6/18-6/36, 52.6% had severe vision loss.

After VR surgery, 27.6% of eyes had visual loss to 6/18-6/36, 39.5% had vision loss ≤ 6/60.

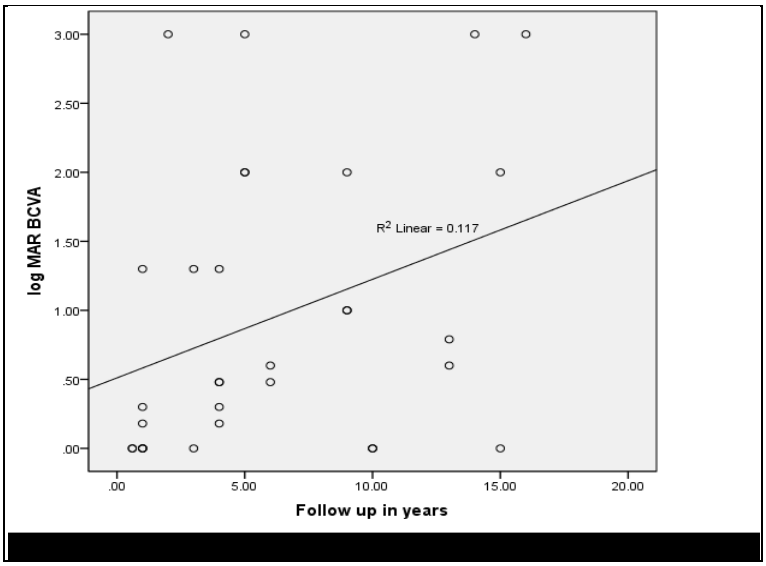
The mean logMAR BCVA pre VR surgery was 1.14 ± 0.84 (0.81 - 1.37 95% CI). The mean logMAR BCVA post surgery improved to 0.62 ± 0.66 (0.57 – 0.37 95% CI); $p < 0.001$.

Figure 4.3 Visual acuity post VR surgery with time.



Univariate analysis of variance shows a positive correlation between visual acuity and follow up time post surgery; Pearson correlation = 0.021(not statistically significant).

Figure 4.4 Visual acuity with time in eyes which underwent membrane peel.



Visual acuity of eyes which had undergone membrane peel declined with time (R^2= 0.117). The Pearson correlation between follow up time and visual acuity was not statistically significant (0.05). However, the correlation between initial visual acuity and visual acuity post membrane peel was highly statistically significant (Pearson correlation = 0.00).

Table 4.19 Causes of visual loss after VR surgery.

Vision loss→ Complications↓	6/18-6/36 n.eyes (%)	≤6/60 n.eyes (%)
CMO	5 (23.8)	5 (16.7)
Glaucoma	5 (23.8)	9 (30)
Hypotony	1 (4.8)	1 (3.3)
Mac ischemia	1 (4.8)	-
Optic atrophy	-	1 (3.3)
Chronic mac damage	6 (28.5)	11 (36.7)
Retinal detachment	3 (14.3)	3 (10)
Total	21 (100)	30 (100)

Chronic macular damage accounted for 28.5% of causes of visual loss to 6/18-6/36, followed by glaucoma and CMO with 23.8% each.

In the group of eyes with severe vision loss, chronic macular damage accounted for 36.7%, followed by glaucoma (30%) and CMO (16.7%).

Chapter 5. Ischemia.

5.1 Introduction

Patients with ischemic retinal vasculitis represent a major management problem. It is important to identify the presence of retinal ischemia in patients with retinal vasculitis because panretinal laser photocoagulation should be considered when angiographic evidence of widespread retinal nonperfusion is present, and before (or shortly after) the development of neovascularisation [517].
Ischemic retinal vasculitis may be secondary to Behçet's disease where retinal vasculitis and recurrent vasoocclusive episodes are the major cause of visual morbidity. In addition, inflammatory retinal vein occlusions are strongly associated with Behçet's disease [688-691].
Retinal ischemia is frequently seen secondary to tuberculosis and retinal vasculitis associated with tuberculoprotein hypersensitivity which is typically, an obliterative periphlebitis affecting the retina in multiple quadrants, starting at or anterior to the equator and progressing posteriorly. Occasionally, it can begin close to the optic nerve head, mimicking a vein occlusion. Ophthalmoscopic findings vary and depend on the stage of the disease. Initially, it presents as active retinal periphlebitis with thick exudates around the retinal veins associated with retinal haemorrhages, and haemorrhagic infarctions of the retina[517]. The periphlebitis may cause nonperfusion of a substantial portion of the retina that may lead to proliferative vascular retinopathy with sequelae such as recurrent vitreous haemorrhage, traction retinal detachment, rubeosis iridis, and neovascular glaucoma [223, 517, 692].

Various ocular inflammatory changes have been described in patients with MS and may be the presenting sign of the disease.[579, 693-697]. Retinal periphlebitis has been described as a common manifestation of MS. It has been observed with an average frequency of 11.5% in more than 3,000 published cases of MS examined for sheathing [698]. The periphlebitis can progress to occlusive peripheral vasculitis, which results in peripheral retinal neovascularisation and tractional or rhegmatogenous retinal detachments or both [579, 696, 697].
Retinal periphlebitis associated with sarcoidosis is usually nonocclusive, sometimes subclinical and only visible on fluorescein angiography, associated with typical segmental cuffing or more extensive sheathing and perivenous exudates, which are usually indicated as ‘‘candle wax drippings’’[699, 700]. Development of capillary nonperfusion and subsequent neovascularisation as well as branch and central retinal vein occlusions have been described [701-704].

The retina is a common site of ocular involvement in patients with lupus. The proportion of patients with SLE who manifest retinal involvement varies depending on the population studied and ranges from 3% in well controlled patients to 29% in patients with more active systemic disease [607, 608, 610-612, 705]. Retinal findings most commonly associated with lupus are cotton wool spots and intraretinal haemorrhages[609]. Other retinal manifestations may include microaneurysms, vascular tortuosity, arteriolar narrowing, retinal oedema, or exudates [610-612]. Most patients with mild retinopathy are at low risk for vision loss [611, 705]. In contrast, severe vaso-occlusive retinopathy is a rare but well described entity that is associated with widespread retinal capillary nonperfusion, multiple branch retinal artery occlusions, ocular neovascularisation, vitreous haemorrhage, and significant resultant visual loss [613, 614].

Severe retinal vaso-occlusive disease and CNS involvement have been associated with the presence of antiphospholipid antibodies in the antiphospholipid syndrome [706].

Wegener's disease may present with ocular symptoms in 8–16% of patients, but the eye becomes involved in up to 40% [707]. Involvement of the posterior segment is uncommon. It can manifest as an occlusive retinal vasculitis affecting either arteries or veins, retinitis or uveitis [708].

In polyarteritis nodosa (PAN), retinopathy is one of the most commonly seen ocular complications, with retinal vascular occlusions, oedema, cotton wool spots and retinal haemorrhages. These findings are secondary to hypertensive retinopathy, especially in patients with renal disease, or from primary retinal vasculitis[709].

Occlusive retinal vasculitis, and subsequent retinal neovascularisation [710] and neovascular glaucoma[711] was also reported in patients with Crohn's disease.

The laboratory work-up of patients with retinal vasculitis has been described in chapter 2.

The management of tuberculous retinal vasculitis or retinal vasculitis associated with tuberculoprotein hypersensitivity requires the use of systemic steroids and appropriate antituberculous therapy. New vessel formation associated with retinal vasculitis and capillary closure responds to panretinal photocoagulation.

In case of peripheral capillary closure which results in peripheral retinal neovascularisation and tractional or rhegmatogenous retinal detachment or both, peripheral scatter photocoagulation and vitrectomy may be required to stabilise the proliferative retinopathy [579, 696, 697].

Early vitrectomy and adequate endolaser photocoagulation should be considered in eyes with nonresolving vitreous haemorrhage associated with active fibrovascular proliferation [712].

In this chapter I looked at eyes which have developed ischemia and see if their visual acuity had worsened with time. I also looked at the impact of different treatments on visual acuity.

5.2 Methods.

Fluorescein angiograms of patient who developed vasculitis were reviewed. Capillary non perfusion was identified as described in chapter 1.

5.3 Results.

5.3.1 *Demographics.*

Sixty five patients (106) eyes were identified. Forty two were males and 23 females, a ratio of 1.8.

The mean age at presentation was 40.2 years ± 11.3 for males and 43 ± 10.8 years for females. The difference was not statistically significant (p = 0.32).

The mean follow up was 6.5 years (range 0.6 – 33).

Table 5.1 Clinical entities in which ischemia developed.

Clinical entities	N.eyes	(%)
Idiopathic retinal vasculitis	33	(31.1)
Eale's disease	20	(18.9)
TB hypersensitivity	4	(3.8)
Ischemic CRVO	7	(6.6)
BRVO	20	(18.9)
AU	4	(3.8)
IU	2	(1.9)
Pu	8	(7.5)
Panu	8	(7.5)
Total	106	(100)

One third of all eyes which developed ischemia had idiopathic retinal vasculitis (IRV). Eale's disease and BRVO accounted for 19% each. Eyes with posterior uveitis and panuveitis accounted for 7.5% each, and 7% had ischaemic CRVO. Four eyes and 2 eyes with AU and IU respectively developed ischaemia. A further 4 eyes had TB hypersensitivity.

Table 5.2 Systemic disease associated with ischemia.

Systemic disease	Ischemia n.patients (%)
Behçet's disease	15 (45.5)
Sarcoidosis	4 (12.1)
MS	4 (12.1)
Diabetes	1 (3.0)
SLE	4 (12.1)
TB	5 (15.2)
Total	33 (100)

BD was the most common systemic disease associated with ischemia accounting for 45%, followed by TB with 15%. Sarcoidosis, MS and SLE accounted equally for 12% each. One patient had diabetes, but not ischemic retinopathy caused by diabetes.

The mean logMAR BCVA at presentation was 0.47 (range 0.00 – 3).

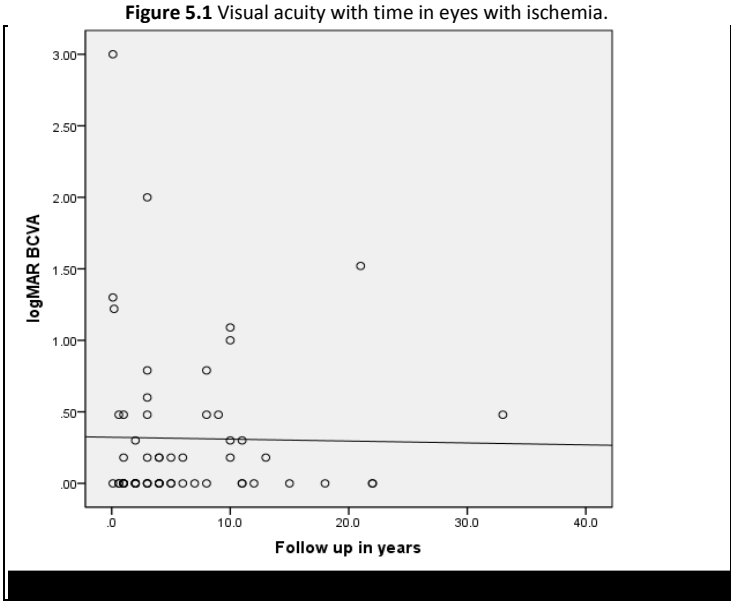
5.3.2 *Visual loss in ischemia.*

Table 5.3 Eyes with BCVA 6/18-6/36 and ≤ 6/60 at presentation.

BCVA 6/18-6/36 N. eyes (%)	BCVA ≤6/60 N.eyes (%)
25 (23.6)	24 (22.6)

At presentation, 24% of eyes had BCVA 6/18-6/36, and 23% were severely visually impaired.

Figure 5.1 Visual acuity with time in eyes with ischemia.



Visual loss developed early in the first 5 years and does not worsen with time. A few number of eyes developed vision loss after 5 years. The correlation between time and visual acuity is not statistically significant (Pearson correlation =0.9)

Table 5.4 Causes of visual loss in eyes with ischemia.

Vision loss→ Complications↓	6/18-6/36 N.eyes (%)	≤6/60 N.eyes (%)
CMO	2 (11.1)	-
Neovasc. Glaucoma	2 (11.1)	3 (11.1)
Mac. Ischemia	8 (44.4)	19 (70.4)
Chronic macular damage	5 (27.8)	3 (11.1)
Op.atrophy	1 (5.6)	1 (3.7)
Phthisis	-	1 (3.7)
Total	18 (100)	27 (100)

Macular ischemia was the main cause of both for visual impairment and severe visual loss accounting for 44% and 70% respectively. Chronic macular damage accounted for 28% of BCVA 6/18-6/36 and 11% for BCVA 6/60 or worse. Two eyes developed neovascular glaucoma leading to BCVA 6/18-6/36. Three other eyes with neovascular glaucoma had severe vision loss. Chronic CMO caused vision loss to 6/18-6/36 in 2 eyes. Two eyes developed optic atrophy. BCVA was 6/18-6/36 in one of these eyes and the other developed severe visual loss. Of the 16 patients who developed macular ischemia, 3 had BD and 3 had SLE.

With time, 20 eyes improved visual acuity by 3 Snellen lines or more, 15 eyes had visual acuity worsened by losing 3 Snellen lines or more. Eyes which developed macular ischemia did not improve visual acuity.

At first presentation, 4 eyes out of 20 affected presented with BCVA 6/18-6/36, the same proportion presented with BCVA 6/60 or worse.

At final follow up, 7 eyes had improved visual acuity, 3 eyes had worsened visual acuity.

Causes of visual loss at final follow- up visit were macular ischemia in 1 eye leading to BCVA 6/18-6/36, secondary glaucoma in 2 eyes and vitreal haemorrhage in 1 eye both leading to BCVA 6/60 or worse.

5.3.3 *Treatment in ischemia.*

Table 5.5 Treatment of eyes which developed ischemia.

Treatment regimen	Ischemic eyes n=106 (%)	
Systemic steroids	39	(36.8)
Systemic steroids+steroid sparing	23	(21.7)
Anti TB agents+systemic steroids	6	(5.7)
IVTA/OFI	7	(6.6)
Vitrectomy	6	(5.7)
Laser	48	(45.3)

Systemic steroids were used to treat 68 eyes (64.1%). For 21.7% of eyes steroid sparing agents were associated. Mycophenolate Mofetil (Cellcept) was used in 6 patients, Cyclosporin A in 6 patients, Azathioprine in 4 patients, Methothrexate in 1 patient, and one patient was started on Infliximab. For 6 eyes, anti TB agents were used in combination with systemic steroids. Intravitreal and/or orbital floor steroids injections were performed on 7 eyes. Six eyes underwent vitrectomy, and laser treatment (PRP or sectorial) was performed on 45% of eyes with ischemia.

Chapter 6. Discussion.

6.1 Demographics

The last big study on visual loss in uveitis was conducted by Rothova et al.[300] in 1996 and included 585 patients. Durrani et al.[296] in 2004 conducted another observational study of 315 consecutive patients on degree, duration and causes of visual loss in uveitis. To my knowledge, this study is the largest to date on causes of visual loss in patients with uveitis.

The mean age at presentation of patients in this series (Table 3.2) is similar to what reported in many other series on uveitis worldwide [290, 713, 714]. In two studies from Bogota and Iran, patients were much younger with mean ages of 31.7 and 32.2 respectively [715, 716].

As in other reports [279, 290, 717], the sex ratio in this study (1:1.2) is slightly in favour of females.(Table 3.3)

Ratinham et al.[718] and Biswas et al.[717] reported lower incidences of 7.3% and 6.44% respectively in adults over 60 in this age group. The distribution of uveitis in different age groups in our series was similar to what many other studies have described. Eight percent of patients were aged between 3 and 16 years, 10% were in the age group older than 63. The majority of patients (82%) were aged between 25 and 63 years.

In a review of 22 studies representative of Australia, North America, Europe, Asia and Africa, Chang et al.[274] concluded that there were similarities and distinct differences in the pattern of uveitis in the various geographic regions. Such patterns may be induced by combinations of geographical, environmental and genetic factors.

The incidence of anterior uveitis in our series (Table 3.3) was similar to that reported in China, Japan, and some European studies, especially in the Netherlands, Germany and Italy [304,315,416,458,461]. Two previous studies in the UK reported incidences of 63 and 87.5% [310, 471]. Higher incidences of anterior uveitis were also reported in Finland, Australia and Turkey, respectively 87.5%, 76% and 52.5%.

The high prevalence of anterior uveitis in Finland was in accordance with the high frequency of the histocompatibility antigen B27 among Finns [292, 302,467]. On the other hand, low prevalences ranging from 22% to 29.6% have been reported in the United States and Japan [293, 673, 719-721].

In a population based study in India, Dandona et al.[271] reported an incidence of anterior uveitis as low as 13%. This could be due to the fact that cases of previous anterior uveitis which did not leave sequelae were overlooked. Looking at the patterns of uveitis in patients admitted to a University hospital in Riyadh, Saudi Arabia, anterior uveitis was reported in 12%. This low prevalence was a referral bias as most cases of anterior uveitis were treated by local ophthalmologists. In addition, most cases of anterior uveitis were investigated and treated in the outpatients clinic and not admitted [722]. In a literature review covering a 37 years period, Chang et al reported a shift in the relative frequency of uveitis cases from anterior toward posterior and panuveitis in tertiary referral centres [274].

Many reports have confirmed that chronic anterior uveitis tends to be more common in tertiary referral practices [226, 716, 721, 723, 724] The prevalence of chronic anterior uveitis reported in this study (Fig.3.1) was higher than that reported by Menezo and Lightman (64.7%) in the same hospital [723]. This could be a sample size effect; the Menezo series included only 68 patients.

Intermediate uveitis usually affects patients from 5 to 30 years old, without gender or racial preferences[131]. In this series, patients with IU were younger than those with AU or Pan and Pu (Table 3.2). The prevalence of IU reported in this study is similar to the report from the largest cohort so far in Germany and in India where intermediate uveitis was reported in 22.9% and 25% respectively [271, 725]. In many other series, the prevalence of intermediate uveitis was very low. Prevalences of 6.1% and 6.7% have been reported respectively in China and Turkey [714, 726], and 2% in Sydney [287] . Two different studies 6 years apart in Japan reported 6.9% and 1.2% of intermediate uveitis [720, 721]. Rothova et al. [300] in the Netherland reported 13%. Looking at these discrepencies, a question as to whether the diagnosis of intermediate uveitis can be easily made needs to be asked. These conflicting results show that intermediate uveitis is not uncommon as previously thought.

Posterior uveitis is reported in incidences varying from 6.8% in China to 31.2% in Japan[721, 726]. Incidences as high as 49.4% for panuveitis have been reported in Japan[720]. Jakob et al. [725] in Germany found 6.2%, and we report 33%.

A study in Canada revealed a striking difference in the subtypes of uveitis diagnosis by comparing ophthalmologist and non ophthalmologist referrals. In the non opththalmologist referral group, the authors found 92.8% AU, 5.4% IU, 1.8% Panuveitis, whereas in the ophthalmologist referral group, 67.4%, 14.0% and 18% we found respectively for AU, IU and Panu [727]. This

highlights the possibility of referral bias and the necessity of meticulous clinical examination in order to ascertain a definit line diagnosis.

We found that 29% of patients in our cohort had a systemic disease associated with uveitis (Table 3.4). Our findings are similar to what has been reported by Rothova et al. [228] in the Netherland reported (26%), and Boskovich et al.(31.3%) [728].

6.2 Vision loss in uveitis.

Although uveitis is a well known cause of blindness, there is only scant knowledge concerning the prevalence and incidence of uveitis among the blind. In most epidemiological studies dealing with blindness, uveitis was not considered a distinct entity [729-734]. The complications of uveitis, for example cataract, secondary glaucoma, and macular abnormalities, are included in many epidemiological studies about blindness, but how many of these are actually attributable to uveitis is not specified [730]. The largest population based study of the Western world, the Framingham Eye Study, illustrates this phenomenon: patients with blindness due to retinal toxoplasma lesions are classified as having macular degeneration; secondary cataract is indicated but carries no aetiological diagnosis for example, uveitis, trauma[730]. Blindness due to uveitis is usually not reflected in results reported on epidemiology of blindness and only few data are available about its incidence. It is estimated that it causes 10% to 15% of all cases of total blindness in the USA [2, 278]. The percentage of blindness in the Western world that was attributed to uveitis was similar in those studies where uveitis was reported, and varied from 3% to 7% of the total blindness [735-737].

Rothova et al.[300] reported that 35% of patients exhibited blindness or visual impairment; bilateral legal blindness developed in 4% patients, 4.5% had one blind eye with visual impairment of the other, 1.5% had bilateral visual impairment. Unilateral blindness developed 14% patients, whereas 11% exhibited unilateral visual impairment. The authors did not report visual acuity at presentation. We report 23.7% of patients who developed irreversible visual loss. The proportion of patients who developed all types of visual loss is low in our series (Tables 3.7; 3.8; 3.9). This improvement is certainely the result of more efficient treatment options developed over the last decade.

The incidence rates for visual loss in AU in this study are 0.03/EY and 0.05/EY respectively for visual impairment and for BCVA 6/60 or worse. The proportion of patient with AU who developed unilateral visual impairment is extremely high (16.3%), when Rothova et al [300] reported only 5%. The incidence rates for visual loss in IU are 0.04/ EY and 0.02/EY for visual impairment and severe visual loss or blindness respectively. While in the Rothova cohort no patient with IU developed

bilateral severe visual loss[300], we report 4.7% of patients with IU who developed bilateral severe visual loss. Jain et al [738] and Donaldson et al.[739] reported 3 eyes with IU which developed vsual loss of 6/60 or worse.

There is a lack of data on visual outcome at different time points in the literature. Since the publication on standardisation of uveitis nomenclature for reporting clinical data by the SUN group in 2005[124], to the best of my knowledge, this is the first study reporting detailed visual outcome at different time points in different uveitis types on a large scale (Tables 3.9 and 3.10)
Vidovic et al.[740] reporting on long-term course and visual outcome in IU found that the percentage of eyes with legal blindness and visual impairment gradually increased over time from 17% at onset to 28% at 10-year follow-up. They also found that one-third of IU patients achieved a remission of their intraocular inflammation for longer than 1 year and had a mean time to remission of 8.6 years. Patients who were younger at onset of IU were more likely to achieve remission than those who were older at onset. This was not confirmed from our data.

Panuveitis yields the worse visual prognosis, with incidence rates of visual loss of 0.08/EY for visual to 6/18- 6/36 and 0.13/EY for severe vision loss or blindness. Our findings are in accordance with other studies where it was reported that panuveitis was associated with poor visual outcome compared with other anatomical types of uveitis [226, 296, 300, 341]. The proportion of patients with panuveitis who developed different types of visual loss in our series was very low when compared with the Rothova series[300]. However the prevalence of bilateral severe vision loss or blindness in this study was similar to that in the latter study.(Table 3.8)

6.3 Causes of visual loss.

CMO regularly leads to a reduction in visual acuity and has been suggested to be a major cause of decreased visual acuity in patients with uveitis. Few data, however, are available on the impact of CMO on visual acuity for different uveitis entities [3, 226, 296, 300]. Rothova et al.[300] reported CMO as the main cause of blindness and visual impairment in 29% and 41% respectively. In the Durrani series[296], CMO accounted for 47% of causes of visual loss, 27% attributable to CMO solely, and 20% to the combination of CMO and cataract. In another study by Bodaghi el al [226], CMO was the main factor influencing visual outcome, with 18.3% of patients presenting the complication at the end of the observation period. Lardenoye et al.[341] reported that CMO caused visual loss in 44% of patients. In their series, patients with intermediate uveitis and panuveitis had the highest frequency of CMO 60% and 66% respectively, and a similar frequency of CMO leading to visual loss, respectively, 40% and 52% of patients. Except in the study by Rothova et al.[300], the

other studies did not specify the role of CMO in the two main categories of vision loss e.g visual impairment and severe visual loss or blindness. We report respectively 28.6% and 10.1% of visual impairment and severe vision loss caused by CMO, incidences by far lower than reported in previous studies. The incidence of CMO in eyes with IU in this study is higher than in AU or panuveitis or posterior uveitis. The incidence of CMO in IU reported in this study was similar to that reported in previous studies [300, 741]. We also report here that this complication decreased with time, from 61.3% at 1 year follow-up to 8 % at 10 years follow up in the group of eyes that developed BCVA 6/18- 6/36, and from 28% at 1 year follow up to only 1% at 10 years follow up in the group of eyes with severe visual loss or blindness.(Tables 3.11 and 3.12). The incidences of CMO in this study should be interpreted with caution because sequelae of CMO are reported separately. Moreover, we have reported only CMO causing visual loss.

Previous studies documented various prognosticators of poor visual outcome in uveitic macular oedema, including prolonged duration of the uveitis and of CMO itself, a large foveal avascular zone, the presence of an incomplete vitreous detachment, and increased macular thickness on optical coherence tomography (OCT)[325, 341, 742]. The advanced age of patients was reported to be an independent factor for early development and poor outcome of CMO in uveitis [325, 677]. We did not report on macular thickness, foveal avascular zone, or vitreous detachment. These limitations were related to the design of our study. However, we found a significant correlation between CMO and the duration of intraocular inflammation (p=0.034). Age at onset did not influence CMO (p= 0.68).

Although CMO can resolve after treatment, its sequelae with macular scarring caused visual impairment and severe visual loss respectively in 41% and 36.4% and these sequelae increased with time,($p < 0.001$).

Glaucoma represents a severe complication of uveitis. Herbert et al.[743] reported a 41.8% prevalence of raised IOP in uveitic eyes and found that raised IOP was present in 26% of eyes with acute uveitis and 46.1% of eyes with chronic uveitis. The authors reported that active inflammation was significantly associated with raised IOP, and Steroid usage, increasing age as well as number of years since diagnosis were significantly correlated with raised IOP. In their series, 9.6% of eyes with raised IOP developed glaucoma. Heinz et al.[744] also reported that patients with chronic inflammatory eye disease had a substantial incidence of glaucoma, increasing with time up to 22.3% after 10 years of follow-up. In their report, 8.8% of patients developed secondary glaucoma. McCluskey et al.[745] reported that uveitis accounts for 10% of blindness in people aged under 65

and pointed out glaucoma as one of the most insidious and, unfortunately, often overlooked complications.

Neri et al.[746] reported 16.6% of glaucoma in patients with chronic uveitis. They found an incidence of 6.5% at 1 year follow up, 11.2% after 4 years and 22.7% after 10 years. In their series, the probability of developing glaucoma in different topographic types of idiopathic uveitis was not different. Rothova et al.[300] found that 11% of uveitis patients developed visual impairment attributable to secondary glaucoma. Higher prevalence of glaucoma (23%) has been reported by Panek et al.[368]. Merayo et al.[349] reviewing the hospital records of patients with uveitis referred to the immunology Service of the Massachusetts Eye and Ear infirmary found that 9.6% of uveitis patients developed secondary glaucoma.

In this study, 16.7% of eyes developed secondary glaucoma. The complication was predominant in eyes with AU (Table 3.13). This can be explained by the fact that there is more damage to the trabecular meshwork when the intraocular inflammation affects the anterior segment. In a study using UBM to characterize the inflammatory changes in the anterior segment in patients with AAU, Yang et al.[185] showed severe changes in the anterior and posterior chambers, and in and around the ciliary body and anterior vitreous at the peak of the inflammation. Although the study assessed changes in acute inflammation, it can be extrapolated that when the inflammation lasts longer, more damage to the iridocorneal angle will occur.

As in previous studies [744, 746], we find that glaucoma increased with time. In this study, 15% of visual impairment and 18.2% of severe visual loss or blindness was caused by secondary glaucoma. The main systemic disease associated with secondary glaucoma was sarcoidosis.(Table 3.16)

Hypotony from decreased production of aqueous humor is often due to inflammation, medications, or proliferative vitreoretinopathy[747]. Chronic hypotony may lead to visual loss and structural changes that alter the function and appearance of the eye [748]. There are very few reports in the literature on hypotony related to uveitis. The largest case series addressing hypotony related to uveitis was published recently by Kapur et al.[749]. Most reports on hypotony in uveitis are case series addressing the management aspect. The actual incidence of hypotony in the context of uveitis is not known. In this study, we report that 12 eyes (2%) developed vision loss due to hypotony secondary to uveitis. Of the 12 eyes which developed hypotony, 6 had CAU and 6 had panuveitis. When looking at the impact on visual acuity, 1% of visual impairment and 3% of severe visual loss or blindness were attributable to hypotony.

Twenty seven eyes (4.1%) developed vision loss attributable to macular ischemia. Of these, 70.3% developed severe visual loss or blindness. Results on ischemia will be discussed further in this section.

The frequency of retinal detachment (RD) among patients with uveitis is not known. In the general population, the incidence of rhegmatogenous retinal detachment (RRD) is approximately 1:10,000 [750]. The frequency of RRD increases with age, the presence of myopia, and after intraocular surgery. It is not known whether the presence of uveitis forms an additional risk for the development of RRD. Hagler et al found that among 2618 patients who underwent surgery for RRD, 44 (1.7%) had previous uveitis[751]. Bosch-Driessen et al. [752] reported that in patients with ocular toxoplasmosis, the frequency of RRD was higher than that of the nonuveitis population, namely 6%. Kerkhoff et al[750] identified a prevalence of 3.1% for retinal detachment in a cohort of 1387 patients with uveitis. RRD occurred predominantly in patients with panuveitis and in those with infectious uveitis, especially in HSV- and VZV-induced retinitis, and the visual outcome was poor[750]. So far, the presence of uveitis has not been associated with a high risk of developing RD, except for specific uveitis entities such as Vogt-Koyanagi-Harada syndrome, ARN, and more recently ocular toxoplasmosis [548, 752, 753]. Population based studies have reported the association between RRD and increasing age [754-756]. The peak incidence of RRD is in the seventh decade and was linked to the increasing prevalence of posterior vitreous detachment (PVD) also occurring in older age [757, 758]. In the Kerkhoff et al.[750] series the mean age of patients with RRD was 42 years, which was significantly lower than in the RRD controls. The authors hypothesized that RRD occurred early in uveitis patients because of the PVD occurence at an earlier age in uveitis [759]. Hikichi et al.[760] investigated the effect of intraocular inflammation on the vitreous and suggested that inflammation induced crosslinks in the collagen of the vitreous, which may damage the gel structure integrity and induces liquefaction of the gel, which is a mechanism that induces PVD. The frequency of RD in this study is in concordance with previous studies [750, 751]. We also find a high prevalence of RD in panuveitis as described in the literature. Kerkhoff et al. and Romero et al. reported that the final visual prognosis for patients with RRD and uveitis was poor, most eyes ending up with BCVA 6/60 or worse[663, 750, 751]. In this study, 70% of eyes with RD and uveitis developed severe visual loss or blindness.

Phthisis bulbi is reported as a complication of severe ocular inflammation [761-765]. Atmaca et al.[766] reported 0.8% of phthisis in Eale's disease. In a review of ocular complications in paediatric uveitis, Rosenberg et al.[767] found 4.1% of phthisis bulbi. The incidence of phthisis in this

study was similar to what reported in the literature. Seventy percent of phthisis developed in eyes with panuveitis, and the complication occurred from 5 years onwards (p=0.002) (Table 3.12).

When looking at systemic diseases associated with different ocular complications, we found that sarcoidosis was the main condition associated with CMO, glaucoma and hypotony. BD was the main disease associated with optic atrophy. In patients who developed macular ischemia, BD and SLE were the most commonly found diseases (Tables 3.16).

6.4 Systemic diseases.

Sarcoidosis occurs worldwide but is predominant in certain ethnic and racial groups (for example, US blacks, Scandinavian and Irish caucasians)[768]. The frequency of sarcoidosis is reported to be low in various parts of the world [769, 770]; it is not known whether this low frequency of sarcoidosis is genuine or whether it represents an underdiagnosis owing to the frequent occurrence of subclinical course, similarity with other diseases, or absence of firm diagnostic criteria. The first international workshop on ocular sarcoidosis (IWOS) proposed diagnostic criteria based on ocular signs, laboratory investigations, and biopsy results [565]. Ocular involvement manifests in 25%–60% of patients with systemic sarcoidosis[700]. This percentage depends on the population studied and the extent of ocular examinations. Japanese sarcoidosis patients develop ocular disease in more than 70% of cases [771].

The most common ocular manifestations are uveitis (30%–70%) and conjunctival nodules (40%) [609, 772]. In large surveys of uveitis patients, the frequency of sarcoidosis was about 5%[700]. Sarcoidosis is one of the most common systemic disease associations with uveitis in the USA and Europe accounting for 3-7% of non infectious uveitis cases [226, 773]. Traditionally, the most common type of sarcoid associated uveitis was attributed to anterior uveitis. It is noteworthy that the high frequency of sarcoid associated anterior uveitis (70%–75%) was noted mainly in the studies where the majority of patients were black [300, 774-776]. Black patients present typically with more severe and acute disease whereas Caucasians usually have asymptomatic and chronic disease [770]. Ocular disease may be the initial manifestation in sarcoidosis and may progress to severe visual impairment or even blindness. Two peaks of incidence were reported for ocular sarcoidosis, the first at ages 20–30 years and the second at ages 50–60 years[777]. Rothova et al.[777] evaluating the risk of developing ocular involvement in patients with biopsy proven sarcoidosis reported that 58% developed uveitis, and that 43% of patients who developed uveitis were black. The authors also found that black patients tend to develop AU, whereas caucasians develop PU. Birnbaum et al.[778] reported that African American patients were more likely to be

diagnosed as having uveitic sarcoidosis and to present with uveitis if they were younger than 50 years, while caucasians were more likely to present when they were older than 50 years. Adan et al.[779] found uveitis as the presenting manifestation of sarcoidosis, especially in women over 60 years of age, with bilateral panuveitis and chronic bilateral anterior uveitis being the most common clinical presentations. In a recent study, Gregoire et al.[780] found Sarcoidosis in 37.4% of patients aged 60 and over who developed uveitis.

Rothova et al.[777] reported that uveitis preceded the non-ocular signs of sarcoidosis in about 30%. In a study by Lobo et al.[781], it was reported that posterior uveitis was evenly distributed between black and white patients. It is noteworthy to mention that in their series like in our own, it was not possible to identify the race of all patients.

In another study, Rothova reported that the visual impact of sarcoid associated uveitis was severe, about 10% of patients developed blindness in at least one eye[300]. Stavrou et al.[782, 783] found that the main cause of visual loss in sarcoidosis related uveitis was cystoid macular oedema. The poor visual prognosis was associated with the advanced age of patients, black race, female sex, chronic systemic disease, and also with posterior segment involvement, peripheral punched out lesions, and the presence of cystoid macular oedema and glaucoma. Chronic anterior uveitis may lead to secondary cataract, glaucoma, and cystoid macular oedema; corneal band keratopathy may also develop [300]. Jabs et al. [775] reported that chronic uveitis and secondary glaucoma were poor prognostic signs, as 73% of patients with uveitis and glaucoma suffered severe visual loss. In a series by Lobo et al., 32% of patients had AU, 21% IU and 46% Pan/Pu. Bilateral disease was seen in 86% and it was not always symmetrical at presentation [781]. The authors reported that 11% of eyes developed visual impairment, 9% developed severe visual loss and found greater age as a risk factor for visual loss. The main causes of visual loss in their study were cataract, glaucoma, macular oedema, vitreous haemorrhage and retinal detachment.

In this study, the proportion of patients who had sarcoidosis associated with uveitis was similar to that reported in previous studies.(Tables 3.14 and 3.15). The prevalence of sarcoidosis in patients aged 60 or more was higher when compared with young patients and similar to that reported in studies by Gregoire et al.[780] and Birnbaum et al.[778].

As in many other reports, females were more affected than males. The majority of patients in our series developed AU.

The prevalence of vision loss with time in this study was lower than that reported by Lobo et al[781] in the same institution. One explanation to this difference could be found in the fact that in the latter study, the cut- off for vision loss was 6/12, while in this study we considered 6/18 as recommended by the SUN group. The proportion of eyes which developed severe visual loss in this

study was similar to that reported by Rothova et al. [300] in sarcoidosis associated uveitis (Table 3.17). We did not find any incidence rates reported in the literature, therefore could not make any comparison.

As in previous studies, we found that the increased risk of a poor outcome is confounded by the adverse influence of increased age at presentation on the visual acuity at follow up. Rothova et al.[700] reported that visual loss was associated with posterior segment involvement and was caused by cystoid macular oedema in the majority of cases. The prevalence of glaucoma was low in the study by Lobo [781], probably because of the lower prevalence of chronic anterior uveitis and the small size of their sample.

In this study where AU was predominant, glaucoma was the most important cause of visual loss, followed by chronic macular damage.(Tables 3.18 and 3.19). Our findings were in concordance with reports by Jones et al[784] and Jabs et al[775]. Although cataract surgery has been shown to be highly successful[785], glaucoma still appears to carry a poor visual prognosis in patients with chronic ocular sarcoidosis, presumably related to a greater inflammatory insult [775, 776] (Tables 3.18 and 3.19).

Behçet's disease (BD) is a multisystem disorder that was described in 1937 by the Turkish dermatologist, Hulusi Behçet (1889-1948) as consisting of the triad of ocular inflammation and oral and genital ulcers. Other systemic manifestations include erythema nodosum, cutaneous thrombophlebitis, arthropathy, gastrointestinal disturbances, and, less commonly, central nervous system involvement and major vessel thrombosis. BD is prevalent in countries lying along the ancient Silk Road, a route of travel and commerce from the eastern Mediterranean to East Asia. Epidemiologic studies have shown that Turkey has the highest prevalence with 20-420 cases per 100,000 [786-788], followed by Japan, Korea, China, Iran, and Saudi Arabia, where the frequency has been reported to range from 13.5 to 22 cases per 100,000 [787, 789]. On the other hand, the prevalence is much lower in Western countries: 0.64 cases per 100,000 in the United Kingdom and 0.12-0.33 per 100,000 in the United States[789]. In a population-based study covering a 45 years period, Calamia et al.[790] recently reported an overall incidence estimate of 0.38 per 100,000 population in the USA. BD is slightly more frequent and has a worse clinical course in men (they have a higher risk of eye involvement and of visual loss, cardiovascular and neurological involvement, a younger age of disease onset and worse evolution of clinical features) [791, 792]. It usually develops between the third and fourth decades of life, rarely appearing before puberty and after the age of 50 [793-796]. The disease generally is more severe in patients with a younger onset age. However, recent studies, one from Korea and one from Turkey, suggested that late-onset BD (age of onset at

or after 40 years) may not be associated with a milder evolution [794, 797].

This study is in agreement with previous reports[794, 798] where males predominated in both centres, in contrast to studies which suggested a more even distribution of disease between the sexes [799] and a predominance of females[790]. The mean age of patients at presentation in this series was similar to what reported in many other studies [556, 790, 800]. In reports from Iran and Turkey [791, 798], patients were younger than in reports from the western world. Similarly to many data in the literature, we did not find a difference in age at first presentation between males and females. In our cohort, only 6 patients were aged below 25, and none were 16 or younger. This confirms the fact that childhood BD is rare in the UK.

The pattern of types of uveitis reported in this study (Table 3.20) is in agreement with most reports Panuveitis or posterior uveitis occur in the majority of patients, while AU has been reported in proportions of 5- 10% [801, 802].

Reports published prior to 1992 indicated that long-term visual prognosis for ocular BD patients was generally poor, and in 60–80% of these cases, visual acuity deteriorated to less than useful levels (worse than 6/60) during the 10-year period following initial diagnosis[561, 803, 804]. However, recent reports have shown some improvements in the visual prognosis for these patients [791, 801, 805, 806]. Notably, reports published after 2004 indicated obvious improvements in 21–34% of patients [805, 806]. Yoshida et al.[806] comparing clinical findings in patients with BD seen in 2 different decades (1980s and 1990s) in Japan reported that 37% of the patients seen in the 1980s had poor VA (6/60 or worse) at the first visit, and this decreased significantly in the 1990s. Tugal-Tutkun et al.[791] reported that at the beginning of the follow-up, potential visual acuity was 6/60 or worse in 30.9% of eyes in males and 24.2% of eyes in females. The Kaplan-Meier survival analysis in their study estimated the risks of losing useful vision (>6/60) at 5 and 10 years for males and females as 21% vs 10% and 30% vs 17%, respectively and found that male patients who presented in the 1990s had a significantly lower risk of losing vision compared with male patients who presented in the 1980s. The incidence of severe visual loss or blindness in this study(Table 3.22) was similar to that reported by Muhaya et al [556] in a comparative study between patients with BD in Japan and in Great Britain. Kaçmaz et al.[801] reported incidence rates of 0.12/EY and 0.09/EY for BCVA 6/15 or worse and 6/60 respectively. The incidence rates reported in the present study were low for both visual impairment and severe visual loss or blindness when compared with the latter study. Kaburaki et al.[807] recently reported that uveitis related BD is particularly aggressive during the first 3 years after its onset, and clinicians should take particular caution during that period. Demiroglu et al. [808] also suggested that treatment of ocular BD within 2 years of disease onset is very important. Another study reported that the number of ocular attacks per year was higher in cases of BD with

poor visual prognosis (6/60 or worse) than in those with good visual prognosis (better than 6/60)[805]. Kaçmaz et al.[801] also suggested the significant relationship between the loss of VA to the 6/60 or worse level and activity of ocular inflammation. In this series it was not possible to establish the frequency and the severity of attacks because of the retrospective nature of the study with no standardization of records, and we could not determine with certainty whether patients with ocular inflammation were seen at this tertiary referral centre within the critical period of 2 years from disease onset. Cho et al. [809] reported that while the long-term visual prognosis for BD uveitis may be affected by many factors, the initial visual acuity appears to be the most significant. Similarly, we found a highly statistically significant correlation between visual acuity at presentation and at final floolw- up visit ($p<0.001$). (Fig.3.3)

Recurrent attacks of inflammation lead to secondary complications namely, posterior and/or peripheral anterior synechiae, iris atrophy, cataract due to inflammation and/or medication, secondary glaucoma (sometimes neovascular), atrophic retina, optic atrophy, macular oedema, macular degeneration, retinal veins occlusion, sheathed vessels, chorioretinal scars and/or proliferative vitreoretinopathy, phthisis bulbi [691, 810, 811]. Repeated ocular attacks result in limited visual recovery and in irreversible alterations of the sensory retina even after the inflammation is under control, which is not typical in the eyes with other types of uveitis[789]. Yu et al.[812]reporting on fluorescein angiography and visual acuity in active uveitis with BD found that diffuse vascular leakage and diffuse macular leakage were the predominant angiographic findings, followed by disc leakage, CMO, peripheral capillary nonperfusion, macular window defect, macular ischemia, and disc neovascularisation in eyes from BD patients and that the main destructive mechanism of BD was vasculitis.

The vasculitic and vasoocclusive episodes in BD uveitis can cause capillary dropout resulting in capillary nonperfusion or macular ischemia[424]. Retinal atrophy, retinal exudates, haemorrhage and retinal–choroidal degeneration may collectively form a macular window defect [813]. These FA characteristics were identified in eyes with chronic and irreversible cases that may not respond to immunosuppressive treatment [812]. In the series by Kaburaki et al.[807], chronic macular damage accounted for 80% of severe visual loss or blindness, optic atrophy and phthisis for 14.3% and 2.4% respectively. Kaçmaz et al.[801] found that 13% and 6.4% of eyes with severe visual loss had chronic macular damage and CME respectively while 4.3% developed optic atrophy and 1.4% had glaucoma. Benchekroun et al.[814] reported 24% of severe visual loss caused by chronic macular damage and 17% by CMO. In this study, we report a higher incidence of optic atrophy and glaucoma than that reported in previous studies. The prevalence of CMO as a cause of severe visual loss in the present study is similar to that reported by Kaçmaz et al.[801] (Tables 3.21 and 3.22). When looking at

different data in the literature, it is surprising that macular ischemia is rarely mentioned. We report 16.7% of severe visual loss or blindness due to macular ischemia. In this study, the patients' profile corresponds to that reported in the literature. In Turkey, the mean age for patients with BD who develop uveitis is 28.5 years and 30 years for males and females respectively [791]. In a series from Taiwan, the male-to-female ratio was 1:6 [815]. Panuveitis is the most common ocular manifestation associated with BD reported in most studies [802, 816]. Our findings are consistent with this pattern. (Table 3.20)

A study from 25 eye centres in 14 countries emphasised that Behçet's disease is still a blinding disorder despite modern treatments, with one quarter of the patients becoming blind [817]. Kump et al.[818] analyzing differences in response to the treatment of ocular Behçet's disease (BD) in the 1960s, 1980s, 1990s found a definitive trend towards improvement in clinical outcome from the 1960s to 1990s. Statistical analysis showed that the mean logMAR score decreased with each decade as a result of newer and more potent corticosteroid-sparing agents being used. However, Kaçmaz et al[801] found that loss of visual acuity and occurrence of ocular complications were common in patients with ocular inflammation associated with Behçet's disease, even with aggressive therapy, persistent inflammatory activity being one of the risk factors for visual impairment. A recent study by Takeuchi et al.[819] demonstrated that visual acuity, sensitivity and retinal thickness decrease with the duration of uveitis in Behçet's disease. This suggests that ocular inflammation in patients with Behçet's can cause severe visual impairment. In the present study, after an improvement at the end of the first year, visual acuity continued to decrease as a result of subsequent ischemic events.(Fig.3.3)

The association between anterior uveitis and diabetes is well known. Despite DM being implicated as a cause of uveitis, little is known about the clinical features of uveitis occurring in patients with preexisting DM[618]. Data on diabetes and uveitis are scarce in the literature. Brewitt at al.[820] found that out of 103 patients with uveitis, 14.5% cases showed pre-clinical diabetes, outnumbering by far the average frequency of approximately 6% of pre-clinical diabetes and concluded that diabetes mellitus was assumed to be a co-factor of the development of uveitis. Rothova et al.[616] reported a prevalence of 6% of patients with AU associated with diabetes. We found diabetes mellitus associated with intraocular inflammation in 4.2%, and the prevalence of diabetes in AU that we report is similar to that reported by Rothova in the latter study (Table 3.24). In an immunological study, Castagna et al.[615] underlined the correlation between AU and type I diabetes. They suggested that the high level of CD8+ T cells found could be an expression of unstable lymphocytic equilibrium. Most of our patients were Type 2 and not induced by the steroid drugs,

few were type I. Looking at clinical features of patients with diabetes mellitus presenting with their first episode of uveitis, Oswal et al.[618] reported that patient may present with severe intraocular inflammation, and found in their series that 31% had the BCVA between 6/18 and 6/60, 22% had BCVA= 6/60 or worse. Probst et al. [821] found elevated intraocular cellular fibronectin (cFN) levels in eyes with uveitis and DM, especially in those with active disease, intraocular vascular damage, and macular edema. Their findings suggested that locally produced cFN levels reflect intraocular vascular damage. It is noteworthy that visual loss in the Oswal series[618] was not merely caused by ocular inflammation and its complications, but 42% of eyes had diabetic retinopathy. We found in this study that diabetic males tend to develop uveitis earlier than females. In our cohort, diabetic patients with uveitis and diabetic retinopathy affecting their visual acuity were not included. We report here incidence rates of 0.036/EY and 0.026/EY for visual loss to 6/18-6/36 and 6/60 or worse respectively. There are no reports on incidence rates in diabetes associated uveitis in the literature to allow any comparison with our findings.

Birnbaum et al.[822] reporting on etiologies of AU at a tertiary referral centre over 35 years found that Multiple sclerosis (MS) showed an increase of approximately 1% in the latest decade (1995–2004) when compared to the earlier decade (1975–1984). The diagnosis of MS has increased in recent years, perhaps related to the increased use of neuroimaging and/or the increased lifespan of patients diagnosed with MS [823]. MS is reported to be associated with uveitis in 1-2% [226, 577]. MS and uveitis are associated with immune dysregulation and the diagnosis of MS is more likely to precede that of uveitis[576]. Biousse et al.[575] reported a 9 years delay between the onset of neurologic and ocular symptoms, emphasising the importance of a sequential diagnostic search throughout the patient's course. Looking at the frequency of uveitis among MS patients, Le Scanff et al. [572] reported that uveitis preceded the onset of MS in 46% of the patients; it occurred simultaneously or after MS, in 18% and 36% of the cases, respectively. Edwards et al.[576] investigated 658 consecutive outpatients attending a specialist MS clinic and found that 2.28% had the association of symptomatic uveitis and MS. In another series, Zein et al.[577] reported that the diagnosis of MS preceded the onset of uveitis in 56%, followed it in 25%, and was made concurrently in 19% of the cases. In a series by Towler et al.[579] the majority of patients had documented MS at the time of presentation of their uveitis, three did not and there was a considerable time-lag before the onset of their neurological disease.

The prevalence of MS and the female predominance in this study was in concordance with most data in the literature. We found that 69% of patients had the diagnosis of MS before they develop uveitis, and the mean time interval between the diagnosis of MS and intraocular inflammation was 8 years. The clinical pattern of uveitis occurring in multiple sclerosis is wide-

ranging and may cover the full range of clinical manifestations [575, 577, 579, 824]. The features of uveitis in the series by Towler were non-specific in that they could occur in association with other disorders, and were of no value in predicting the subsequent development, clinical type or course of MS, unlike the known association of asymptomatic peripheral periphlebitis with optic neuritis and its predictive value for a subsequent diagnosis of MS. They reported intermediate and posterior as the commonest types of uveitis[825]. Granulomatous uveitis has been noted to occur in MS patients[577] and attributed to MS when the typical diseases associated with granulomatous uveitis (tuberculosis, sarcoidosis and syphilis) have been excluded [826], and this has been hypothesised to be at least partly due to the disordered immunity occurring in MS [827]. Boskovich et al. [728] identifying the clinical features of intermediate uveitis and assessing its association with systemic diseases found that 7% of patients with IU had MS associated. Khairallah et al.[828] reported 2.3% of MS associated with IU. Following Rucker's first report of the association of retinal periphlebitis with multiple sclerosis (MS) in 1944[829, 830], the observation has been confirmed by many other studies [831-833]. The reported incidence of retinal vascular sheathing has varied considerably in different series, from as low as 2% to 44%, but with an average of around 20%[834]. In the majority of patients the retinal vascular changes are not associated with symptoms and are not a threat to vision. In addition, the presence of peripheral retinal venous sheathing in individuals presenting with isolated optic neuritis has been shown to be predictive of the subsequent development of MS, with a relative risk of 14.4[825]. In this series, we report IU in 83% and the prevalence of MS among all cases of IU was similar to what reported in other series. Over the follow-up period, visual outcome was very satisfactory as only 1 eye developed visual loss of 6/18-6/36 due to macular damage and 1 eye developed severe visual loss due to optic atrophy. CMO was the main cause of visual loss in the Towler series. Better management options of this complication have been developed over the last decade, and this explains its absence from our study.

Vogt-Koyanagi-Harada (VKH) disease is a chronic, bilateral, granulomatous panuveitis and exudative retinal detachment associated with poliosis, vitiligo, alopecia, and central nervous system and auditory signs[548]. Exudative retinal detachment during acute disease and sunset glow fundus during the chronic are highly specific to this entity [551]. Results from previous studies have shown that, worldwide, VKH disease is slightly more common in Japan (10.1% of all uveitis referrals) and less common in the USA (1–4%)[548], India (2%) [835] and Brazil (2.5%) [550]. Prevalences as high as 18 to 35% associated with panuveitis were reported in Los Angeles [280], and up to 38% in one study in Argentina [836]. Most studies have reported a female predominance.

Ocular complications of VKH syndrome include cataract, glaucoma, serous retinal detachment, subretinal fibrosis, subretinal neovascularisation, epiretinal membrane formation,

macular atrophy or pigmentary degeneration [837, 838]. In the series by Moorthy et al.[548], cataract developed in 25%, glaucoma in 33% and subretinal neovascularisation in 10%. Khairallah et al [839] reported cataract in 33.9%, glaucoma in 16.9% and subretinal neovascularisation in 1%. In their series 40.8% of eyes had BCVA 6/60 or worse at presentation. In another series by Al-Karashi et al.[840], 31.6% of eyes had severe visual loss. A similar proportion of eyes with BCVA 6/60 or worse at presentation was reported by Chee et al.[841]. Initial visual acuity was also shown to be significantly associated with final visual acuity by Read et al. [842] and Ohno et al. [843] with those eyes possessing better visual acuity at presentation more likely to have better final visual acuity and conversely those eyes with poor acuity at presentation more likely to have poor final visual acuity. If initial presenting VA has been found to correlate well with final visual outcome in most studies, Chee et al.[841] found that the VA at one month after starting treatment was an important prognostic factor. They reported that eyes that had good VA at one month were more likely to have good VA at three years, and were less likely to develop persistent/recurrent inflammation, cataract, or CR degeneration. This was consistent with the finding of better outcomes in eyes that had received early and adequate immunosuppressive therapy [844-846]. Hence, the response to treatment is the main prognostic indicator for a good outcome and VA at one month is a useful early indicator of the adequacy of treatment. Therefore, patients who have not achieved a VA of better than 6/60 at one month after starting treatment should be considered for more aggressive immunosuppression[841]. Rubsamen and Gass [847], however, found no correlation between visual acuity at presentation and final visual acuity.

The prevalence of VKH in our cohort was similar to that reported in other studies in Western countries. We also report a predominance of female (sex ratio 3:1). The proportion of eyes with vision loss at presentation was lowerr than that reported in previous studies. We found a strong correlation between visual acuity at initial presentation and visual acuity at final follow-up visit (P = 0.003). Chronic macular damage was the main cause of visual impairment, and 2 eyes developed glaucoma leading to severe vision loss. Noteworthy, our sample of VKH patients was very small, so we could not draw more on statiscal analysis. However, visual outcome was overall satisfactory.

JIA is the most common rheumatic disease in childhood, occurring in approximately 1:500 children[848]. Pauciarticular JIA is associated with intraocular inflammation (uveitis) early during the arthritic disease course[589]. The mean age at the uveitis diagnosis was 4.5 years in the Marvillet's series [588]. In their cohort, uveitis antedated joint manifestations in 13% of patients; in 24.7% both were diagnosed simultaneously; and in 62.3% arthritis antedated uveitis. It was not possible for us to determine which between uveitis and arthritis preceded. Sixty percent of patients with JIA related uveitis in the present study were females. The female predominance reported in this study is in

agreement with the literature. Saurenmann et al [584] reported that among girls, the risk was maximal (47%) in those who were ANA positive and were ages 1-2 years at the time of the onset of JIA; this risk decreased to <10% in those in whom the age at onset was >7 years. AU is the most common uveitis reported. It accounted for 60% in this study. Patients considered at higher risk of developing JIA related uveitis are those with an age of onset of arthritis under 7 years, pauciarticular involvement and positive ANA titers. Ophthalmological examinations of these patients are recommended every 3 months. Medium risk patients include those with an age of onset under 7 years, polyarticular or pauciarticular involvement, and negative ANA titers. All pauciarticular patients with onset after age 7 are also considered at medium risk. Ophthalmological examinations are recommended for medium risk patients every 6 months. All patients with systemic JIA are considered low risk, and ophthalmologic examinations are recommended annually [588]. Marvillet et al.[588] recommended ophthalmological follow-up at regular intervals, even if their joint disease is quiescent. In a study covering an eight years period, Bolt et al.[849] reported that uveitis occurred in 35/265 patients (13.2%) of their JIA cohort. In a series by BenEzra et al.[589], uveitis was detected in 9.2% of children with JIA during the first ophthalmic examination and in an additional 11.2% during the follow up period of up to 15 years. Twelve percent in their study presented initially with uveitis. The authors reported that in children developing uveitis before or along with arthritic manifestations, the ocular disease was chronic with a high rate of secondary complications (band keratopathy, glaucoma, posterior synechiae and cataract). In all affected eyes the initial ocular inflammation was typically confined to the anterior segment. On longer follow up however, most children developed binocular disease and posterior segment involvement [589]. In a cohort of 55 consecutive patients with JIA associated uveitis, Skarin et al.[850] found that uveitis was still active 24 years after onset. They reported that cataract developed in 42% at 7 years, and in 51% at 21 years, uveitic glaucoma developed in 5% at 7 years and in 22% at 24 years. Looking at visual outcome of children with JIA associated uveitis, Kump et al.[851] found that 64% developed cataracts, 20% developed increased intraocular pressure, and 46% developed band keratopathy.

JIA-associated uveitis has been reported to result in significant impairment of visual acuity as a consequence of structural ocular complications such as cataract, band keratopathy within the macular axis, glaucoma, and macular pathology [852]. The same was reported by Thorne et al.[853]in a recent study. In their series, Woreta et al[585]also reported 67% of ocular complications at presentation. They found that 36% and 24% of eyes had respectively BCVA 6/15 or worse and 6/60 at presentation. Thorne et al. [853] reported incidence rates of 0.10/EY and 0.08/EY for BCVA 6/15 or worse and 6/60 or worse respectively. They reported incidence rate of 0.04/EY for cataract. The proportion of eyes with BCVA 6/18-6/18 at presentation in this study was inferior to that

reported by Woreta et al. [585], but we report a higher proportion of eyes with severe visual loss or blindness at first visit. Incidence rate for cataract in our study was similar to that reported by Thorne et al [854], but rates for vision loss were by far lower than that reported by the same authors in another study [853].

While male gender has been reported as an independent risk factor for poor visual outcome in previous studies [376, 855], we did not find a gender influence on visual outcome. This could be a sample size effect.

When we consider the high proportion of patients who presented with severe visual loss or blindness and the mean age at first visit in our series, there could be a referral bias in that only the most severe cases of JIA-associated uveitis were referred. The delay in referring to a tertiary care centre or uveitis specialist has been reported to be a risk factor for poor clinical and visual outcomes in patients with JIA associated uveitis, presumably because of the delay in aggressive management of the inflammation [856]. While it is generally accepted that JIA related uveitis bears a reserved visual prognosis, Sabri et al.[857] and Bolt et al.[849] reported good visual outcome in JIA-associated uveitis despite uveitic complications. Heilingenhaus et al.[858] suggested that in order to reduce severe disease at presentation and achieve an excellent long term visual outcome, earlier ophthalmological screening should be initiated after arthritis onset and the intervals be related to the JIA subgroup.

6.4 Idiopathic uveitis.

Birdshot chorioretinopathy (BSCR) is a chronic intraocular inflammatory disease of unknown origin that is responsible for 1% to 2% of all uveitis cases [229, 290, 300, 478]. It occurs in the early to mid fifties [482]. BSCR is predominantly considered to be an ocular disorder without systemic manifestations [477]. Occasionally, systemic hypertension has been noted, and a small number of patients complained of hearing loss, vitiligo, and mood disorders[859]. Rothova et al. [860] found the prevalence of systemic hypertension as high as 46%. This high prevalence of hypertension could be explained by the fact that in the Dutch population older than 55 years, 31% to 39% suffer from systemic hypertension [860]. The course of BSCR is, in the majority of patients, chronic and progressive. Various studies have shown that BSCR usually remains active for approximately 10 to 12 years, and after that the active inflammation slowly declines, resulting in atrophic changes of the retina and optic disc [861, 862]. One study reported a self-limiting course in 20%[861]. Although some authors argued that BSCR is most severe during the first 2 to 4 years of activity and, in consequence, requires most aggressive treatment in this initial period of the disease, others report

on a prolonged course with frequent remissions[863]. In a literature review, Shah et al.[479] reported that Birdshot choroidopathy is a slowly progressive disease with profound dysfunction of vision that may not be reflected in Snellen visual acuity, and CMO is the main cause of visual loss. Oh et al.[864] looking at the long-term course of BSCR at the University of Iowa found that the retinal function in this inflammatory ocular condition deteriorated progressively over a period of years despite stable visual acuity. In their study, they reported that late in the course of the disease, visual acuity may be lost due to chorioretinal atrophy in the posterior pole, and that visual acuity alone was not an adequate parameter with which to monitor disease activity as it may falsely suggest that the patient is stable or well. Rothova et al.[860] reported a gradual loss of VA, and a long association between VA at onset and visual outcome after 5 and 10 years. In their series, 8% of eyes had BCVA 6/60 or worse at presentation, proportions increased to 30% at 5 years follow-up and to 39% at 10 years follow-up.They did not find any difference in annual loss of VA between patients on standard treatment and untreated patients. They concluded that the visual prognosis of BSCR was poor in the spectrum of uveitis. Thorne et al.[865] reported that in affected eyes, the frequencies of vision loss to 6/15 or worse and to 6/60 or worse and of CMO at presentation were 33%, 13%, and 20%, respectively. They found that patients who presented with a duration of disease of > or = 30 months had higher frequencies of visual impairment to 6/15 or worse (68% vs 32%; P = 0.004) and to 6/60 or worse (32% vs 9%; P = 0.01), and had a higher frequency of CMO (38% vs 14%; P = 0.02) than patients who presented with a duration of disease <30 months. They also reported on incidence rates on follow-up, 0.13/EY and 0.04/EY for 6/15 or worse and 6/60 or worse respectively. Long-term visual prognosis of BSCR was repeatedly reported to be poor: 16% of BCR patients in Europe and 22% of BSCR patients in the United States developed a VA of 6/60[477, 482, 861].

In this series the prevalence of BSCR in this study (1.5%) was similar to that reported in many studies [290, 291, 300, 478]. In our cohort, 2 patients had diabetes; this association was thought to be coincidental. The female preponderance and the age at onset was in concordance with the literature, and the proportions of eyes with vision loss at presentation were similar to that reported by Rothova et al.[860]. Although we found the same proportion of eyes with BCVA 6/60 at presentation as in the latter study, we did not find an increase in the number of severely impaired eyes with time (Fig.3.4). The proportion of eyes with 6/60 vision or worse and 6/15 or worse at presentation and the incidence rate for vision loss to 6/15 or worse in the series by Thorne [865] was very high. Rothova et al.[860] found that patients who had cardiovascular risks/disease were prone to developing severe visual loss. They suggested that hypertension might negatively influence visual prognosis in BSCR patients. Whether this hypothesis could explain the difference in visual outcome between their study and our own remains a question to answer. As in most studies, CMO and its

sequelae was the main cause of visual loss, accounting for 82.3%. This high incidence of CMO was similar to that reported in the cohort by Rothova et al.[860]. In their cohort, CMO accounted for 84%, vs 30% in the uveitis population. Thorne et al[865] reported that patients who presented at a later date after the onset of the disease were more likely to have visual impairment and CMO. A prevalence of subretinal neovascularisation was previously reported in approximately 6% to 14%[482, 860, 861, 866]. In our series, this complication was not found, but again, this could be a sampling effect. Our findings confirm the fact that the disease is very active during the first 3 years during which vision was severely impaired. The rise in the number of eyes with BCVA 6/18-6/36 from 10% at presentation to 50% after 10 years reflects the effect of macular chronic inflammatory insults over a long term (Fig. 3.4). Macular and chorioretinal atrophy in long-standing birdshot retinochoroidopathy has been mentioned in the literature [860, 864, 867]. Birch et al.[487] corroborated the long-term visual prognosis in patients with BSCR and provided further evidence that the decline is because of progressive deterioration of function of photoreceptors, RPE, and choroid. Kiss et al.[868] reported that long-term preservation of visual function is attainable with systemic corticosteroid-sparing immunomodulatory therapy (IMT) for patients with BSRC. Prompt treatment with systemic IMT may offer the best hope of maintaining retinal function in what is often thought of as a chronically progressive disease resistant to treatment.

Birdshot chorioretinopathy patients complain frequently of having problematic vision outside, abnormal color vision, and reading difficulties. Therefore, central VA alone is not the only parameter for treatment efficacy; VF examinations and electroretinogram might be extremely helpful parameters when assessing the degree of visual impairment and progression of the disease. Visual fields and electroretinograms were abnormal even in BSCR patients with full central acuity [861, 864, 869, 870].

Multifocal choroiditis (MFC) is thought to be an autoimmune inflammatory condition affecting one or both eyes characteristically with a chronic relapsing course. The first description of MFC with panuveitis as a distinct clinical entity is attributed to Dreyer and Gass in 1984 [871]. It is a chronic progressive inflammatory disease which is more common in young to middle-aged myopic women. MFC frequently is complicated by structural ocular complications involving the posterior pole which can result in loss of central VA over time [871-874]. Pathologically MFC represents a non-granulomatous choroiditis with a predominantly B-cell infiltrate and can be associated with choroidal neovascularisation (CNV)[875]. Acutely the foci may show chorioretinal inflammation that leads to destruction of Bruch's membrane, retinal pigment epithelium and the outer neural retina [876]. It has been shown that despite steroid treatment, MCP progresses to significant permanent visual loss in 60% to 75% of reported cases [871, 872, 877]. The vision loss occurs as a consequence

of chronic or recurrent inflammation [871, 872, 877](CMO, ERM, other maculopathy, optic neuropathy, subretinal fibrosis, and subretinal neovascular membrane) and/or from steroid complications (glaucoma)[873]. It has been reported that CNV occurs in 32%–46% of MCP cases [872, 878]. Palestine et al.[877] found that only 25% of their cases had some benefit from steroid therapy, whereas Cantrill and Folk[879] reported that 40% responded and 60% progressed despite steroid treatment. Brown and associates[872] found that more than half their patients progressed to vision of 6/60 or less despite steroid treatment. And Nölle et al.[880] reported their patients to be refractory to local and systemic steroid therapy, with deterioration in vision during steroid treatment. In the largest series of MFC to date, Thorne et al[881] reported repectively 55% and 38% of vision loss to 6/15 or worse and 6/60 or worse at presentation. In their series, 20% and 15% of patients respectively presented with bilateral visual loss to 6/15 or worse and 6/60 or worse. They reported incidence rates of vision loss to 6/15 or worse and 6/60 or worse of 0.19/EY and 0.12/EY respectively.

The mean age at diagnosis of MFC and the female preponderance in this study is in concordance with the literature [882, 883]. In our series, the proportion of patients who presented with bilateral vision loss was five times less than reported in the latter study. We also report a low incidence of visual loss at presentation and very low incidence rates of visual loss. The incidences of visual loss to 6/60 or worse at presentation and at five years follow-up in the present study (Fig.3.5) were similar to that reported by Vianna and MacLaren[874, 884]. We do not have a plausible explanation as to why patients in our series presented with better visual acuities when compared with the series by Thorne. In this study, chronic macular damage was the most common cause of visual loss. The incidence of CNVM in affected eyes was similar to that reported in most studies [871, 872, 878]. Low incidences of CNVM have been reported by Vianna et al[885] and by Michel et al[873]. Unlike the study by Michel et al[873] who found a high incidence of glaucoma, we did not find any glaucoma in our series (Table 3.26). The paper by Michel et al[873] does not make it clear as to whether the authors considered transient ocular hypertension secondary to corticosteroid therapy as glaucoma. Our findings corroborate the fact that visual acuity in eyes with MFC decreases with time (Fig.3.5).

Punctate inner choroidopathy has classically been described as an idiopathic ocular condition that presents as a single episode with rare recurrences [452, 872]. Usually it is an incidental finding of scars on routine refraction, or sudden onset of visual loss. The visual prognosis is usually favorable if CNVM does not develop. In addition, the majority of patients with PIC have been reported to be young, myopic, otherwise healthy women [452, 872, 882, 886]. In the biggest series to date, Essex et al. [451] reported that the condtion was unilateral in 47% at baseline. The rate of CNVM occurrence has been reported between 27%–77%[452, 872, 882]. In a series by Bouzas

et al.[887], 44.4% of affected eyes had BCVA 6/15 or worse and 33.3% had BCVA 6/60 or worse at presentation. Patel et al.[888] reported an equal proportion (10.5%) of visual loss to 6/15 or worse and 6/60 or worse in eyes with PIC at presentation. The demographics of patients who developed PIC in our series were similar to many previous reports [882, 888, 889]. Patients were in their early thirties, and 88% were females. Visual loss to 6/18-6/36 at presentation in this study was similar to that reported by Patel et al.[888]. The proportion of CNVM reported in this study was on the lower end of the range of proportions reported in the literature.

When comparing the clinical characteristics of MCF and PIC at presentation, Kedhar et al.[882] found that patients with PIC were much younger than those with MFC, with mean ages of 29 years and 49 years respectively. They also reported a higher frequency of structural complications and a higher tendency to develop bilateral visual impairment in MFC. In their series, no patient with PIC had bilateral visual loss despite the fact that CNVM was more common (76.9%) than in MFC (27.7%). In our cohort, 2 patients developed bilateral vision loss, one of them having bilateral severe visual loss and 1 having BCVA 6/18-6/36 in his better eye. As in most series, CNVM was the main cause of visual loss in this study accounting for 87.5%.

Acute posterior multifocal placoid pigment epitheliopathy (AMPPE) is a chorioretinal inflammatory disease, first described in 1968 by Gass[453]. The condition has been described as an acute self-limiting inflammatory disorder [890-892]. Characteristically, patients with AMPPE experience sudden loss of vision, followed by a rapid recovery, with resolution of the acute lesions, leaving a permanently altered retinal pigment epithelium [890-894]. Although most patients ultimately have good visual acuity [891, 892, 894, 895], some authors have reported persistent troubling symptoms such as blurred vision, metamorphopsia, and scotoma [896, 897]. Furthermore, to the best of my knowledge, there are only two reports in the literature examining the long-term visual outcome of AMPPE [896, 897]. The long-term visual outcome after an acute episode of AMPPE does not appear as favorable as initially reported [891, 892, 894, 895]. There is general agreement regarding the poor initial visual acuity.

Many authors remarked that patients with AMPPE have good visual recovery with an excellent prognosis [891, 892, 894, 895]. Other reports [896-898] however, show that nearly 50% of eyes reached incomplete recovery of visual acuity (6/9) and that approximately 25% of the eyes have a more limited visual recovery (6/12). The visual prognosis of the disease is strongly affected by the presence of initial foveal involvement. In fact, the percentage of eyes with full visual recovery is 88% and 53%, respectively, in the eyes without and with initial foveal involvement. Although initial foveal involvement does not preclude good recovery, eyes with poor visual recovery are usually those ones with initial foveal involvement and poor visual acuity at presentation [898]. Fiore et

al.[898] reported 23% of vision loss to 6/15 or worse and 30.7% of vision loss to 6/60 or worse at presentation. In another study by O'Halloran et al. [454], visual loss to 6/15 or worse and 6/60 or worse at presentation were reported in 31.2% and 6.2% respectively. Williams et al.[895] reported 22% of visual loss to 6/15 or worse and 16.6% of visual loss to 6/60 or worse at initial presentation and demonstrated a favourable long-term visual prognosis. The demographics of patients who developed AMPPE in our series were in concordance with the literature. The trend of visual loss at presentation in our cohort was similar to that reported by O'Halloran et al.[454] and Williams et al.[895]. Our findings were in agreement with previous reports in that a guarded visual prognosis should be considered in cases with initial foveal involvement [898-900]. The main cause of visual loss at the end of the follow-up period was macular damage/scarring. Although not commonly reported, SRF may occur in AMPPE and should not decrease the suspicion of this diagnosis [901]. Noteworthy, 1 patient in our series developed SRF in both eyes causing vision loss to visual impairment in one eye and severe visual loss in the other.

Fuchs' Heterochromic uveitis (FHU) is a chronic, low-grade, typically unilateral anterior segment inflammation. About 5-10% of cases are bilateral. It is an important and often overlooked cause of uveitis. Failure to make this diagnosis occurs because the hetrochromia may be subtle or absent, especially in those with brown irides[374, 902]. The aetiology of FHU is still unknown. Schwab[903] found an epidemiological association between FHU and toxoplasmosis. He presented the idea that toxoplasmosis might create a chronic condition resembling FHU. A case report supporting this concept was presented by Ganesh et al [904]. By contrast, La Hey et al.[905] claimed that there is no association between FHU and toxoplasmosis. In another study, intraocular synthesis of rubella antibodies was found in 52 eyes of 52 patients with FHU [906]. The rubella genome was detected in the aqueous humour in some younger patients and the authors concluded that FHU is a virus-driven disease. Some of their results were reproduced by de Groot-Mijnes et al.[907]. In an epidemiological study, Birnbaum et al. reported a decrease in the proportion of patients developing FHU after the introduction of rubella vaccination in the US with a corresponding increase in percentage of foreign-born cases[908].

Previous series have reported cataract in 23–90.7% of eyes [909]. The most serious problem with FHU is glaucoma. The prevalences of glaucoma reported in earlier studies vary markedly. In 13 reported series of FHU cited in a review by Jones [910], the incidence of glaucoma varied between 6.3% and 59%. The mean incidence of all patients in these series was about 20%[910]. La Hey et al.[911] reported a prevalence of 27%, including glaucoma suspects. In our study, glaucoma developed in 4 eyes (7.7%). The large variations in reported incidences of glaucoma probably result

from differing definitions of glaucoma. In concordance with the literature, in the present study the condition was mainly unilateral with no gender preponderance. The prevalence of cataract reported here was on the lower side of the range of incidences reported in previous reports.

The diagnosis of FHU is important to make for the following reasons: (1) patients with FHU are at a significant risk for developing secondary glaucoma and need to be monitored for life for early glaucoma detection; (2) corticosteroids do not reduce the inflammatory activity in FHU patients, do not produce any long-term change in the clinical course, and on a long-term basis can hasten the formation of cataract and induce glaucoma, and should therefore not be used. (3) FHU has a fairly good prognosis for the patient. Unilateral cases of FHU have not been reported to become bilateral; (4) cataract extractions are generally tolerated well by FHU patients and result in the restoration of good vision. Only glaucoma, is difficult to control therapeutically [374, 912]. Our data corroborate the favourable visual prognosis in FHU.

The true incidence of sympathetic ophthalmia has been hard to establish due to its rare occurrence and its diagnosis based on clinical findings. In 1979, sympathetic ophthalmia following intraocular surgery was reported to have an incidence of 0.1%, while open globe injuries had an incidence of 0.2% to 0.5% [913]. Kilmartin et al. [499] conducted a prospective study in England and Ireland with a surveillance of 59 million citizens, where 23 patients with a new diagnosis of SO were reported in a 15-month period. The resulting incidence was estimated to be 0.03 in 100,000. The study also demonstrated ocular surgeries as the most common cause of SO. Most of the newly diagnosed cases occurred in patients with multiple ocular trauma incidents, suggesting a possible additive risk [914]. Surgical interventions noted to be associated with sympathetic ophthalmia include glaucoma surgery, cataract extraction, scleral buckling, pars plana vitrectomy and cyclodestructive procedures that affect the integrity of uveo-retinal tissue[915]. In the year 2000, the calculated risk of SO was estimated to be 1 in 1152 retinal surgical procedures[499]. In a review of 32 patients with SO at the National Eye Institute Bethesda during a 10 year period, 1.4% of 2287 of patients who presented with uveitis had SO. The age range was from 3 to 80 years old, affecting all age groups with no racial predilection noted [916]. The incidence of SO in our uveitis population and the patients profile were similar to that reported in previous studies[916, 917]. Although earlier studies found traumatic SO to be more common, Kilmartin and associates demonstrated ocular surgery to be the most common cause[499, 502, 916, 918, 919]. In a study in the same institution as us 20 years ago, Hakin et al.[502] reported that 83% of patients developed SO following trauma in the inciting eye, only 17% of eyes sympathised after repeated retinal detachment surgery in the inciting eye. The type of trauma in the inciting eye was not established in the present study.

Sympathetic ophthalmia in itself is a sight-threatening disease with a high rate of visual loss; approximately half of patients experience 6/12 or worse vision, and one-third of patients become legally blind[916]. Although improved immunosuppressive therapy may reduce chronic inflammation, there is still a risk of visual loss from complications such as chorioretinal scars, macular edema, and choroidal neovascularisation[490]. In this study, 47.4% of eyes maintained visual acuity of 6/12 or better. A quater of patients had worsened visual acuity at the end of the follow up period, while only 10% improved visual acuity in the sympathizing eye. Parikh et al[74]recently reported that in SO, photoreceptor mitochondrial oxidative stress occurs in the absence of leukocytic infiltration of the retina and may lead to photoreceptor apoptosis and subsequent vision loss. The current anti-inflammatory therapy combined with agents that could prevent oxidative stress may prevent photoreceptor damage in SO and may preserve vision. Sen et al.[920] emphasised the significant vision loss associated with SO and highlighted the importance of early diagnosis and prompt, aggressive treatment.

6.5 Uveitis in children.

Children with uveitis present a number of unique diagnostic and therapeutic challenges [921-923]. Uveitis in childhood differs in various noteworthy aspects from uveitis in adulthood. Firstly, the association with systemic diseases is different in children and ANA positive oligoarticular juvenile idiopathic arthritis (JIA) presents as the most common systemic disorder (41.5%) [377, 924]. Secondly, the use of standard systemic medications such as corticosteroids and immunosuppressive drugs for non-infectious uveitis in childhood has an impact on the immature immune system and developing bones. A growing body of evidence suggests that prolonged administration of corticosteroids is associated with a significant number of permanent adverse effects and steroid sparing drugs are recommended [925-929]. Thirdly, the onset of ocular inflammation in children is often asymptomatic despite severe ocular inflammation and with decreased visual acuity already present. Hence, the ocular inflammation is often discovered by routine screening only in the advanced stages of the disease. At the time the child is first seen by an ophthalmologist, ocular complications with negative effects on visual prognosis are regularly detected [856, 930]. In addition, in children younger than 7 years, the risk of amblyopia must be considered. Finally, the results of surgical procedures for the various complications of uveitis (for example, cataract, glaucoma) in children are often discouraging [931, 932].

Children account for only 2.2% to 13.8% of patients in many uveitis clinics, and most published series of pediatric uveitis are limited to a small number of patients [281, 314, 933]. Cunningham et al[127] reported that children constituted only 5% to 10% of patients with uveitis.

Biswas et al[717] found 3.6% of uveitis in children below 10 years of age. Narayana et al.[934] reported 6% of uveitis in children in a referral eye care centre in India. In a population-based study, Paivonsalo[935] identified 4.9% of uveitis in children. Some authors have proposed that uveitis in children has a relatively severe course and is more likely to lead to vision loss[127]. Delayed diagnosis, extended burden of disease over a lifetime, limited treatment options in children, difficult examinations, and the risk of amblyopia are all challenges specific to childhood uveitis[310, 311]. The age range is often a problem in comparing different studies: recent series about pediatric uveitis generally involved patients <16 years old, one even 18, while in reports from some decades ago the upper age limit was 14[281, 936, 937]. Moreover, conclusions from children eye hospitals or from referral centres not always fit together [937]. The mean age at presentation of children who developed uveitis in our series was in agreement with many previous reports, and we did not find any gender predominance.

Table 6.1 Comparison of distributions of uveitis etiology and anatomic location in studies of pediatric uveitis published after 2000.

Study	Current	Smith[309]	BenEzra[281]	deBoer[308]	Kadayifcilar[938]	Edelsten[314]	Rosenberg[767]	Kump[312]
Year	2011	2007	2005	2003	2003	2003	2004	2004
n.patients.	95	527	276	123	219	249	148	269
AU	40%	44.6%	13.4%	36%	43.4%	70%	30.4%	56.9%
IU	32%	28%	41.7%	24%	11.9%	-	27.8%	20.8%
Pan/PU	28%	27.3%	14.9%	40%	44%	30%	41.9%	22%
JIA	8.4%	21%	14.9%	20%	13.2%	47%	23%	33%
Toxo.	5.3%	5%	7.2%	10%	21%	2%	7.4%	3.3%
Idiopathic	74.7%	29%	25.4%	53.7%	36%	44%	26.4%	51.7%

The present study confirms the lower incidence of paediatric uveitis compared to adult uveitis. In the 1950s and 1960s anterior uveitis accounted for 11–49% and posterior uveitis for 22–67.7% of all pediatric uveitis[127]. In our study, anterior uveitis was the largest group(Fig.3.2.14.1), in agreement with many other reports about pediatric uveitis from North America and Europe [308, 312, 314, 933, 935, 937]. The higher incidence of IU was reported by BenEzra et al[281]. Edelsten et al[314] reported the higher incidence of AU, and no IU was reported in their cohort. Their study was conducted in district hospitals, and it is possible that there is a referral bias, more complex cases being referred to tertiary referral centres. Also, some cases require an examination under general anaesthesia(EUA). The incidence of posterior uveitis was similar to the findings by many authors [127, 312, 933, 937]. Children under eight to ten years of age with uveitis are at risk of developing

amblyopia. Furthermore, surgery carries added risks in children compared to adults[922, 923], both because children tend generally to mount more inflammation following surgical procedures than adults and because one of the most common causes of uveitic cataract in children is juvenile idiopathic arthritis, a condition in which intraocular surgery is generally associated with a more guarded prognosis[127].

The causes of uveitis in children differ somewhat from the causes of uveitis in adults [921, 922, 939, 940]. The most frequent form of endogenous uveitis in children is JIA. Other less frequent causes of endogenous causes of uveitis include HLA-B27-associated uveitis, which may occur in the setting of ankylosing spondylitis, Reiter's syndrome, inflammatory bowel disease, or psoriatic arthritis, Fuchs' uveitis syndrome, Behçet's disease, VKH, ocular sarcoidosis, and sympathetic ophthalmia [127]. In a review of different studies reporting on the prevalence and patterns of uveitis in children, prevalences of JIA were reported to vary between 5.6% and 41%, and Toxoplasmosis between 7% and 39% [127]. In one study, the prevalence of JIA was reported to be as high as 81.5%[377]. The proportion of children who developed uveitis with an underlying condition in this study was similar to that reported in the literature (Fig.3.7). The prevalence of idiopathic cases in this study was similar to that reported by Azar et al.[933] in Australia, and by Cunningham et al [127] in the US. This is in contrast to most studies where the proportions of idiopathic uveitis have been reported to be as low as 25%. One explanation of this difference is that our selection criteria excluded infective cases excepting Toxoplasmosis.

Table 6.2 Comparison of visual acuities in children at different time points between this study and the study by Smith et al[309].

Time pointS→	Baseline		1 year		3 years		5 years		10 years	
BCVA↓	S*.	C**	S.	C.	S.	C.	S.	C.	S.	C.
> 6/18 (%)	80.2	80.9	84.1	88.3	80.9	77	72.3	73.3	69.2	61.5
</=6/18 (%)	39.7	12.7	27.5	8.5	28.5	17	51.4	6.6	46.1	-
</= 6/60 (%)	9.2	6.4	6.5	3.2	3.2	6	15.1	20	7.7	38.5

S*= Smith et al., C**= current study

A review of the literature indicated that up to one third of all children with uveitis ended with severe visual impairment[127]. The trend of visual outcome over time was similar to that reported by Smith et al[309]. However, the proportion of eyes with visual impairment reported by Smith and associates was very high throughout the follow-up period when compared with our own data. In both studies, we note an improvement in visual acuity at one year follow-up. Afterwards, the proportions of eyes with visual impairment and those with severe vision loss increased. This demonstrates that most cases of vision loss at presentation are reversible. The prevalence of baseline legal blindness in this study was similar to what reported by Smith et al.[309] , but lower

when compared with 18% and 53% reported by Rosenberg et al[767] and Edelsten et al[314]. As in most series, we found that posterior uveitis is a major risk factor for poor visual outcome.

The course of IU in children can be worsened by many sight-threatening complications [740, 941]. Nevertheless in many children and young adults IU can reach remission with maintained good visual acuity in the absence of ongoing therapy; their disease can resolve and 'burn itself out' [132, 739, 740]. In a series by de Boer et al. [132] 9.4% of patients developed unilateral legal blindness. One of the major questions in IU is whether it is possible to predict which patients are at greater risk of developing severe course of IU with visual loss before the sight-threatening complications actually occur[942]. It has been reported that children with IU might have a more severe disease and worse outcome than patients with onset at older age [943, 944]. Visual prognosis in IU in this study was favourable as no eye developed legal blindness(Tables 3.30). In a recent study, Ayuso et al.[945] showed a negative effect of young age at onset of IU on the clinical course and visual outcome up to 3 years' follow-up. We did not find a difference in BCVA at presentation between children who were aged </=7 at onset of IU and those who were aged > 7 years. Contrary to the report by Ayuso et al., young age at onset of IU was not an independant risk factor for poor visual outcome in our series. Interestingly, children who developed visual impairment in our cohort were aged >7 at onset of IU. Our findings are in agreement with previous studies [660, 740] where young age at onset of IU was not found to be a negative factor on visual oucome.

A review of the literature indicated that up to one third of all children with uveitis ended up with severe visual impairment[127]. De Boer et al.[308] reported that 2% of children became legally blind and an additional 17% had one legally blind eye caused by uveitis. The most frequent causes of blindness in their study were chorioretinal scars in the macular area and glaucoma. In our cohort, 22% of children developed vision loss in at least one eye at the end of the follow-up period. Ten percent developed severe visual loss in at least one eye, one child (1%) developed bilateral legal blindness. The pattern of causes of severe vision loss was similar to that reported in the latter study.(Table 3.32)

JIA has been reported to be the most common underlying disease in paediatric uveitis in most series [308, 312, 314, 933, 935]. A definite association exists between the articular and ocular manifestations in children with JIA. The prevalence of uveitis in JIA varies widely across case series, from 11.4% to 20.1% [582, 946]. The cumulative incidence of uveitis was found to vary depending on the country of origin of the study, being significantly greater in Scandinavian series, followed by series from the US, East Asia and finally India[947]. Factors that may explain this variability include changes in the classification scheme for JIA, small sample sizes, and differences in populations recruited at rheumatology departments compared to ophthalmology departments. There is general

agreement, however, that the risk of ocular involvement is highest in pauciarticular JIA, which predominantly affects girls before 5 years of age. The risk of uveitis persists for years after arthritis onset, extending into adulthood [586, 948]. Less severe ocular disease has been reported in some series [946, 949-951]. A minority of studies provided data for visual outcome [947]. Bolt et al.[952] reported an excellent longterm visual outcome despite a relatively high complication rate. They found that 90.6% of patients in their cohort had normal visual acuity,1 patient (3.1%) had impaired visual acuity in 1 eye, and 2 patients (6.25%) had legal blindness in 1 eye each at last ophthalmologic follow-up. None of their patients had developed bilateral reduced visual acuity at last follow-up. This rate was much lower than in the majority of other studies [953, 954]. Cassidy et al.[955] reported that 16% of the afflicted children experienced either unilateral or bilateral blindness. In a study by Wolf et al.[932] 22% of eyes had visual loss to 6/60 or worse. The authors reported that severity of visual loss and complications correlated with the degree of inflammation found on initial ocular examination. In their series, Azar et al.[933] found that 33.3% of eyes with JIA-associated uveitis developed visual loss to 6/18 or worse, and 28.7% of eyes had severe vision loss or blindness. The proportion of eyes in the group of JIA-associated uveitis which developed severe visual loss (33.3%) in this series was similar to that reported in the latter study. One patient in our cohort developed bilateral legal blindness (Table 3.31). Woreta et al [585] reporting on the frequencies and risk factors for ocular complications and poor visual acuity at presentation in a cohort of patients with JIA-associated uveitis found that 36% and 24% of eyes had BCVA 6/18 or worse and 6/60 or worse respectively. We found a similar incidence of vision loss to 6/60 or worse at presentation, but none of the children with JIA-associated uveitis presented with vision loss to < 6/12. Thorne et al [853] reported incidence rates of 0.10/EY and 0.08/EY for vision loss to 6/18 or worse and 6/60 or worse respectively. In this study incidence rates for vision loss were higher than those reported by Thorne. Despite the fact that girls are at higher risk to be affected by anterior uveitis [950, 956, 957], many studies have demonstrated that male gender is an independent baseline risk factor associated with multiple ocular complications of JIA-associated uveitis [376, 958-960].

The big limitation of our study as far as JIA-associated uveitis in children is concerned is that we had a very small sample (8 children). Hence, we could not perform more statistical analysis. However our data confirm, as reported by others [406, 585, 932, 961] that severe complications with loss of vision are still to be feared in children with JIA who develop uveitis, particularly if there is a long delay in referral to a tertiary care center. Prompt referral of these patients to a uveitis specialist and early aggressive therapy with immunosuppressive agents may decrease the odds of poor vision [585].

Toxoplasmic retinochoroiditis appears to be more common in Brazil than in Europe or North America and more severe. It is a leading cause of blindness in Brazil[962] but not in Europe or North America[3, 308]. The estimated incidence of acute symptomatic chorioretinitis for all people born in Britain was 0.4/100,000/year and for black people born in West Africa 57/100,000/year[963]. The exact contribution of congenital and postnatal infection to OT is not known because the ocular involvement occurs predominantly during the chronic phase of infection and because, to date, no laboratory tests discriminate between the prior congenital and postnatal acquisition of infection[508]. Many studies have reported that postnatal acquisition of toxoplasmosis might also be an important cause of ocular disease [510, 964-967]. Most infected newborns have no clinical signs but are at risk of developing visual impairment as a result of retinochoroiditis in childhood or adolescence [968]. Gilbert et al.[969] compared ocular sequelae of congenital toxoplasmosis in Brazil and in Europe and found that children with congenital toxoplasmosis in Brazil developed retinochoroiditis earlier than children in Europe. They reported that affected children tend to have multiple lesions more frequently, and the lesions were larger and more likely to affect the posterior pole and hence to threaten vision. Tan et al.[970] reported that severe bilateral impairment occurred in 9% of children with congenital toxoplasmic retinochoroiditis. Half the children with a posterior pole lesion and one in six of those with peripheral lesions alone were visually impaired in the affected eye. Wallon et al.[971] reporting on the clinical evolution of ocular lesions and the final visual function in a prospective cohort of 327 congenitally infected children found that none of the children had bilateral visual impairment. In the 24 children with known unilateral visual impairment, 1 patient developed vision loss to 6/15 or worse and 5 patients (20.8%) developed severe visual loss or blindness. In this study, all children had unilateral lesions of ocular toxoplasmosis. Severe visual loss or blindness due to toxoplasmosis did not occur in our cohort. A better visual oucome in ocular toxoplasmosis had also been reported by Koppe et al.[972]and Mets et al.[973] in children who were treated at birth or perinatally with pyrimethamine and sulfadiazine for 1 year.

Clinicians and parents should be informed that, despite early diagnosis of congenital toxoplasmosis and treatment, relapses and late-onset ocular lesions can occur late after birth. They cannot be predicted at the present time but fortunately do not lead to severe visual impairment[971]. Reactivation is uncommon under 16.

6.6 Uveitis in patients aged > 60.

Uveitis in patients older than 60 years has been considered uncommon, but two recent epidemiologic studies showed that the burden of uveitis in elderly population is significant [279, 974]. Little is known about the epidemiology of uveitis in the elderly population over the age of 60 years as there is a paucity of population-based epidemiology data for this age. Only 7 studies have specifically evaluated the clinical characteristics of uveitis de novo in the elderly [283, 316, 975-978]. All these studies were retrospective and all but two were published more than 10 years ago. First, Gritz and Wong reported a cross-sectional study of 2070 people within 6 Northern Californian medical center communities[279]. They observed that the incidence of uveitis rose with age, peaking at 102.7/100,000 in subjects aged 65 years and older. Prevalence findings were similar, rising up to a high of 234.6/100,000 in patients at the age of 60 or more years. Reeves et al.[974] used longitudinal Medicare claims data to estimate the annual incidence and prevalence of uveitis in the U.S. elderly population. They found an average cumulative incidence of 340.9/100,000 persons per year and a doubling of the cumulative incidence from 511/100,000 in 1991 to 1231/100,000 in 1999.

The prevalence of uveitis in this age group reported in this series was similar to that reported by Chatzistefanou et al.[979]. Higher prevalences of uveitis in the elderly have been reported in many other studies [284, 976, 977]. Our data confirm the female preponderance found in pevious reports [976, 979]. In an epidemiological study calculating the incidence and prevalence of uveitis by anatomic location in the elderly, Reeves et al.[974]reported that AU was the most common incident diagnosis for all locations from 1993 through 1999, with a mean of 243.6/100 000, and ranged from 171/100 000 (1997) to 304/100 000 (1996). The mean incidence of PU was 76.6/100 000. Intermediate uveitis was almost nonexistent in their population. Overall prevalence of uveitis more than doubled during the 9 years of the study, from 511/100 000 in 1991 to 1231/100 000 in 1999. They found that AU increased almost 3-fold from 338/100 000 in 1991 to 935/100 000 in 1999 and the prevalence of PU doubled from 108/100 000 in 1991 to 286/100 000 in 1999. As in most studies, we found that AU was the most common uveitis type. The anatomic distribution of uveitis in Gregoire's series[976] of elderly patients differed from younger patients. The authors reported that Panuveitis was statistically more common in the first group and the percentage of older patients with AU was much lower than those reported by most of authors in previous studies. We found similarities in the trend of uveitis types in the elderly and in children in our cohort, and the prevalence of IU is the highest reported to date.

The proportion of idiopathic cases found in this study (31%) was close to that reported by many authors [284, 976, 979]. The highest proportion of idiopathic cases (68%)was reported by Barton et al.[316]in the same institution as us more than fifteen years ago. In their series, diabetes

was the most common systemic associated with uveitis in the elderly (7%). We found a similar proportion of diabetes (8.3%) which was not exceptionally high when compared with the whole uveitis population. In our series, sarcoidosis was the most common systemic condition(13.7%). The proportion of sarcoidosis reported here was close to that reported by Favre et al.[284] and by Bouillet et al.[975].

Ocular neoplasia, especially lymphoma has been a major concern. Ocular lymphoma has been described most commonly in patients over 60 years of age[980] and is characterized by a chronic uveitis which responds poorly to corticosteroids. The anterior segment signs are usually discrete, although a hypopion may appear during evolution. The vitreous is often markedly involved. The chorioretinal lesions are variable in aspect. Subretinal infiltrates or solid retinal pigment epithelial detachments are the most characteristic fundus signs of the disease. Other fundus signs may be present, such as retinal vascular occlusions, perivasculitis, macular oedema, optic disc oedema or ischaemic optic neuropathy[981].

Vitreous biopsy is recommended only in patients with abnormal-looking vitreous cells, a poor response to steroid treatment, or classical chorioretinal lesions in the presence of vitritis, when a definitive diagnosis has not been made and progressive posterior segment inflammatory disease threatens vision[316]. As reported by other authors, intraocular lymphomas represent a small proportion of our population of elderly patients. Our 1% prevalence of intraocular lymphoma among elderly patients was similar to that reported by many authors [295, 673, 975]. Chatzistefanou et al.[979] reported 3.4% of intraocular lymphoma. In spite of these low prevalences, it is important to keep this diagnosis in mind because of its sinister implications. Since PIOL is a potentially fatal malignancy, early and accurate diagnosis is critical for the initiation of appropriate therapy [982].

Reports on visual outcome in the elderly are scarce. Chatzistefanou et al.[979] reported that 35.6% of affected eyes presented with BCVA 6/12 or better, 31% were visually impaired and 32.6% had severe visual loss or blindness. A comparison of visual outcome in children and in the elderly showed that patients who developed uveitis after 60 years presented with poor visual acuity. Incidence rates for visual impairment in children was higher than in the elderly (0.10/EY vs 0.05/EY respectively), and incidence rate for severe visual loss in the elderly was higher than in children (0.06/EY vs 0.05/EY respectively). The prevalence of CMO in the elderly reported in this series was similar to that reported by Chatzistefanou et al.[979]. The 21.9% of glaucoma could be an underestimation as we only reported glaucoma affecting visual acuity. Some cases of glaucoma with preserved visual acuity may have been overlooked.

6.7 Treatment of uveitis.

Although some disorders such as acute anterior uveitis may be either monophasic or episodic and recurrent, most types of non-infectious uveitis are chronic and typically require chronic suppressive therapy [983]. Furthermore, those types of uveitis requiring treatment beyond topical corticosteroids (intermediate uveitis, posterior uveitis, and panuveitis) are associated with a frequency of visual loss ranging from 28% to 59% respectively[300]. As such, appropriate management of these disorders is critical in minimizing visual loss and preserving visual function [983].

Topical corticosteroids have provided the mainstay of treatment for anterior uveitis since the 1950s, but do not penetrate far enough into the eye to control intermediate or posterior disease[984]. Most cases of AU in this study were managed successfully with topical corticosteroids alone (Table 3.36).

Systemic corticosteroids are generally advocated for intermediate and posterior uveitis that requires treatment that is either bilateral or associated with systemic disease [985-987]. They are the standard treatment in patients with anterior uveitis and visually significant cystoid macular oedema and those with sight-threatening complications of posterior uveitis[986]. Most eyes with Panuveitis and poaterior uveitis and one third of eyes with IU in this study were treated with oral steroids (Table 3.36).

In patients with unilateral or asymmetric disease, or in whom systemic administration of medication is less desirable, e.g. during pregnancy or in patients with a history of gastric ulceration, periocular injection can be useful to provide a depot of corticosteroid that successfully reaches the posterior segment to control inflammation[985, 988-992]. Periocular corticosteroid injections are a valuable therapy for intermediate uveitis which needs only an occasional injection in order to control the process and as adjunctive therapy for CMO.[993] Although repetitive periocular corticosteroid injections also are used for more severe forms of uveitis, such as posterior uveitis and panuveitis, this approach appears to be more problematic in the long run. Typically these patients require chronic suppressive therapy and

control of the inflammation to prevent long-term visual loss[993].

In our cohort, orbital floor injection was used on 2% of eyes, mainly eyes with IU which have developed CMO (Table 3.36).

The use of intravitreal injections of triamcinolone acetate (IVTA) in the treatment of uveitis is now commonplace, and involves the injection of corticosteroid directly into the vitreous body, thus achieving a higher concentration of intraocular corticosteroid [994]. The dose most commonly used

is 4 mg, and the typical duration of the effect is 4–5 months, with the maximum effect on visual acuity occurring at 1–6 months after injection [995, 996]. It tends to be most effective in younger patients with a limited duration of macular oedema, and can allow the cessation and/or reduction of immunosuppressive therapy [997].

The fact that both OFTA and IVTA were mostly used in eyes with IU in this study is understandable. The frequency of CMO was higher in this type of uveitis when compared with others. It has previously been shown that uveitic CMO may resolve completely with repeated IVTA injection[998], but that the improvement in BCVA and reduction of CMO after a single TA injection is mostly transient [999-1001].

Previous studies have demonstrated that a single IVTA injection is more effective than a single OFTA injection for improving uveitic macular oedema and this favors its use [992, 997]. The better efficacy of IVTA may be attributed to the higher intravitreal concentrations of TA that were detected after intravitreal drug injection as compared to a posterior periocular injection [994]. Kok et al[997] reported that eyes with most visual improvement had CMO for less than a year. They also found that in some eyes, there was subjective clinical improvement in CMO by biomicroscopy and FA that was not accompanied by improvement in vision, and eyes of younger patients attained better vision after treatment. This is not surprising, as chronic CMO results in ultrastructural changes in both the retina and the retinal pigment epithelium (RPE), some of which can be observed clinically[220, 1002]. The ability of photoreceptors and the RPE to recover from insult declines with age, as is also observed in central serous chorioretinopathy [1003].

Indications for immunosuppressive drugs are: 1) failure of the disease to respond to oral corticosteroid therapy, 2) serious side effects of oral corticosteroids, 3) requirement for a chronic dose of oral corticosteroids likely to result in serious side effects (e.g. >10 mg daily), and 4) a disease known to be poorly responsive to corticosteroid therapy alone [1004].

The comparative efficacy of different treatments modalities was not the aim of the present study.

6.8 Surgery in uveitis.

Cataract surgery in uveitic eyes is more complex than in healthy eyes and has a considerable potential for an unfavorable postoperative outcome mainly due to worsening or relapsing of intraocular inflammation [1005, 1006]. The uveitic cataract poses for the surgeon special challenges given the commonly encountered consequences of chronic inflammation, which include a miotic pupil, iris atrophy, posterior synechiae, pupillary membrane, band keratopathy, and bleeding from abnormal fragile iris vessels[1007]. Previously, cataract surgery in eyes with intraocular inflammation

was considered a high-risk procedure or a contraindication because of the high number of postoperative complications such as severe inflammatory reaction, IOP elevation, or glaucoma[1008]. These complications can lead to poor visual outcome. Intracapsular cataract extraction, a surgical method in which the cortical material is completely removed within the capsular bag, was the preferred method many years ago because it was thought to reduce the risk for postoperative inflammatory response[1008]. Cataract surgery in patients with uveitis is indicated in four settings: active inflammation secondary to leakage of lens proteins (i.e. phacoantigenic uveitis); visually significant cataract with preoperatively controlled inflammation and expected good visual prognosis; cataract impairing proper assessment and treatment of possible retinal inflammation; and cataract impeding posterior segment visualization in a patient requiring posterior segment surgery (e.g. pars plana vitrectomy)[401].

Apart from the recommendation to perform cataract surgery during a quiescent interval three months with little or no inflammation, supplementary antiinflammatory treatment prior to cataract surgery has been advocated in several studies [1009]. The improved visual prognosis after cataract surgery in eyes with uveitis in recent years seems to be related to the more consistent use of perioperative antiinflammatory and immunosuppressive treatment regimens [1010]. New technologies, including phacoemulsification, modern equipment for irrigation and aspiration, and foldable acrylic IOLs, have been introduced. As a result, phacoemulsification and IOL implantation are now the most common type of cataract surgery procedures in patients with uveitis [1011-1014]; however, the outcomes have been evaluated in small groups of patients only. We report in this series on the largest number of eyes (615) which underwent cataract surgery. We indentified only 7% of eyes which underwent intracapsular extraction vs 89% which underwent phacoemulsification and IOL implantation, 1.6% underwent ECCE (Table 4.4).

In this study, we found that phacoemulsification in patients with uveitis led to a significant improvement in BCVA immediately after cataract surgery and this vision remained stable during follow-up(Table 4.7). This is in agreement with several other studies that reported short- and long-term visual improvement in up to 93% of patients [413, 680, 1015-1018]. Kawaguchi et al.[1019] reported that the overall visual prognosis in eyes that had undergone phacoemulsification was favorable in 84.7%, with 74% of eyes attaining a final visual acuity of 6/12 or better. In a recent study, Ram et al.[1020] found that 71% of eyes had a BCVA 6/12 or better at the final postop follow-up visit. In their series, 16% of eyes were visually impaired and 13% developed severe vision loss. In another series, Estafanou et al.[1016] reported that 87% of eyes which underwent phacoemulsification improved VA to 6/12 or better at final follow-up visit. Kang and Lee [1021] and Harada and associates[1022] reported visual improvement in 89% and 96% of eyes, with final visual

acuities of 6/12 or better in 64% and 82% of eyes, respectively. In this study, 66% of eyes had BCVA 6/12 or better at final follow-up postsurgery (Table 4.5). This proportion was inferior to that reported by Okhravi et al.[1018](90%) in the same institution a decade ago. However, proportions of eyes with visual impairment and those with severe visual loss after cataract surgery were similar in the two studies and in agreement with the study by Ram et al.[1020]

As in many other reported data, we found that eyes with Panuveitis and posterior uveitis bore the poorest visual prognosis post cataract surgery. Yoeruek et al. [1009] reported that eyes with preoperative macular lesions were likely to have a poorer visual outcome. They found that aetiology of uveitis, gender of patients, age at cataract surgery (<30 years), and anterior segment pathology, such as anterior synechiae, were not predictive for poor visual outcome after cataract surgery. Our data corroborate preoperative macular lesions as a predictive factor for poor visual outcome. Moreover, in a multivariate model analysis, we found that the type of cataract surgery influenced visual outcome ($p< 0.001$). Eyes which underwent ECCE and ICCE had the worse visual outcome as compared to phaco (Table 4.7).

In our series, CMO was the third most common postoperative complication (Table 4.8). The incidence reported in this study was close to that reported in previous studies [413, 1020]. A lower incidence (2.3%) has also been reported by Suresh et al [1023] in a cohort of 86 eyes with uveitis undergoing phacoemulsification.

Cataract surgery in a patient with uveitis warrants thorough diagnostic evaluation, diligent pre, peri and postoperative control of inflammation, and meticulous surgery[1007]. Identifying patients who are at risk for poor visual outcome is of importance for preoperative counseling and postoperative care [1009].

Historically, experts have cautioned against primary placement of intraocular lens (IOLs) in patients with JIA because of the risk of secondary cyclitic membranes and development of hypotony [406, 1024, 1025]. With more widespread practice of strict control of uveitis at least 3 months prior to surgery and using systemic immunomodulatory therapy, good postoperative results can be achieved[414]. Even so, the presence of an IOL can still incite recalcitrant inflammation necessitating removal of the implant [1026]. Alternatively, pars plana lensectomy with anterior vitrectomy and subsequent aphakia can be an effective way to manage uveitic cataract [1027]. Pars plana vitrectomy (PPV) in combination with phacoemulsification has been reported to successfully improve vision in adults and children with chronic uveitis [1028-1030].

A recent retrospective study by Sijssens et al [1031] examined long-term complications after cataract surgery in aphakic and pseudophakic eyes of children with JIA-associated uveitis. They found no statistically significant difference in complications between the two groups. Cystoid

macular oedema was higher in the aphakic group, but did not achieve statistical significance. Visual acuity was significantly better in pseudophakic eyes than in aphakic eyes up to 7 years after cataract extraction. The authors did not report any hypotony, perilenticular membranes or phthisis in the pseudophakic group. In our series, all cases of secondary glaucoma and hypotony developed in aphakic eyes and visual outcome was worse in this group. The number of pseudophakic eyes in our cohort was too small for us to do any statistical calculations and compare the two groups. Recent studies have reported that implantation of an intraocular lens in selected cases of JIA-associated uveitis was associated with good visual results [1032-1034]. The poor visual outcome post cataract surgery in JIA associated uveitis in our series is explained by the fact that more than half the number of affected eyes underwent ICCE and this was done a long time ago. In a comparative study between children with JIA-associated uveitis and those with non JIA-associated uveitis, Nemet et al[1033] recently reported that those with JIA-associated uveitis tend to have more severe manifestations of disease when first seen and after surgery, but they found no significant difference in postoperative course or complications. The authors concluded that intraocular lens implantation, including small-incision, foldable intraocular lenses, is well tolerated when combined with aggressive medical treatment for controlling inflammation [1033]. This was confirmed by most recent studies [1031, 1034, 1035]. Sijssens et al[1031]suggested the following relative contraindications for IOL placement in patients with JIA-associted uveitis: age less than 4 years, hypotony, fellow eye IOL-related complication and shallow anterior chamber.

The management of uveitic glaucoma may be difficult because of the numerous mechanisms involved in the pathogenesis[368]. The condition becomes more challenging when the elevated intraocular pressure (IOP) is unresponsive to medical treatment. To improve the surgical outcome of these cases, alternative approaches such as trabeculectomy with antiproliferative agents[1036-1038], aqueous drainage devices with or without trabeculectomy, trabeculodialysis[1039, 1040], and transscleral diode laser cyclophotocoagulation[1041] have been proposed. Most studies suggest using antiproliferative agents in terms of long-term IOP control in those patients [1036, 1038]. Stavrou and Murray[1038] observed a high rate of trabeculectomy survival (53%) after 5 years without antiproliferatives. A higher success rate (67%) at 5 years was obtained by Towler et al.[1042]by using intraoperative 5-fluorouracil. However, even with adjunctive antiproliferative use, increased inflammatory cells and fibroblasts in uveitic patients result in significant inflammatory response and excessive fibrosis. Furthermore, antiproliferative agents have potential complications such as corneal epithelial defects, increased incidence of bleb rupture, late bleb leak, bleb-related endophthalmitis, and chronic hypotony[1043]. To minimize these complications and the risk of trabeculectomy failure due to excessive scarring and fibrosis, shunting devices may be considered as

a primary surgical procedure for IOP control in uveitic patients [1044]. Aqueous shunts traditionally have been reserved for treatment of the most refractory glaucomas. However, more recent studies have suggested that aqueous shunts offer similar outcomes to trabeculectomy with mitomycin C in eyes that are at a lower risk of failure, that is, in patients with primary glaucomas who are pseudophakic or who have had 1 failed trabeculectomy[1045-1049]. Consequently, aqueous shunts have been used increasingly in the management of medically uncontrolled glaucoma[1050].

The aim of this study was not to report on the efficacy of different filtering procedures. Hence we did not report on IOP control, but the impact on visual acuity. We report that trabeculectomy with mitomycin C was the most common surgical procedure (70%). Clinical trials [1051-1053] have shown that the lowering of intraocular pressure (IOP) is associated with reduced progression of glaucomatous visual field (VF) loss. Francis et al.[1054] have recently reported that unexplained permanent vision loss (or snuff-out) can occur after trabeculectomy with mitomycin C treatment. Risk factors for long-term vision loss are preoperative split fixation on VFs, preoperative number of quadrants with split fixation, and postoperative choroidal effusion with eventual resolution. They concluded that transient vision loss after trabeculectomy is common and may take up to 2 years for recovery.

In a recent study, Malone et al.[1055] reported that visual acuity improved in every eye after a combined Fluocinolone Acetonide Intravitreal Insertion and Glaucoma Drainage Device Placement for chronic uveitic glaucoma. They attributed improved visual acuity to excellent postoperative inflammation control, cataract extraction in eyes with pre-existing cataract, and decreased macular oedema in eyes with pre-existing macular thickening. In this study, we found a slight, but statistically significant improvement in visual acuity post glaucoma surgery. Fifty percent of eyes which underwent glaucoma surgery in our cohort had also cataract surgery. When comparing visual outcome in eyes which underwent glaucoma surgery only with those that underwent cataract and glaucoma surgery, we did not find any statistically significant difference. The mechanism behind visual improvement post glaucoma surgery needs to be elucidated.

Vitrectomy has been advocated for management of complications of uveitis, including vitreous hemorrhage, persistent dense vitreous inflammation, persistent cystoid macular edema, and epiretinal membrane formation [1056-1058]. The possible efficacy of pars plana vitrectomy (PPV) in inflammatory macular oedema has been studied for many years[1059], but randomized trials are lacking, except for one: a beneficial effect on visual function and angiographic findings is reported in a randomized controlled pilot study compared to a slighter effect of systemic treatment with steroids and immunosuppressants[1060]. Theoretically, the value of PPV for inflammatory macular oedema might be even better than in macular oedema of other origins since many

inflammatory mediators accumulate in the vitreous and a removal of these mediators may have a good effect on macular oedema; in addition, an enhanced fibrosis of the vitreoretinal interface occurs often and may result in the formation of epiretinal membranes and subsequent macular oedema. A review of studies on vitrectomy in the treatment of uveitis shows that conclusive evidence for a benefit of PPV in improving visual or disease outcomes in uveitis does not exist, but there is suggestive evidence [1059]. The presence of an epiretinal membrane has been proven to be a significant factor associated with medical treatment failure [1061] and a removal of this membrane can help to reduce macular oedema. Gutfleisch et al.[1062] performed a PPV with ILM peeling and injection of 4 mg triamcinolone in 19 patients with refractory macular oedema and found in 44% of the eyes a decrease of macular oedema on FA, but in 22% of all eyes a worsening of visual acuity. Schaal et al.[1063] reported a positive effect of a surgical posterior vitreous detachment on retinal thickness and visual acuity. In this sudy refractory macular oedema was not an indication for vitrectomy. Epiretinal membranes (ERM) have been removed by pars plana vitrectomy for decades [396, 397, 1064, 1065] but visual outcomes vary considerably. Membrane peeling has resulted in a favorable outcome in the management of idiopathic epiretinal membranes,[396, 1066, 1067] but epiretinal membranes associated with chronic uveitis reportedly have a poorer visual prognosis after vitrectomy[396]. Michels et al.[1067] reported postoperative visual acuities ranging from 6/7.5 to 6/12 in 28% of eyes, from 6/15 to 6/30 in 52% of eyes, and from 6/60 or worse in 20% of operated eyes. In a series by Kiryu et al.[1068], 82% of eyes gained two or more lines of visual acuity within 12 months after vitreous surgery, but after 24 months of mean follow-up, only 45% retained at least two lines of visual improvement. Ghazi-Nouri et al[1069] found that visual acuity improvement post epiretinal membrane peel was not statistically significant. Our data confirm the poor visual prognosis post membrane peel and the strong correlation between postop and preop visual acuities as reported in previous studies [397, 1070, 1071]. We found that only 3% of eyes that underwent membrane peel gained 3 Snellen lines or more, while 12% had lost 3 Snellen lines or more at the final postop follow-up visit (Fig.4.2.4.2). Suh et al.[1072] demonstrated that once photoreceptor cells have been impaired attributable to macular traction by ERM, they hardly recover with time after surgery. In their series, only 5 of 22 eyes with preoperative photoreceptor disruption showed recovery at 3 months after surgery, and only 2 eyes at 6 months, suggesting that prompt surgery is beneficial to prevent irreversible photoreceptor impairment. On the other hand, they found a relatively large number of eyes (12eyes) with newly developed photoreceptor disruption after surgery, and this was confirmed in 8 eyes by Cirrus HD OCT, while only 5 eyes showed photoreceptor recovery. This finding suggests that surgery can lead to the new development of photoreceptor disruption. Shimada et al.[1073] recently suggested that the central retinal thickness (CRT) to

amplitude macular ERG (amERG) ratio could be used in predicting the post-operative visual function along with the pre-VA and the duration of symptoms in eyes with ERM.

6.9 Ischemia.

Patients with ischemic retinal vasculitis characterised by a posterior uveitis and capillary closure on fluorescein angiography are rare but represent a major management problem [443]. Such patients generally do not respond well to immunosuppressive drugs, several of which have the potential to exacerbate disease because they are prothrombotic at high dosage (corticosteroids, cyclosporine). Furthermore, these patients usually present with the complications of retinal ischemia (i.e. poor vision resulting from macula ischemia or vitreous haemorrhage secondary to neovascularisation), and primary medical treatment is unlikely to reverse the situation in these circumstances[524]. The vasculitic and vaso-occlusive episodes in BD can cause capillary dropout resulting in capillary nonperfusion or macula ischemia [1074]. Macular ischemia secondary to occlusive parafoveal vasculitis has previously been described in cases of BD[203, 525, 1075], sarcoidosis and idiopathic retinal vasculitis[525]. Forooghian et al.[1076] observed macular ischemia in eyes with these syndromes as well as in eyes with idiopathic intermediate uveitis, idiopathic granulomatous panuveitis, sympathetic ophthalmia, and lupus vasculitis. Furthermore, they observed angiographic evidence of active occlusive parafoveal vasculitis in eyes with idiopathic intermediate uveitis, BD, and lupus vasculitis. In active phase of BD, drastic macular changes such as macular oedema or retinal ischemia could lead to the direct and persistent damage of the fovea [203, 1077, 1078].

Although all macular aspects of visual morbidity have been reported, macular ischemia has not been well documented[203]. Garcher et al.[1075] have reported a case of bilateral visual loss and macular ischemia related to BD and Bentley et al.[525] have reported macular ischemia in 12 patients with posterior uveitis, of whom 4 were diagnosed with BD. Behçet's disease was the commonest systemic disease associated with retinal ischemia in this study. Little attention has been paid to macular ischemia in the past; it is a rare finding in BD and there are no established criteria concerning its treatment in these patients[1079]. However, Yilmaz et al.[1079] reported that when inflammation is brought under control, macular ischemia may also improve. They suggested that every effort should be made to control ocular inflammation in BD. Garcher et al.[1080] reported a case of recovery of macular ischaemia and visual acuity with high dose corticosteroid treatment. Out of 16 patients who developed macular ischemia in our series, 3 had BD and 3 had SLE.

Vascular occlusion in the antiphospholipid syndrome can occur in vessels of all sizes; histologically the lesion is one of (non-inflammatory) bland thrombosis[1081]. Antiphospholipid antibodies are found in approximately 30% of patients with SLE.

The antiphospholipid syndrome may develop in 50–70% of patients with both SLE and antiphospholipid antibodies after 20 years of follow up[1082, 1083]. Important risk factors for a thrombotic event are a history of thrombosis, the presence of lupus anticoagulant antibodies, a high titre of IgG anticardiolipin antibodies and persistence of antiphospholipid antibodies. However, once a thrombotic event occurs, the risk of further thrombosis is lifelong, irrespective of the presence or disappearance of these antiphospholipid antibodies[1084]. Asherson et al.[1085] showed a four-fold increase in the prevalence of ocular vaso-occlusive disease in the presence of antiphospholipid antibodies. Jabs et al.[609] in their case series of patients with this form of severe retinal vaso-occlusion described very poor visual outcomes despite the use of different regiments of immunosuppression. Visual acuity was worse than 6/60 in 55% cases.

In a literature review, Au et al[1086] reported that patients developed visual loss in 80% of cases with visual acuity being 6/18 or worse at follow up or at presentation in 40% of these patients. A significant factor affecting visual outcome was the high rate of neovascularisation and/or vitreous haemorrhage arising from the retinal ischemic events.

Our study is in concordance with previous reports with regards to the poor visual outcome in ischemia, particularly in eyes with macular ischemia (Table 5.3 and Fig.5.1).

Clinical manifestation of Eales' disease is due to three basic pathological changes: inflammation (peripheral retinal perivasculitis); ischemic changes (peripheral retinal capillary non-perfusion); and neovascularisation of the retina or disk, which often leads to vitreous haemorrhage[692]. Vision in these patients can be normal to hand movements or light perception only. Bilaterality is quite common (50–90% of the patients)[766, 1087]. Although the disease may proceed to its full-blown picture, visual prognosis in these patients is not totally hopeless[766]. Elliot,[1088] for example, reported that 25 of the 46 eyes he followed for an average of six years had a visual acuity of 6/18 or better, whereas 26% had a vision of 6/60 or worse. Atmaca et al. reported that 47.5% of eyes had a visual acuity of 6/12 or better at the final examination, after a mean followup of 142.4 months[766]. The prognosis for visual acuity improvement is good after vitrectomy, because the patients tend to have relatively little coexisting structural retinal damage [1089]. Another study reported that the final visual acuities improved in all eyes after vitrectomy[1090]. Severe visual loss in Eales' disease usually results from complications of neovascularisation, such as persistent vitreous haemorrhage, retinal detachment, and anterior segment neovascularisation with secondary glaucoma[766]. Visual outcome of Eales' disease in our

cohort was favourable and in line with previous studies. We report 3 eyes out of 20 with severe visual loss due to neovascular glaucoma in 2 eyes and vitreous haemorrhage in 1 eye.

Bentley et al.[202] suggested that all patients with posterior uveitis should have a fluorescein angiogram before systemic treatment, when special attention should be given to the early venous phase to detect signs of macular ischemia. If visualisation is not sufficiently clear the angiogram should be repeated after or during treatment when the ocular media clears. The authors advised that full immunosuppression should be given to all patients at the start, but if macular ischemia is demonstrated and the vision fails to improve, the rationale for treatment should be revised. Some patients may still require high dose treatment for either their systemic disease or to control frequent relapses of acute uveitis, but in many the dose of these toxic drugs may be reduced[202].

A literature review suggests that treatment outcomes with immunosuppression in the case of retinal vaso-occlusions in SLE have been largely disappointing [613]. Although it has been shown that corticosteroids may result in the reduction or disappearance of lupus anticoagulant activity; and that immunosuppression can decrease anticardiolipin antibody titres (independent of its effect on disease activity in SLE), the role of immunosuppression in preventing thrombosis remains unclear [1091-1093].

There are only two reports where immunosuppression and treatment of the underlying systemic disease resulted in some opening of previously occluded retinal vessels [613]. In only one of these was immunosuppression used alone. In the first case described by Pfaffenbach et al.[1094], where heparin was used in combination with corticosteroids, some reperfusion of previously occluded vessels was noted but in other areas of the retina progressive occlusions of the retinal arterioles were also present. Gold et al.[1095] described a patient with bilateral extensive arterial occlusions treated with prednisolone and azathioprine. On follow-up examination gradual disappearance of the area of retinal infarction and reperfusion of a previously occluded branch retinal artery were noted, but this was in the setting of extensive neovascularisation. Montehermoso et al[608] reported improvements in the ‘retinal lesions’ in all five of their patients with retinal arterial occlusion in the setting of SLE treated with immunosuppression and anticoagulation, although it is unclear if revascularisation of previously occluded vessels occurred. Only small improvements in visual acuity occurred in three of these patients, with visual acuity worse in two patients following treatment. There is one anecdotal report to show that treatment with anticoagulation, despite the tapering of immunosuppression, resulted in the stabilisation of the retinal vaso-occlusive disease[1096]. However, with the exception of the case described by Pfaffenbach et al.[1094], it appears that once established the retinal vaso-occlusions do not resolve with anticoagulation. Therefore, treatment

should be aimed at halting the progression of this microthrombotic disease and should include anticoagulation [613]. Panretinal photocoagulation and vitrectomy have been found to be useful in preserving vision[1097].

The management of Eales' disease depends on the stage of the disease[1098]. It includes non-treatment with periodic evaluation in the regressed stage of periphlebitis or fresh vitreous haemorrhage, treatment with oral or periocular steroid in the active perivasculitis stage, and laser photocogulation in case of neovascularisation of retina or optic disk, or gross capillary nonperfusion. Vitreous surgery is indicated in nonresolving vitreous haemorrhage (usually more than 3 months). Any associated retinal detachment will, however, warrant early vitreoretinal surgery[1098]. The role of anticoagulant hyperbaric oxygen [1099] and anti-tubercular therapy remains controversial[1098]. Several studies regarding the management of Eales disease in various stages have been reported. Yet, in the absence of a randomised controlled clinical trial, a definite guideline is not available. Management options include the following: observation, medical, photocoagulation, and vitreoretinal surgery. A particular patient may require one or more of the above modalities of treatment, as quite frequently the other eye has a different stage of the disease[1098].

Chapter 7 Conclusion

Uveitis is a potentially blinding condition in the active population and should be cited among causes of blindness. Amongst different uveitis types, Panuveitis yields the worse visual prognosis. The main causes of visual loss are glaucoma in AU, CMO in IU and chronic macular damage in panuveitis and posterior uveitis. The proportion of CMO reported in this study is lower than that reported by Rothova et al.[300]more than a decade ago. This illustrates the effect of different treatment options developed over the past decade. Causes of visual loss within the first year of intraocular inflammation are reversible. Hence, it is important to initiate early and aggresive treatment to avoid irreversible macular damage. We also report in the present study a high prevalence of glaucoma, especially in eyes with chronic anterior uveitis.

Visual outcome after cataract surgery in uveitic eyes is favourable. Careful selection of cases, pre, peri and post cataract control of inflammation are important. Pre-op macular lesion is the main risk factor for visual loss post cataract surgery. Glaucoma surgery stabilizes visual acuity over time. We found no evidence of visual acuity improvement after membrane peel.

Visual loss in eyes with ischemia develops within the first five years and does not worsen with time. It is important to identify macular ischemia; when present, patients should be spared from aggressive immunosuppresion as this will have no impact on vision.

We could not determine the patients' ethnicity in this study. This information could have helped to determine whether race has any influence on visual prognosis in different types of uveitis.

Clinicians should familiarize with the SUN standardisation of criteria on reporting clinical data in uveitis to allow comparison with further studies.

This study was conducted in a tertiary referral centre. There is a selection bias inherent to the retrospective nature of this study, and the severity of cases attending this tertiary referral centre. The results cannot be therefore extrapolated to the general population. Population-based studies are needed.

Chapter 8. References

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CAUSES OF VISUAL LOSS IN UVEITIS/ MEH

Study Number: ..... Hospital Number: .....

DOB.

Gender: 1=M, 2=F

Ethnic origin: 1= Caucasian
2= Afro-carribean
3= Asian
4= Indian
5= Mixed

Systemic/ Ocular co-morbidity: (1= YES, 0= NO)

- Diabetes: 1/ 0

- HTN : 1/0

- Others(Specify).....
.....

Medications: .....
.....

Studied eye: R L BOTH

VA @ 1ST VISIT..... /...../...../..... IOP: .....mmHg.

VA< 6/12..1 / 0..... ..... /...../...../..... IOP.....mmHg

VA @ LAST VISIT...../...../...../.....

Uveitis site: Anterior/ Intermediate/Posterior Diagnosis.....
Panuveitis/ Scleritis

BCVA: ..... /...../...../.....

Worse VA: ..... /...../...../..... Cause of worse VA.....

Lens: Cataract 1 / 0 Type :.....

Fundoscopy: ..... (1=normal, 2= CMO, 3=CNVM, 4=ERM, 5= RD , 6=scar, 7= atrophy

8=optic neuropathy, 9= Ischaemia)

Other(specify).....

OCT: ..... (1=normal, 2=CMO, 3=CNVM, 4=ERM, 5=PED, 6=CSR)

FFA : .....(1=normal, 2= CMO, 3= Closure, 4= Leakage,)

.

BScan:……(1= normal, 2= Sclera thickening, 3= subtenon fluid, 4= RD)

Ishihara:……(1=normal, 2= abnormal)…..

Electrophysiology:……(1=normal, 2 abnormal)

Other Investigations:……..

TREATMENT:(1= YES, 0= NO)

Steroids: 1 / 0 Topic steroids/ Systemic steroids/.....

IMMT: 1 / 0.....
.....

OFI : 1 / 0 ..... /...../...../.....

IVTA : 1 / 0 …… /……/……/…….

Surgery: 1 / 0 What for? ..... /...../...../.....

VA Post: Surgery / IVTA/ ORFI/ LASER

2weeks	1month	2months	3months	6months	1year	18 months	2 years

Other(Specify).....

COMPLICATIONS DEVELOPPED : (1= YES, 0=NO)

Cataract: 1/ 0 /……/……/……

-Type: .....

Raised IOP: 1/ 0 /……../……./……..

-Highest IOP.....

-Glaucoma: 1/ 0

Ischaemia : 1 / 0

-Affected area.....

RD : 1 / 0

-Macula affected? 1 / 0

CMO : 1 / 0 Present at baseline: 1 / 0

Was it adequately treated? 1 / 0.

Macula .....(1=scarring, 2= atrophy,2=ERM, 3= Hole) .....

Other (Specify)……

IOP Rx 1 / 0 ..... With what? ....

Laser: 1 / 0...../...../...../.....

Further IVTA: 1 / 0..... How many: .....

Further OFI: 1 / 0 ..... How many: .....

Are the complications refractor to treatment? 1 / 0 .. ……(1=yes, 0=no)