Elevated intraocular pressure in uveitis: effects on the retinal nerve fiber layer, clinical course and surgical outcome in adults and children

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Thesis submitted for the degree of Doctor of Philosophy

2014

Thesis Declaration

I, Norshamsiah Md Din confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Acknowledgements

I would like to express my deepest gratitude to my supervisors, Professor Sue Lightman and Mr Simon Taylor. It was a priviledge to be supervised by these two inspiring researchers. I want to thank them for believing in me, for supporting my work, for their guidance and for their understanding in my limitations. With both, I learned how much more to persevere with whatever hurls there might be. Also to Mr Keith Barton who have advised me on the first few parts of this project.

Nothing would be the same without my loving husband who has been with me through thick and thin, for his sacrifice, unlimited support and understanding. This moment is much more precious with my beautiful children who have been patient and understood my time away from them.

My deepest gratitude goes to my parents, whom without their nurture; I might not be the person I am today.

My sincere thanks goes to Hazel Lawrence and Sarah Mayhew who have painstakingly helped with retrieving the patients' files and other documentations.

And finally, I would like to thank my friends, Hazlita, Lazha, Oren and Asaf who have given great ideas and input into this project, shared my joy and sorrow throughout this journey, and have brought warmth to the fellows' room. You are the best!

Abstract

Intraocular Pressure (IOP) elevation is a pertinent risk factor for glaucoma in uveitis. Macula oedema and disc swelling may mask glaucoma assessment making glaucoma detection challenging. This thesis aimed to evaluate whether peripapillary retinal nerve fiber layer (RNFL) measurement with the spectral-domain optical coherence tomography (SD-OCT) can be a conjunctive method.

We reviewed records of 309 patients with uveitis and analysed the SD-OCT results. Mean RNFL was thicker in uveitic compared to normal eyes. RNFL thinning was seen in all except the temporal quadrant of glaucomatous but only in the inferior quadrant of hypertensive uveitic eyes. RNFL defect was detected in approximately 20% of hypertensive eyes without clinical signs of glaucoma. Older age, higher maximum IOP and uveitis-induced IOP elevation were risk factors for RNFL defect and glaucoma. Reduced RNFL thickness correlated with worsening Humphrey visual field (VF) mean deviation.

A chart review of 103 children with non-Juvenile Idiopathic Arthritis-related uveitis revealed IOP elevation occurred in approximately 40% of children, steroid-induced in 35% of eyes with nearly 70% of them being high responders. Chronic uveitis was a strong risk factor for IOP elevation and glaucoma. The RNFL was thicker in uveitic compared to normal eyes. We found no RNFL thinning in hypertensive but significant thinning only in the inferior quadrant of glaucomatous uveitic eyes.

The outcome of the second compared to the first eyes of 30 patients with bilateral uveitis and raised IOP who underwent bilateral glaucoma surgery was assessed. We postulated the second eyes would suffer more from oral acetazolamide omission following early phases of surgery. The surgical success rates were comparable with no

significant visual acuity progression. Although the survival rate of the cup-to-disc ratio progression was worse in the second eye within the first 5 postoperative years, no significant difference was detected in the Humphrey VF progression.

Publication arising during the period of the thesis

1. Din NM, Isa H, Taylor SR, Barton K, Lightman SL. Intraocular pressure elevation in uveitis. Expert Rev Ophthalmol. 2012 Feb;7(1):45–59.

2. Din NM, Taylor SR, Isa H, Tomkins-Netzer O, Bar A, Talat L, Lightman SL. Evaluation of the Retinal Nerve Fiber Layer Measurement in Hypertensive Uveitic Eyes. JAMA Ophthalmol. 2014 Jul;132(7):859–65.

Conference presentations

1. Identification of a subgroup of uveitic patients at risk of visual loss from glaucoma. Presented at the The Royal College of Ophthalmology Annual Congress, Liverpool, 15-17th May 2012.
2. Evaluation of retinal nerve fiber layer measurement in adult uveitic patients with elevated intraocular pressure. Accepted for poster presentation at the World Ophthalmology Congress, Tokyo, 2-6th April 2014.

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List of abbreviations

ANA	Anti Nuclear Antibody
AROC	Area Under the Receiver Operating Curve
AS	Ankylosing Spondylitis
ATP	Adenosine Tri Phosphate
BCVA	Best Corrected Visual Acuity
BD	Behcet's Disease
BMO	Bruch's membrane opening
CAI	Carbonic Anhydrase Inhibitor
CCT	Central Corneal Thickness
CDR	Cup to Disc Ratio
CMO	Cystoid Macular Oedema
CSLO	Confocal scanning laser ophthalmoscopy
FE	First Eye
5FU	5 Fluorouracil
GDI	Glaucoma Drainage Implant
GON	Glaucomatous Optic Neuropathy
HLA	Human Leukocyte Antigen
IOHS	Inflammatory Ocular Hypertension Syndrome
IVTA	Intravitreal Triamcinolone Acetonide
JIA	Juvenile Idiopathic Arthritis
LogMAR	Logarithm of the Minimal Angle of Resolution
MMC	Mitomycin C
MTMT	Maximum Tolerated Medical Therapy
OCT	Optical Coherence Tomography
POAG	Primary Open Angle Glaucoma
RGC	Retinal Ganglion Cell

RNFL	Retinal Nerve Fiber Layer
SD-OCT	Spectral Domain Optical Coherence Tomography
SE	Second Eye
SLP	Scanning laser polarimetry
SUN	Standardized Uveitis Nomenclature
TD-OCT	Time Domain Optical Coherence Tomography
UG	Uveitic Glaucoma
VA	Visual Acuity
VF	Visual Field

1 Chapter 1: Introduction

1.1 Uveitis

Uveitis is defined as the presence of inflammation within the structures of the eye, but literally speaking, is inflammation involving the uveal coating of the eye.(Durrani et al., 2004) However, the inflammation can spread to neighbouring structures such as the vitreous causing vitritis, the retina causing retinitis and the optic disc causing papillitis, the sequelae of which may lead to sight threatening conditions such as cataract, cystoid macula oedema (CMO), optic neuropathy and retinitis. It was estimated that over 2 million people worldwide are affected by uveitis.(Siddique et al., 2013) Despite the advances in therapeutics, the prevalence of blindness due to uveitis has not been reduced in the last 30 years with about 10% of patients go blind from it. (Suttorp-Schulten and Rothova, 1996)

In the United States, the incidence of uveitis has increased 3 fold compared to the estimates 40 years back, with an incidence of 52.4/100 000 person-years and a period prevalence of 115.3/100 000 persons. (Gritz and Wong, 2004) The incidence and prevalence were lowest in children and highest among patients 65 years or older, and affected more women than men, with the largest difference between genders seen in older age groups.

The uvea plays an important role in the immunological defence of the eye. The blood-retinal barrier, blood-aqueous barrier and the absence of lymphatic drainage confer the eye a deviant and priviledged position from the immunological point of view. These special defence mechanisms play an important role in preservation of vision, failing which will result in intraocular inflammation.(Streilein, 1994)

1.1.1 The SUN Classification

Uveitis can be caused by infectious agents or immune- mediated processes. Many immune mediated uveitis are associated with systemic diseases such as sarcoidosis, the HLA-B27 associated spondyloarthropathies and Behcet's disease. Others are confined to the eye, for example iridocyclitis, Fuch's heterochromic cyclitis and syampathetic ophthalmia. With this vast variability in uveitis entities and how uveitis is diagnosed, attempts have been made to standardize categorisation to allow comparisons to be made among clinical research from different centres, permit meta-analyses and assist in the development of a more complete and meaningful picture of their clinical course and response to treatment.

In 1987, the International Uveitis Study Group devised a classification system for uveitis based on the anatomic location of the inflammation. (Bloch-Michel and Nussenblatt, 1987) However, there were ambiguities in its use, and it did not provide criteria for the diagnosis of specific uveitic entities. As a result, in 2004, the Standardization of Uveitis Nomenclature (SUN) Working Group revised certain issues not addressed by the previous nomenclature. (Jabs et al., 2005) Thereafter, uveitis was classified into categories according to Table 1.

This classification also defined the use of the terminology acute, recurrent and chronic (Table 2). The term "*acute*" was used to describe the clinical course of a uveitic event characterised as sudden onset and of limited duration, such as the HLA-B27-associated "acute anterior uveitis". "*Recurrent*" should be used to describe repeated episodes of uveitis separated by periods of inactivity without treatment, and this period of inactivity is at least 3 months in duration. The term "*chronic*" is used to describe

persistent uveitis with prompt relapse (in less than 3 months) upon discontinuation of therapy.

Table 1: The SUN* Working Group Anatomic Classification of Uveitis. (Jabs et al., 2005)

Type	Primary Site of Inflammation§	Includes
Anterior uveitis	Anterior chamber	Iritis
		Iridocyclitis
		Anterior cyclitis
Intermediate uveitis	Vitreous	Pars Planitis
		Posterior cyclitis
		Hyalitis
Posterior uveitis	Retina or choroid	Focal, multifocal or diffuse choroiditis
		Chorioretinitis
		Retinochoroiditis
		Retinitis
		Neuroretinitis
Panuveitis	Anterior chamber, vitreous, and retina or choroid	

***SUN=Standardization of uveitis nomenclature §As determined clinically. Adapted from the International Uveitis Study Group Anatomic Classification.** (Bloch-Michel and Nussenblatt, 1987)

Apart from classifying uveitis, the SUN Working group also defined key visual acuity thresholds to standardize definition in visual outcomes across studies. The basis for reporting results of uveitis studies include 6/15 or worse (20/50 or worse) and 6/60 or worse (20/200 or worse). Additionally, the term "*glaucoma*" should not be considered synonymous with elevated IOP in a patient with uveitis. It should only be used when there is either observed glaucomatous disc damage or demonstrated VF loss.

Table 2: The SUN* Working Group Descriptors of Uveitis (Jabs et al., 2005)

Category	Descriptor	Comment
Onset	Sudden	
	Insidious	
Duration	Limited	≤3 months duration
	Persistent	>3 months duration
Course	Acute	Episodes characterised by sudden onset and limited duration
	Recurrent	Repeated episodes separated by periods of inactivity without treatment ≥3 months in duration
	Chronic	Persistent uveitis with relapse in < 3 months after discontinuing treatment

*SUN=Standardization of uveitis nomenclature.

1.1.1.1 Anterior uveitis

Anterior uveitis is the commonest form of uveitis, accounting for 40-90% of cases. (Biswas et al., 1996) (McCannel et al., 1996) Also known as iridocyclitis, it predominantly affects the iris and ciliary body. The genetic marker HLA B27 is present in about 50% of patients with acute anterior uveitis. (Martin et al., 2002) Ankylosing Spondylitis (AS) an idiopathic chronic arthritis is strongly associated with anterior uveitis, affecting primarily young men and to a lesser extent, young women. (Rosenbaum, 1992) About 25% of AS patients will develop anterior uveitis and approximately 95% of them are HLA-B27 positive. (Brewerton et al., 1973)

In children under the age of 16, Juvenile Idiopathic Arthritis (JIA) is the commonest disease associated with anterior uveitis. (Cunningham, 2000) Pauciarticular involvement, the lack of systemic features and positive anti-nuclear antibodies (ANA) are the highest risk factor for uveitis. (Kanski, 1990)(Rosenberg, 2002) Uveitis in this condition is usually insidious in onset and preceeded by arthritis. (Foster, 2003)

1.1.1.2 Intermediate uveitis

According to the SUN Classification, intermediate uveitis should be used for the subset of uveitis where the major site of inflammation is the vitreous. The presence of peripheral vascular sheathing and macula edema should not change the classification. (Jabs et al., 2005) Pars planitis is a diagnostic terminology which should be used only for that subset of intermediate uveitis where there is snowbank formation occurring in the abscence of an associated infection or systemic disease (i.e “idiopathic”). The occurrence of snowball and snowbanks in the presence of a systemic disease (e.g sarcoidosis) or an associated infection (for example, Lyme disease) should warrant the use of the term “Intermediate uveitis”.

Intermediate uveitis accounts for 7-15% of uveitis cases in a general ophthalmology practice and between 10-33% of cases in children.(Guex-Crosier, 1999)(Cunningham, 2000)(Clarke et al., 2013) It is usually bilateral and can be associated with systemic diseases like multiple sclerosis and sarcoidosis.(Biousse et al., 1999) (Heiligenhaus et al., 2011)

Intermediate uveitis is characterized by a mild anterior chamber reaction with vitreous cells, retinal vasculitis and macular edema. Snowbank is an opacified ridge of exudates in the peripheral retina, especially inferiorly, but also can be superiorly.(Henderly et al., 1987) It is unique to intermediate uveitis and in cases of severe long standing inflammation, may lead to fibrotic condensation of the inflammatory exudates in the form of a cyclitic membrane and also retinoschisis from thinning of the inner retinal layer, which may result in tractional retinal detachment. (Majumder and Biswas, 2013) Vitreous snowballs are yellow-white inflammatory aggregates found commonly in the

midvitrous and the inferior part of the peripheral vitreous. (Manohar Babu and Rathinam, 2010)

1.1.1.3 Posterior and pan-uveitis

Posterior uveitis primarily involves the posterior segment which includes choroiditis, retinitis, papillitis and vasculitis. It is often associated with anterior uveitis of which it is classified as pan-uveitis. According to the SUN Classification, the term panuveitis should be reserved for those conditions in which there is no predominant site of inflammation, but inflammation is observed in the anterior chamber, vitreous, and retina and/or choroid (i.e retinitis, choroiditis, or retinal vasculitis). Structural complications such as macular edema or neovascularisation should not be considered in classifying the anatomic location of the uveitis. (Jabs et al., 2005) Most of them are idiopathic but systemic conditions such as Behcet's disease, Vogt-Koyanagi-Harada Syndrome and infectious causes such as tuberculosis, syphilis and toxoplasmosis are among the underlying causes. (Durrani et al., 2004)

1.2 IOP elevation in uveitis

An indirect consequence of inflammation but is as sight threatening as the others is elevated intraocular pressure (IOP), widely accepted to have a causative link to glaucoma, an insidious complication of uveitis and a regularly occurring clinical problem and perhaps under recognised as such, which may lead to permanent visual loss. (Neri et al., 2004) Elevated IOP in uveitis is often a result of a delicate situation whereby it can be provoked by both the disease and treatment of uveitis itself. The first line of uveitis treatment is often corticosteroid, the use of which has to be balanced against the risk of IOP elevation, a well known side effect of steroid use. With

a prevalence of up to 42% and treatment requiring in almost 30% (Herbert et al., 2004), IOP elevation in patients with chronic uveitis is a significant risk factor for glaucoma. Apart from chronic uveitis, increasing age and longer duration of uveitis are also identified risk factors for IOP elevation. Eyes with chronic uveitis were nearly 3 times more likely to develop raised IOP requiring treatment than eyes with acute uveitis (Herbert et al., 2004).

Glaucoma ranked as the third most common complication of uveitis after CMO and cataract, but while the other two are often reversible, glaucoma often leads to irreversible visual loss.(Rothova et al., 1996) In children, however, glaucoma takes precedence over CMO and cataract as the commonest complication of uveitis. (de Boer et al., 2003a) Disturbances in IOP, both ocular hypertension and hypotony, were found to be associated with increased risk of visual loss. (Kaçmaz et al., 2008) (Thorne et al., 2007)

1.2.1 Prevalence of IOP elevation and glaucoma in uveitis

Uveitis accounts for 10% to 35% of blindness in people under the age of 65 years. (McCluskey et al., 2000)(Rothova et al., 1996) In a retrospective review of 216 uveitic patients, the prevalence of IOP elevation was 41.8% and nearly 30% of them required treatment for raised IOP after a mean follow-up period of 7.5 years. (Herbert et al., 2004) The prevalence of raised IOP in a survey of 1736 adult uveitis patients was 8.6% and out of those, 28.8% had glaucoma after a mean period of 5.7 years was reported. (Heinz et al., 2009) This difference in prevalences of both IOP elevation and glaucoma in reported studies depends partly not only on the definitions used, but also on the case mix reported. IOP elevation exceeding 21 mmHg (Herbert et al., 2004) or 24 mmHg(Heinz et al., 2009) has been used as the cut-off point.

Several uveitic entities such as anterior uveitis caused by certain viruses, in particular Cytomegalovirus (CMV), Herpes Simplex virus (HSV), Varicella Zoster virus (VZV) and Rubella virus (RV) are particularly associated with IOP elevation. (Sungur et al., 2010)(Wensing et al., 2011) The incidence of secondary ocular hypertension and secondary glaucoma in these conditions has been reported to be 47.3% and 13% respectively.(Sungur et al., 2010) Although IOP of more than 30 mmHg was reported to be slightly more frequent in HSV (50%) and VZV anterior uveitis (46%) compared to RV (25%), glaucoma developed at similar rates (18-30%) in all three groups. (Wensing et al., 2011) Despite that, majority of them respond very well to hypotensive agents and anti-inflammatory treatment and therefore glaucoma surgery was rarely required. (Sungur et al., 2010)

Among the paediatric population, the prevalence of IOP elevation was reported to be 35% in children with all types of uveitis within a mean follow-up period of 5 years. (Sijssens et al., 2006) The prevalence was found to be commoner in JIA-associated uveitis and those who are ANA positive without evidence of arthritis. Two-third of these children developed raised IOP within the first 2 years of diagnosis of uveitis. (Sijssens et al., 2006) The prevalence of glaucoma among all uveitic children was reported to be 19%; and almost half of them had JIA - associated uveitis, out of which 15% eventually developed a VA of less than 20/200. (de Boer et al., 2003a) However, there are other conflicting reports that found glaucoma to be commoner in other types of uveitis such as Vogt-Koyanagi Harada syndrome (50%) compared to JIA (33%). (Hamade et al., 2009)

1.2.2 The effect of raised IOP on the optic nerve head

Glaucomatous optic neuropathy occurs due to accelerated loss of retinal ganglion cells (RGC). The long axons of the RGC in the retina and optic nerve are susceptible to damage and the major site of this damage is at the level of the optic nerve head, particularly the lamina cribrosa. Axonal injury at this level is reflected in damage to the RGC body, which is in turn reflected in thinning of the retinal nerve fiber layer (RNFL). (Blumenthal and Weinreb, 2001)

Although IOP elevation is not the only risk factor for glaucoma, at present it is the only modifiable risk factor to decelerate glaucoma progression, such that even a person with normal tension glaucoma benefits from IOP-lowering treatment (Collaborative Normal-Tension Glaucoma Study Group,(1998). Nickells has summarized a 5 staged possible sequence of events that leads to ganglion cell death from elevated IOP gathered from rat and mouse models of glaucoma. (Nickells, 2007)

1. **Stage 1: Elevation of IOP and activation of optic nerve glia in the lamin acribrosa.**

   High pressure from within the eye exerts force around the globe especially at the weakest point which is at the scleral canal and lamina cribrosa,(Quigley and Addicks, 1980) based on the fact that both antegrade and retrograde axonal transport were blocked at this site in glaucomatous eyes. (Quigley et al., 2000)(Glovinsky et al., 1991) Under normal conditions, glia provide supportive functions to the neurons such as regulation of extracellular K+ levels, removal of glutamate and gamma-aminobutyric acid (GABA) neurotransmitters, metabolic renewal of precursors for synthesis of glutamate, ammonium ion detoxcification, regulation of extracellular pH levels and osmolarity and

provision of energy to neurons by providing lactate and/or glucose from the breakdown of intracellular glycogen stores.(Ransom et al., 2003) Elevated IOP causes the optic nerve glia in the lamina cribrosa to undergo an "activation" response, whereby glia change their behaviour and alter their gene expression profile. In a glaucomatous eye, activated astrocytes and microglia in the optic nerve head begin to express genes that are involved in proliferation, cell adhesion and synthesis of new extracellular matrix.

2. **Stage 2: Damage to the axon and the process of degeneration.**

   Activated microglia synthesizes and release toxic compounds such as nitric oxide resulting in damage to ganglion cells axons and neighbouring cells. (Liu and Neufeld, 2000) They also stimulate vasoconstriction of regional small capillaries, inducing micro-strokes in the optic nerve head. The damaged axons then execute a self-destruction program that involves systematic dismantling of its cytoskeleton and other organelles, including the breakdown of microfilaments and microtubules, and deregulation and swelling of mitochondria. (Raff et al., 2002) The pattern of degeneration, termed "die back" is characterized by a slow degeneration of the axon beginning at the synaptic end and progressing in a retrograde fashion towards the neuronal soma.

3. **Stage 3: loss of neurotrophic support and apoptotic death of ganglion cell somas in the retina (Primary Degeneration).**

   Like any other neurons, the RGC can execute apoptosis which is a complex series of events that results in activation of a cascade of proteases that systemically digest the internal contents of dying cells. (Nickells, 2004) This leaves behind very little cellular debris which when not removed, may lead to

inflammatory response causing damage to the surrounding tissue. There are two distinct pathways of apoptosis, the “intrinsic” and “extrinsic” pathways. The “intrinsic” pathway results in mitochondrial dysfunction, leading to generation of reactive oxygen species, loss of ATP production and release of cytochrome C. (Green and Reed, 1998) The “extrinsic” pathway involves cell surface signaling between a ligand and a receptor which activates a death domain which then directly activates caspases. The RGC, like most neurons in the central nervous system, die by intrinsic apoptosis. It was speculated that the primary cause of ganglion cell death is neurotrophin deprivation, a consequence of stage 1 and 2. (Sawai et al., 1996)

4. **Stage 4: Signalling ganglion cell apoptosis (Secondary Degeneration).**

   The dying cells from stage 3 were thought to adversely affect their neighbouring cells by presumably expelling their glutamate and killing surrounding ganglion cells, causing secondary degeneration. This theory was supported by the evidence that glutamate level was found to be increased in the vitreous of glaucomatous eyes. (Dreyer et al., 1996) Glutamate at high doses damages neurons by hyperstimulating the receptor N-methyl-D-Aspartate (NMDA) receptor causing a toxic influx of extracellular Ca2+.

5. **Stage 5: Glial activation in response to neurodegeneration.**

   Glial activation in stage 5 is dissimilar to the process in stage 1 in that in stage 5, glial cells appear to respond to the progressive degeneration of the RGC instead of to the effects of elevated IOP. In the retina, Müller cells initially respond by producing neurotrophic factors, possibly to provide neurotrophic support to the degenerating RGCs. (Honjo et al., 2000) However, as ganglion cells die and the RNFL thins, Müller cells and astrocytes lays down new

connective tissue to generate glial scars replacing neural tissue loss. (Nickells, 2007)

Based on this possible sequence of events, the use of neuro-protective agents has been explored in an attempt to modify the disease process independent of IOP. Drugs like Timolol which appears to have a neuroprotective effect, possibly act by blocking Ca2+ influx into axons. (Brain Res Bull 2004, 525) The ultimate therapy would then be to include lowering IOP, prevent or reverse glial activation, block axonal degeneration and block ganglion cell soma apoptosis.

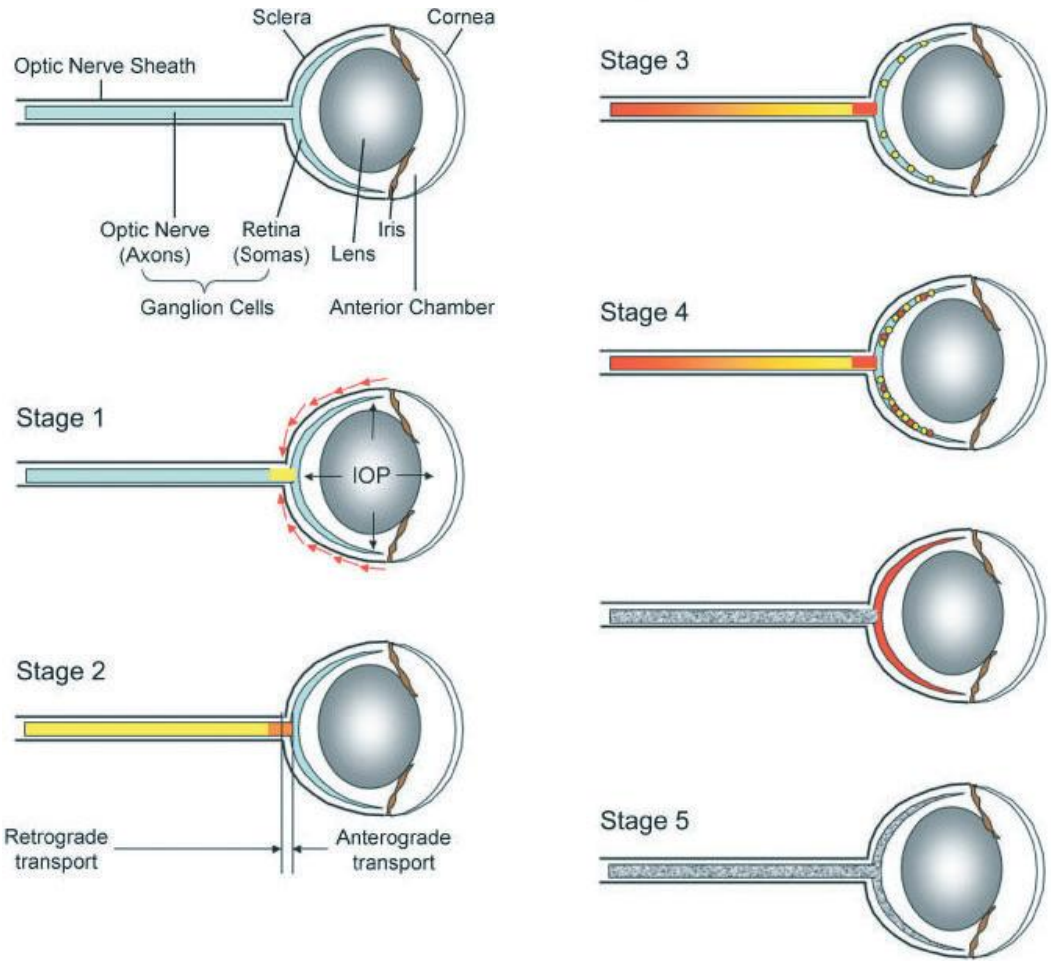

Figure 1: The possible sequence of events explaining the effect of raised IOP to ganglion cell death.

A mouse eye is depicted because details of the events emerged from studies carried out in rodent eyes. Ganglion cell structures, depicted in light blue, are made up of axons in the optic nerve and their somas and dendritic trees in the retina. In stage 1, elevated IOP exerts force around the eye ball, especially at the weakest point, the sclera canal, causing changes in the glia at the optic nerve head. In stage 2, the activated optic nerve glia probably cause damage to the axons (red shading) likely affecting both antegrade and retrograde axonal transport. This initiates an autonomaous axonal self-destruction programme (yellow shading). In stage 3, the axons undergo disassembly in a retrograde fashion (red-yellow gradient shading) and complete blockage of the neurotrophins transport to the retina occurred at the level of the lamina (red shading). As a result, ganglion cell somas in the retina begin their own apoptosis (yellow circles in the retina). In stage 4, the dead gaglion cells from stage 3 releases excess glutamate into the extracellular space causing their neighbouring cells to die as well, by apoptosis in secondary degeneration (yellow circles in the retina). Ganglion cell soma death translates into significant loss of neuronal tissue in the optic nerve and glial cells responds by generating scar tissue (grey shading). In stage 5, glial scar replaces all remnants of gaglion cell structure both in the retina and optic nerve (grey shading). Adapted from (Nickells, 2007)

1.3 Aetiology of IOP elevation in uveitis

The aetiology of raised IOP in uveitis can be broadly divided into two categories (Figure 2). The first category is IOP elevation as a result of uveitis itself, occurring either during an acute uveitis attack, or as a chronic sequelae of inflammation. The second category is iatrogenic, occurring as a result of corticosteroid use for the treatment of uveitis, or steroid-induced IOP elevation.(Din et al., 2012) However, in any given eye, both factors often contribute to IOP elevation to a certain degree.

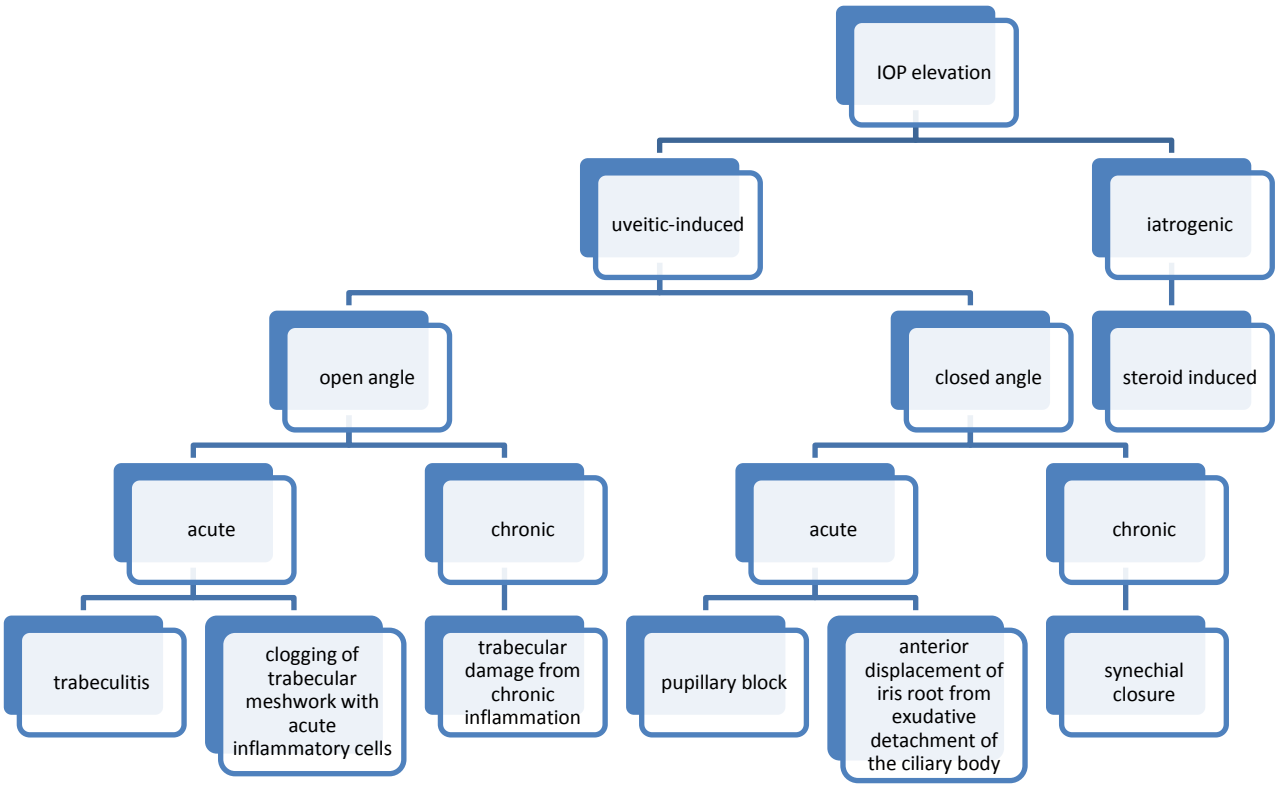

Figure 2: Algorithm of the aetiology of IOP elevation in uveitis.(Din et al., 2012)

1.3.1 Uveitis-induced IOP elevation

Uveitis-induced IOP elevation can be further divided into open and closed angle. In both conditions, raised IOP may occur acutely or chronically. (Din et al., 2012) Acute and transient IOP elevation with open angles is believed to be due to trabeculitis or clogging of the trabecular meshwork with inflammatory cells, causing reduced aqueous outflow.(Moorthy et al., March) Chronic inflammation leading to damage of the trabecular meshwork can also contribute to open angle IOP elevation.

Closed angle, on the other hand, can be subdivided into acute and chronic IOP elevation. (Kok and Barton, 2002) Acute rise in IOP with closed angle can be due to extensive posterior synechiae and secclusio pupillae giving rise to pupillary block and iris bombe (Figure 3), exudative detachment of the ciliary body leading to anterior displacement of the iris root, or from forward movement of the lens-iris diaphragm in conditions such as posterior scleritis. Chronic rise in IOP can be due to anterior synechial closure of the trabecular meshwork following scarring from recurrent uveitis attacks or neovascularisation from persistent intermediate uveitis or occlusive vasculitis in the posterior segment. Finally, patients with uveitis are just as likely to have constitutionally narrow angles as the normal population.

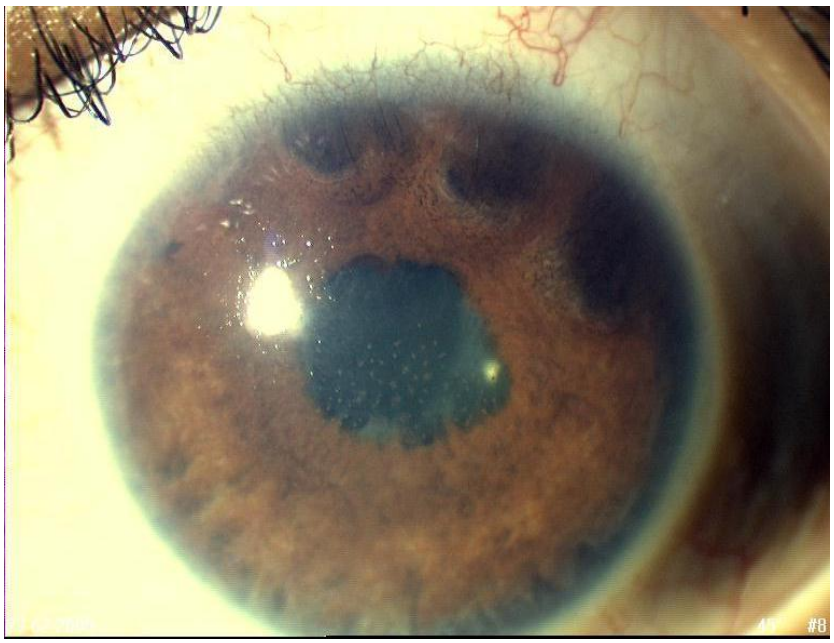

Figure 3: An example of an eye with intense inflammation causing secclusio pupillae and iris bombe.(Din et al., 2012)

There is no standardized terminology used in the Glaucoma Guideline by the Royal College of Ophthalmology to define IOP elevation in uveitis (Guideline Development Group, 2009). Various names has been used such as inflammatory ocular hypertension syndrome (IOHS)(Reddy et al., 2007)(Kok and Barton, 2002), hypertensive uveitis, or simply ocular hypertension (Sijssens et al., 2006), to describe different aspects of elevated IOP secondary to uveitis. While IOP elevation is not considered one of the defining features for primary open angle glaucoma (POAG) or primary angle closure glaucoma, in eyes with a secondary form of ocular pathology, like uveitis, IOP elevation above the normal limit leading to optic nerve damage must be present to define secondary glaucoma. (Foster et al., 2002)

The term IOHS has been used by Kok and Barton to describe conditions commonly associated with IOP elevation of more than 21 mmHg, which include Posner Schlossman Syndrome, Herpetic Keratouveitis, Fuch's Hetereochromic Iridocyclitis and

toxoplasma chorioretinitis. (Kok and Barton, 2002) Syphilis was also included in this terminology in a separate study.(Reddy et al., 2007) In such conditions, the incidence of uveitic glaucoma is higher than other types of uveitis and therefore patients with these conditions should be given particular attention for the development of glaucomatous optic neuropathy (GON).

Because measurement of the IOP depends on the biomechanics of the cornea, any changes in the central corneal thickness (CCT) influences the IOP reading. The corneal thickness, on the other hand, has been shown to be influenced by uveitic activity. Ozdamar et al reported an increase in CCT in eyes with active compared to inactive Behcet's Disease (BD) and healthy control group. (Ozdamar et al., 2010) The mean CCT in inactive BD was normal and recurrent uveitis did not lead to permanent change in CCT. Therefore measuring the IOP in an eye with active uveitis might produce a falsely high reading during such event and therefore giving a false impression of uveitic ocular hypertension. This study may also suggest that intraocular structures other than the cornea might also be thickened. This was supported by the fact that the macula was found to be thicker in active iridocyclitis compared to controls, although it did not necessarily translate into cystoid macular edema. (Castellano et al., 2009)

1.3.2 Steroid-induced IOP elevation

Corticosteroid–induced IOP elevation, also known as steroid response, is a great challenge in the management of intraocular inflammation. It is usually associated with topical steroid use, but may also develop following oral, intravenous, inhaled, nasal and especially periocular steroid injection.(Behbehani et al., 2005) (Carnahan and Goldstein, 2000) The exact mechanism has not been fully understood, but a few theories have been postulated.

Corticosteroids has been shown to increase aqueous outflow resistance (Armaly, 1963). Other studies reported the abundance of elements accumulated in the extracellular matrix such as basement membrane-like material, fine fibrillar-like material or proteoglycans in the iridocorneal angle tissues of steroid induced glaucoma patients. (Rohen et al., 1973)(Johnson et al., 1997) Evidence from cell culture studies also suggest that corticosteroid induced cytoskeletal changes of the trabeculocytes could inhibit pinocytosis of the aqueous humor or inhibit the clearance of the waste product glycosaminoglycans. (Clark et al., 1994)(Tawara et al., 2008) In the majority of cases, the IOP lowers spontaneously to baseline levels after steroid therapy is stopped. (Sallam et al., 2009)

As often is the case in glaucoma-related research, the definition of IOP elevation varied between studies of steroid-induced IOP elevation. An elevation of more than 5 mmHg from baseline (Yamamoto et al., 2008), an IOP above 21 mmHg, (Herbert et al., 2004) or 24 mmHg (Heinz et al., 2009) or both (Levin et al., 2002) after corticosteroid treatment has been used to define steroid response.

1.3.2.1 The grading of steroid response

1.3.2.1.1 Armaly classification

Armaly in 1963 first graded an individual response to corticosteroid into high, intermediate and low responses according to the amount of IOP increase after exposure to topical steroids. (Armaly, 1965) He studied 80 normal subjects under the age of 40 years who were instructed to apply 0.1% dexamethasone 21-phosphate (Decadron, Merck Sharp & Dohme) three times daily to the right eye. Within the first 2 weeks, subjects with increase in pressure greater than 8-10 mmHg had discontinuation

of therapy. The remaining patients had continuation of therapy for a total period of 4 weeks. The IOP was measured before treatment and at weekly intervals. The response to the above therapy resulted in the categorization of the subjects into 3 distinct groups:

1. Group I: exhibiting a low level of response with a mean pressure rise of < 6 mmHg. This group formed 66.2% (53 subjects) of the sample group. The hypertensive response in this group virtually completed after the second week and maximum response was attained at the end of the third week. No further change in IOP was produced by the additional fourth week of dexamethasone application.
2. Group II-A: exhibiting an intermediate level of response with a mean pressure rise between 6 to 15 mmHg which comprised of 28.8% (23 individuals) of the sample.
3. Group II-B: exhibiting a high level of response with a mean pressure rise of > 15 mmHg and it comprised of 5% (4 subjects) of the sample. In both groups II-A and II-B, the pressure rise continues throughout the 4 weeks without significantly reducing its rate of progress.

1.3.2.1.2 Becker Classification

In 1965, Becker also studied the level of steroid response in 50 normal volunteers, 75 offsprings of patients with normal tension glaucoma, 50 glaucoma suspects and 26 normal tension glaucoma patients. (Becker, 1965) All normal tension glaucoma patients had IOP of ≤23 mmHg at study entry. The subjects were subjected to topical betamethasone four times daily to only one eye and IOP was measured weekly for six weeks. Topical corticosteroids were discontinued once the IOP reached greater than

31 mmHg. He divided the response to topical steroids into low (peak IOP < 20 mmHg), intermediate (peak IOP 20-31 mmHg) and high response (peak IOP >31 mmHg). He found that in:

1. The normal tension glaucoma patients: All eyes developed IOP ≥20 mmHg and 24 eyes (92%) were high responders. Only 10 patients completed the six weeks topical corticosteroids as the remaining patients had dramatic IOP elevation and the steroids had to be discontinued.
2. The offsprings: 65 of the offsprings of normal tension glaucoma patients (87%) had IOP elevation of ≥20 mmHg and 14 (19%) were high responders.
3. The glaucoma suspects: 49 (98%) of them had IOP ≥20 mmHg or more, and 12 (24%) were high responders.
4. The normal volunteers: 15 (30%) of them had IOP ≥20 mmHg and 2 (4%) were high responders.

1.3.2.2 Topical steroid

As illustrated above, topical corticosteroid has varying effects on the IOP depending on their pharmacokinetics and pharmacodynamics, particularly the strength, penetration ability, duration of usage and the dose of the agent. It also depends on the patient's age and ocular condition. The effects in children are especially dose and age dependent (Lam et al., 2005) (Fan et al., 2001). Steroid response to topical dexamethasone in children occurs more frequently, more rapidly and more severely compared to adults. (Kwok et al., 1997) Younger children develop higher peak IOP earlier than older children.

Dexamethasone alcohol 0.1% (Maxidex, Alcon Laboratories, Fort Worth, Texas, USA) is one of the most potent steroids used to treat ocular inflammation. The incidence of IOP elevation in healthy individuals receiving a combination of dexamethasone 0.1% and tobramycin 0.3% four times a day was reported to be 7.5% over a period of 28 days. (Holland et al., 2008) This figure doubled in eyes with blepharoconjunctivitis receiving the same drug at the same dose after a shorter duration with 14.4% of eyes developing IOP elevation between 5-9mmHg after 14 days. (White et al., 2008)

Prednisolone acetate 1% (Pred Forte 1%, Allergen, Inc., Irvine, California) is another preferred topical steroid in uveitis. In the treatment for anterior uveitis, the risk of IOP elevation with this medication was reported to be between 1.7 to 8 times more compared to rimexolone 1% ophthalmic suspension (Vexol 1%, Alcon Laboratories, Inc., Fort Worth, Texas) although with similar efficacy. (Biswas et al., 2004) (Foster et al., 1996) In treatment for various types of uveitis, the incidence of raised IOP induced by the use of 1% Prednisolone was reported to be 13%. (Shrestha et al., 2013)

Fluoromethalone alcohol 0.1% causes an increase in IOP elevation between 2.6 to 5.8 mmHg with the peak IOP between 17.1 to 20.6 mmHg after a mean duration of 6 to 15 days in children. (Kwok et al., 1997)(Fan et al., 2001)(Fan et al., 2003) Its IOP-elevating potential is also low in adults who are known to be steroid responders and comparable to that of Rimexolone 1.0%. (Leibowitz et al., 1996) However, because of its low intraocular penetration, its use for treating uveitis is limited. (Din et al., 2012)

Loteprednol etabonate 0.5% (Lotemax; Bausch & Lomb, Inc., Rochester, NY) is another less favourable steroid for treatment of uveitis because of its low efficacy in uveitis, especially with involvement of the posterior segment. (Loteprednol Etabonate US Uveitis Study Group,(1999)(Pavesio and Decory, 2008) It was reported to cause an IOP

increase of 9.2 mmHg after a mean duration of 55 days, with 24% requiring IOP-lowering medication and a further 8% requiring surgery to control the IOP. (Rajpal et al., 2011)

Recently, difluprednate ophthalmic emulsion 0.05% (Durezol™, Alcon, Fort Worth, texas), a topical diflurinated derivative of prednisolone, was developed to treat inflammation and pain after ocular surgery with an off-label use for treatment of other anterior segment inflammatory condition. IOP elevation occurred in only 3% of patients when used post-operatively. (Korenfeld et al., 2009) A dose of 4 times a day was found to be as effective as prednisolone acetate 1% (Pred Forte) 8 times a day in the treatment of uveitis. (Foster et al., 2010) However, 80% of children and 45% of adults developed elevated IOP by 10 mmHg or more when used for treatment of various kinds of uveitis. Sixty percent of children and 18% of adults had peak IOP ≥30 mmHg and an additional 5% of adults experienced IOP of 50 mmHg or greater. (Birnbaum et al., 2011)

Steroid-induced IOP elevation limits the therapeutic options in uveitis. Although more potent topical steroids like dexamethasone sodium phosphate and 1% prednisolone acetate can be substituted for weaker steroids such as rimexolone 1% ophthalmic suspension, the lower potency of these topical steroids may not adequately treat ocular inflammation.

1.3.2.3 Regional corticosteroid injection

Regional steroid injection such as orbital floor injection of methylprednisolone and subtenon's triamcinolone injection delivers a sustained release of local steroids and resolves the problem of patients' non-compliance and side effects of systemic steroids.

However, an irretrievable steroid depot may result in severe and recalcitrant IOP elevation.

Levin at el examined the effect of a sub-tenon corticosteroid injection in eyes known to respond to topical steroids or the fellow eyes of patients who had previously received posterior subtenon's corticosteroid injection for various types of uveitis. They found a higher rate of recurrent IOP elevation in the known steroid responder compared to the non-responders eyes (44% vs. 13%) but most of these eyes were successfully managed with topical anti-glaucoma therapy (Levin et al., 2002). This study suggested that a topical steroid response is not an absolute contraindication to depot corticosteroid injection, and that patients not known to be topical steroid responders can still develop raised IOP when given depot injection of corticosteroid. It is therefore crucial for any patient who have received topical or depot steroids to be monitored closely.

In eyes with intractable IOP elevation occuring within 6 months after sub-tenon triamcinolone injection and which have failed medical hypotensive therapy, surgical excision of steroid depot has been attempted. The mean IOP reduction achieved was 20.5 mmHg and all glaucoma medications were discontinued in about 60% of the patients after 6 months of follow-up. (Okka et al., 2010)

Over the last 10 years, there has been a favourable use of intravitreal triamcinolone acetonide (IVTA) to treat various uveitic complications such as CMO and vitritis. It has been shown that the IOP can rise to more than 10 mmHg from baseline in up to 43% of uveitic patients receiving IVTA which was more commonly seen in patients younger than 40 years of age. (Kok et al., 2005) Although the majority can be controlled with topical hypotensive agents, some required more aggressive measures such as

vitrectomy to remove the triamcinolone crystals (Agrawal et al., 2005), or glaucoma surgery (Singh et al., 2004).

In conditions other than uveitis such as diabetic maculopathy and maculopathy due to vein occlusions, there were varying incidence of IOP elevation with IVTA injections reported.(Yamamoto et al., 2008),(Tawara et al., 2008) IOP elevation following IVTA can be much delayed in diabetic macula edema. Interestingly, IOP elevation was more prolonged in those who received posterior subtenon injection compared to intravitreal injection. (Yamamoto et al., 2008)

1.3.2.4 Intravitreal steroid implant

Sustained released intravitreal corticosteroid implants such as Ozurdex (dexamethasone intravitreal implant, Allergan Inc., Irvine, CA, USA) and Retisert (fluocinolone acetonide intravitreal implant, Bausch & Lomb, Rochester, NY, USA) have been developed to provide a more prolonged release of intraocular steroids providing better local control of uveitis and may avoid complications of systemic steroid and other immunosuppressive agents.

The risk of IOP elevation with the use of the Ozurdex implant has been shown to be lower compared to a single injection of IVTA. Surprisingly, the percentage of eyes with IOP elevation did not correspond to the dose of the implant. An IOP elevation of more than 25 mmHg was seen in 7.1% of eyes receiving the 0.7 mg implant and 8.7% of eyes which received the 0.35mg implant. Less than 5% of the eyes developed IOP of 35 mmHg or greater and less than 10% of the eyes developed IOP of 25 mmHg or greater across all treatment groups. (Lowder et al., 2011)

Retisert and recently Ozurdex are currently two intraocular steroid implants which are FDA-approved and also available in the EU, designed to treat non-infectious posterior segment uveitis. However the risk of developing vision-threatening IOP elevation in Retisert may be higher compared to Ozurdex. Over a 3-year follow-up, 71% of implanted eyes had an IOP increase of ≥ 10 mmHg than baseline, 55.1% of eyes reached IOP of ≥ 30 mmHg, 24.7% reached ≥ 40mmHg and 6.2% reached IOP of ≥ 50 mmHg; and these figures increases with time.(Goldstein et al., 2007)

The pattern of IOP elevation with the Retisert implants often occurs suddenly and late, with increasing percentage of hypertensive eyes with time although less number of eyes developed higher IOP each year. (Bollinger and Smith, 2009) Approximately 37% of eyes required IOP-lowering surgery, most of them being trabeculectomy. A major complication of surgery was hypotony (defined as IOP ≤ 5 mmHg), with 42.5% of the eyes developing hypotony within the first week following surgery. Additionally, eyes receiving the Retisert implant were also predisposed to hypotony independent of IOP-lowering surgery. However, despite the high rate of hypotony, VA was stable with the average eye gaining about one line of acuity.(Bollinger and Smith, 2009)

1.3.2.5 Oral steroid

IOP elevation following systemic corticosteroid has been reported for treatment of non-uveitic related conditions, although it is less severe compared to topical or injected steroid. (Tripathi et al., 1992) At an average daily dose of 12.4 mg/day, 36.2% of patients developed IOP > 20 mmHg but about 57% of them showed a decrease in IOP to within 2 standard deviation of the mean control IOP with cessation of treatment. Often, cataract coexists, especially the posterior subcapsular cataract type.

1.4 Diagnosis and monitoring

Detecting and monitoring glaucomatous changes in uveitis patients with ocular hypertension remains a challenge. The recurrent relapse and remission nature of the disease could lead to numerous uveitic changes that can mask or influence detection of glaucomatous optic disc and VF changes.

1.4.1 Gonioscopy

Gonioscopy is fundamentally important in diagnosing glaucoma. It not only gives tell tale signs of the underlying cause of raised IOP, but also helps in planning of the management and provides prognostic outcomes of uveitic eyes suffering from raised IOP. For example, in pure steroid-induced IOP elevation, the angles are often wide open without any other changes indicative of damage due to uveitis, such as peripheral anterior synechiae or pigment deposition in the trabecular meshwork. However, more commonly, IOP elevation occurred due to a mixture of both mechanisms. Pigment deposition in the trabecular meshwork of an eye with an otherwise open angle is often indicative of significant inflammation to the trabecular meshwork and therefore IOP elevation may not be steroid-induced alone (Kok and Barton, 2002). The prognosis in this kind of mixed aetiology is often worse.

1.4.2 Retinal nerve fiber bundle

Thick and thin retinal nerve fibers are regionally distributed throughout the retina. Thin nerve fibers from the foveola enter the optic disc mainly through the temporal aspect of the disc. (Radius and Anderson, 1979) The thick nerve fibers originate predominantly from the peripheral part of the retina and enter the optic nerve head via the inferior, superior and nasal disc region. These areas are more susceptible to

glaucomatous damage. The distribution of the retinal nerve fibers in the retina and how it transcends into the the optic nerve is reflected in the physiologic configuration of the rim of the optic disc which was described to follow the ISNT rule, which states that the inferior rim is broader than the superior rim, followed by the nasal and finally the temporal rim. (Jonas et al., 1988a)

By definition, glaucomatous optic nerve atrophy is associated with optic nerve fiber loss, either diffuse or localized, and therefore decreased visibility of the RNFL. (Jonas et al., 1999) The retinal nerve fiber bundles can be assessed ophthalmoscopically with the green light, using red-free photographs (Sommer et al., 1977) or by using imaging techniques such as scanning laser tomography or laser polarimetry. (Weinreb et al., 1995a)(Weinreb et al., 1995b)

The RNFL bundles when assessed using the ophthalmoscope will be seen as bright and fine striations in the inner retinal layer fanning off the optic disc to the retinal periphery. It is less visible in eyes with opaque media, yellow lens discoloration and a low degree of pigmentation of the retinal pigment epithelium. (Jonas and Dichtl, 1996) Most wedge-shaped RNFL defects can be detected by examining eyes with clear optical media and normal fundus pigmentation. In juvenile individuals, evaluation of the RNFL is more difficult than adults because of the reflectivity of the inner limiting membrane in children.

1.4.3 Optic nerve head assessment

Optic nerve head assessment remains the gold standard of glaucoma diagnosis. As opposed to POAG, the presence of glaucomatous optic disc changes is sufficient for

diagnosis of secondary glaucoma, like uveitic glaucoma, without evidence of VF changes. (Foster et al., 2002)

1.4.3.1 Preperimetric diagnosis of glaucomatous optic nerve damage

The following are the most important variables for early detection of glaucomatous optic nerve damage in ocular hypertensive eyes before the development of VF loss: (Jonas et al., 1999)

1. If the inferior and superior rim is not markedly broader than the temporal disc region, this should raise the suspicion of glaucomatous loss of rim tissue in the inferior and superior disc regions.
2. The size of the optic cup in relation to the size of the optic disc.
3. Diffusely or segmentally decreased visibility of the RNFL
4. Occurrence of localized RNFL defects and disc haemorrhages.

1.4.3.2 Glaucomatous optic nerve changes

The optic disc size is usually normal in POAG and pigmentary glaucoma. However, in all glaucomatous eyes with high myopia, the optic disc is abnormally large because of secondary macrodisc acquired as a result of high myopia. (Jonas et al., 1999)

Neuroretinal rim loss may involve all sectors of the optic disc depending on the disease severity, following the sequence of inferotemporal, superotemporal, temporal, horizontal, nasal inferior and nasal superior. (Tuulonen and Airaksinen, 1991) This sequence correlates with the progression of VF defects, with early perimetric changes seen in the nasal upper quadrant and a last island of vision in the temporal inferior part of the VF in almost absolute glaucoma. (Hart and Becker, 1982)

In mild glaucomatous damage, rim loss predominantly affects the inferotemporal and superotemporal disc regions (Figure 4). In moderately advanced glaucomatous atrophy, the temporal horizontal rim region is most markedly lost. In very advanced glaucoma, rim remnants are located in the nasal sector, with a larger portion on the upper than the lower nasal region. (Jonas et al., 1993)

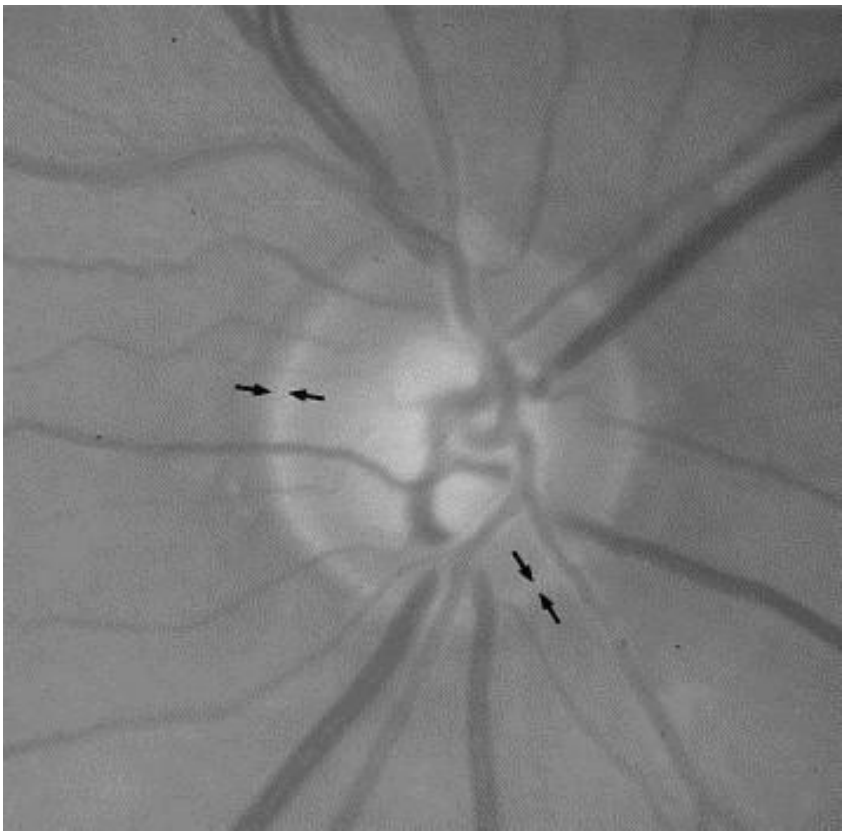

Figure 4: Rim loss affecting the superotemporal and inferotemporal disc regions in mild glaucoma. The black arrows point towards the peripapillary scleral ring. (Jonas et al., 1999)

The optic cup size in relation to the optic disc size, or the cup to disc ratio (CDR), is also used to evaluate glaucomatous changes. The distribution of the optic cup area however, is not Gaussian. Pseudoglaucomatous disc may appear from primary macrocups occurring in primary macrodiscs, and are physiologic (Figure 5).

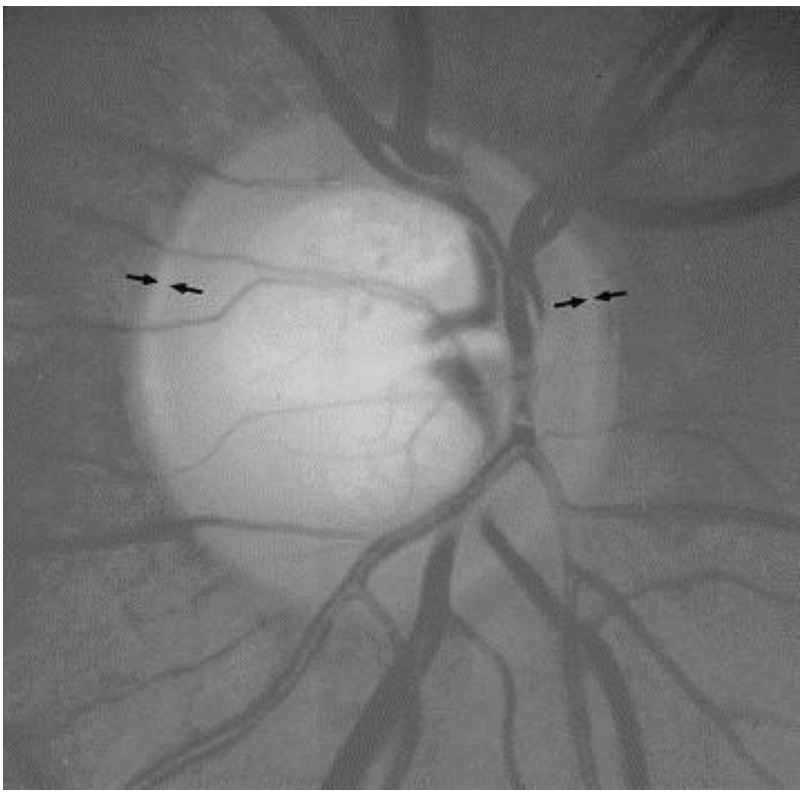

Figure 5: Large otherwise normal optic disc (primary macrodisc).

The black arrows point towards the peripapillary scleral ring. (Jonas et al., 1999)

The optic disc is vertically oveal and the optic cup is horizontally oval. As a result, the CDR in normal eyes is significantly larger horizontally than vertically, with the quotient of the horizontal to vertical CDR normally higher than 1.0. (Jonas et al., 1988a) In early to medium advanced stages, the vertical CDR increases faster than the horizontal CDR, causing an increase of the quotient of horizontal to vertical CDR to less than 1.0. (Jonas et al., 1988b)

Glaucomatus optic nerve head assessment in the majority of primary glaucomas is easily done without the interruption of any other pathology. However, uveitis causes a number of changes that interferes optic disc assessment. Optic disc swelling, present not only in posterior uveitis but also in some cases of severe anterior uveitis, obscures disc cupping.(Monheit and Read, 2005) (Eckert et al., 2007) On the other hand, there

are anecdotal reports of neurosyphilis and chorioretinitis causing optic disc cupping in the abscence of raised IOP. (Mansberger et al., 2013) However, the severity of uveitis has been shown to cause insignificant difference in the CDR.(Berker et al., 2007)

To achieve standardization of the optic nerve head assessment in longitudinal follow-up, stereo disc photography is considered the gold standard and remains part of the cornerstone of glaucoma diagnosis. However, there is a significant variability even between glaucoma specialists in the evaluation of the CDR from stereo-disc photographs. Between 4% to 19% of cup-disc estimates made by 2 different specialists differed by 0.2 disc diameters or more.(Zangwill et al., 1995)(Tielsch et al., 1988)

1.4.4 Visual Fields

Localized VF defects in glaucoma result from damage to the retinal nerve fiber bundles. The RNFL transmits axonal bundles from its respective place on the retinal surface and transcends into the optic nerve head in a unique configuration (Figure 6). Axonal damage therefore causes characteristic patterns of VF changes. (Piltz-Seymour et al.) The characteristics of glaucomatous field defects are as follows: (Foster et al., 2002)

1. Asymmetrical across the horizontal midline (in early/ moderate cases)
2. Located in the mid-periphery (in early/ moderate cases)
3. Clustered in neighbouring test points
4. Reproducible on at least two occasions
5. Not explained by any other diseases
6. Considered a valid representation of the subjects functional status (based on performance indices such as false positive rates)

Figure 6: The retinal nerve fiber layer in the right eye.

Damage to localized bundles of nerve fibers result in characteristic patterns of visual field loss in glaucoma. (Harrington DO, Drake MV: The Visual Fields: Textbook and Atlas of Clinical Perimetry. St Louis: CV Mosby, 1990.) (Piltz-Seymour et al.)

VF evaluation is even more subjective than stereo-disc photo assessment. Eighty six percent of VF abnormalities could not be replicated on retesting in a study of 1637 patients without uveitis.(Keltner et al., 2000) Furthermore, perimetric tests in children are difficult and often unreliable.

Uveitis does not only impair VA but also VF sensitivity. Eyes with macula edema had worse VF sensitivity as measured by Humphrey 24-2 perimetry. (Taylor et al., 2011) Diffuse retinal changes such as that seen in multifocal choroiditis (Reddy et al., 1996) and birdshot retinochoroiditis (Gordon et al., 2007) can also cause VF defects not attributable to glaucomatous changes. Therefore, patients with these conditions and raised IOP should be evaluated with caution when assessed for glaucoma.

1.4.4.1 Monitoring progression of visual field

Evaluation of VF progression is important in determining glaucoma progression. However, test variability even in reliable series of tests makes the evaluation difficult. (Heijl et al., 1989) VF progression from glaucoma can be measured by a number of methods such using VF indices that measure overall change, (Chauhan et al., 1990) cluster analysis whereby the change in depth and location in the VF is used to systematically score research protocols, (1994), and trend analysis whereby linear

regression slope is generated to detect change over time. (Noureddin et al., 1991)(Wild et al., 1997)

1.4.4.2 The Progressor software

The Progressor software is a pointwise comparison programme to measure progression in the Humphrey VF test. (Fitzke et al., 1996) It has been designed primarily for use with the HFA 30-2, 24-2, 30-1, and 24-1 programs. It uses pointwise linear regression analysis of luminance sensitivity values (dB) against time of follow-up and uses all the data from all the fields within a series of examinations. The analysis is presented in a single colour coded graphical display that depicts the spatial and temporal characteristics of field loss on each point tested. The software includes database facilities and checks of data validity. This is especially helpful in automating large parts of the analysis. The graphical output is visually easy to understand and interpret and it gives useful information in identifying significant progression of VF loss.

If a patient has undergone VF testing with different stimulus sizes, the program will automatically analyse each stimulus size sequence separately. Similarly, when VF sequences include both 30-2 and 24-2 results, these are automatically combined to make use of all the available data in the analysis.

Figure 7: An example of a Progressor data display (Fitzke et al., 1996)

An example or the graphical display is shown in Figure 7. It analyses and summarizes the entire VF tests of the patient. The type of display or analysis can be altered. The

30-2 VF locations are maintained in the display and the foveal thresholds and global indices are shown in the top right of the image represented by bars whereby the length of the bar is proportional to a reference value minus the measured threshold value. A very short bar is nearly normal while a bar of increasing length (going downwards) represents greater sensitivity loss at that particular location. A calibration marker for 30 dB is shown on the lower left of the image. At each VF location the series of bars represent the measured values at the different test dates going from left to right. The separation between bars can be selected for equal spacing or as proportional to time. The scale for time is at the lower left of the figure. In this example the measurements were made at approximately 3 months intervals and the display selected used equal spacing between the bars. However, the statistical analysis used the actual time scale. It can be seen that thresholds are nearly normal throughout the inferior field while there is evidence of VF loss in the superior field encompassing an area extending from the blind spot to the nasal field.

The analysis performs linear regression analysis to each of the individual field locations to determine any statistically significant progression. If there is any location in the VF with repeated measurements, the mean will be used in the linear regression. Linear regression analysis starts with the third field, and subsequent fields were added thereafter. The linear regression provides values for the slope (i.e rate of change in dB/year) by least square fit. The statistical significance of the critical value of the slope, defined by the magnitude divided by the standard error of the fit is also generated. Colour coding is then introduced to denote the results of the statistical significance of the fitted slopes (Figure 8):

1. Grey indicates no change i.e the slope is less than the criterion value ('flat', default value used = 0 dB loss/year)
2. Bright red indicates highly significant progression i.e the slope is negative (indicating loss of retinal sensitivity) with an associated p value of less than 0.01. Other significant negative slopes ($p<0.05$ and $p<0.10$) are highlighted with different colour codings.
3. Yellow indicates negative slopes in which the longitudinal sensitivity fluctuations are not statistically significant.
4. Positive slopes indicating improvement, possibly from a learning effect or other factors, are also represented by different colours. A cyan coloured bar indicates a non-significant improvement ($p>0.05$) while green indicates significant increases in sensitivity ($p<0.05$). A bright blue bar indicates an excluded point from the analysis because the value for that location and that field was found to lie outside the 2 SD value expected for the entire sequence.

This colour coding is summarised on the bottom line of the figure. The analysis is continued and repeated for all the test locations of all examination dates and the final graphical display summarises the results. (Fitzke et al., 1996)

Figure 8 shows a magnified version of the analysis at one field location. Figure 9 shows the same data as a sequential plot of the sensitivity (dB) against time of follow-up. The first linear regression initialised after three fields gave a negative slope, although not statistically significant ($p=0.22$)

Figure 8: Magnified version of the analysis in one test location.(Fitzke et al., 1996)

Figure 9: Sequential plot of the sensitivity (dB) against time of follow-up.(Fitzke et al., 1996)

The linear regression analysis takes into account the difference in variability to allow significant progression to be detected even though the losses can be quite small. This is to ensure that *noisy* values at locations of high variability do not produce significant slopes unless the rate of loss is considerable. Therefore, steady, reliable loss can become apparent although at a lower rate. (Fitzke et al., 1996)

The Progressor software provides the number of progressed points in the entire location tested, the local slope of progression/linear regression for each of the points that has progressed, and the global slope of progression. While the Pointwise linear regression analysis requires a minimum of two fields to generate a slope, it needs at least five fields to be clinically useful. (Holmin and Krakau, 1982)(Spry et al., 2000)

1.4.4.3 STATPAC 2 glaucoma change probability analysis

The STATPAC2 software uses pointwise comparison of the Humphrey VF thresholds that estimates deterioration in serial glaucomatous VFs on the Humphrey field analyser. (A HEIJL, 1991) It is an event analysis that detects change based on a predetermined threshold. (Morgan et al., 1991) The glaucoma progression analysis selects two of the three initial fields as a 'baseline' and subsequent fields are compared with this baseline in a pointwise manner. It performs linear regression analysis to identify changes across serial VFs. Points are labelled with a black triangle if they are associated with a p-value of <0.05 for a change against a reference database (Figure 10).

While some studies have found the Progressor software to be comparable to STATPAC 2,(McNaught et al., 1996) other studies have shown that the Progressor software

consistently detected progression earlier than STATPAC2. (Viswanathan et al., 1997) and was also shown to agree favourably with the earlier available STATPAC2 software to separate progressing from stable retinal locations with a kappa value of 0.62. (Fitzke et al., 1996)

Figure 10 Example of a section of the STATPAC 2 glaucoma change probability analysis.

The test locations highlighted is labelled as showing significant deterioration in each of the three consecutive fields. From (Fitzke et al., 1996)

1.4.5 Ocular imaging

Ocular imaging for detection of glaucomatous optic disc changes is a relatively new modality used as an adjunct to other means of glaucoma diagnostic tools. In the past decade, a few instruments have been developed to evaluate in vivo intraocular structures. Among other things, they offer an opportunity to objectively quantify early changes and monitor glaucomatous progression by means of a non contact and non invasive imaging technique. Scanning laser polarimetry and Heidelberg retinal tomography are among the instruments that document changes by means of either objective topographic measurement of the optic nerve head, such as the disc area, cup area, and cup-to-disc ratio or cross-sectional thickness (Weinreb, 1993)(Kamal et al., 2000).

1.4.6 Optical coherence Tomography

The optical coherence tomography (OCT) is a high-resolution imaging device that uses laser light to acquire in vivo images of the human microstructure. It captures images in excellent micrometer resolution images from within the optical scattering media. It applys the principle of interferometry, whereby images are created based on the

different reflectivity of different ocular structures. Light which is emitted from a superluminescent diode goes through a beam splitter to the eye and a reference mirror andas the light returns from the eye and the reference mirror, the interference pattern is processed by a photodetector whose data is then used to create a 2D image. (Chen, 2009)

The OCT typically uses near-infrared light, a relatively long wavelength light which allows it to penetrate into the scattering medium. The interferometric technique is used to interpret reflectance data from a series of multiple side-by-side A-scans combined to form a cross-sectional image. (Schuman et al., 1995) It is often said that OCT is analogous to ultrasound; however, instead of using sound, it uses light. Images are created based on the different reflectivity of different ocular structures. Similar to an A scan in ultrasound technology, an A line in OCT represents a 1-dimensional unit of data. With ultrasound, many A-scan can be combined to create a 2-dimensional image on B scan. In OCT, many A-lines can be combined to create a 2D OCT image. However, because light travels so fast, processing of the information required a fundamentally different technology. Depending on the light source (e.g superluminescent diodes, ultrashort pulsed laser and supercontinuum lasers), the OCT has achieved sub-micrometer resolution.

For glaucoma detection, an in-depth cross-sectional measurement of the RNFL thickness in a circular scanning area around the optic disc or a block section of the optic nerve head has been used to relate to glaucomatous RNFL loss. An additional advantage in uveitic glaucoma is that it enables concurrant measurement of the macula thickness, allowing objective documentation of macula edema and its severity which is especially useful in the follow-up of uveitic patients. (Naithani et al., 2007)

Therefore it has been recommended as part of glaucoma management decisions together with good clinical assessment. (Hwang and Kim, 2012)(Mansoori et al., 2010)

1.4.6.1 History of the OCT

The OCT was first described by Huang et al (Huang et al., 1991) to describe a non-invasive cross-sectional imaging tool of the biological system. This first prototype of time domain OCT uses low-coherence interferometry to produce a two-dimensional image of optical scattering from human internal structure which is analogous to pulse-echo ultrasound imaging. They demonstrated in vitro tomographic imaging of the retinal peripapillary area and the coronary artery to demonstrate imaging through transparent and turbid media respectively.

All commercially available OCT thereafter were based on time domain OCT. This included the Stratus OCT (Carl Ziess Meditec Inc, Dublin, California) and the Visante (Carl Zeiss Maditec Inc). However, its use was limited by a slow acquisition speed and lower resolution. For posterior segment imaging for example, a typical time domain Stratus OCT scan can be acquired in 1.28 seconds and can produce a 2D image with an axial resolution of about 10µm. (Chen, 2009)

In 1991, an ultrahigh-resolution time domain OCT imaging was developed to improve resolution, and axial resolutions of about 3µm were achieved. (Drexler et al., 1999) However, this traded ultrahigh resolution for slower acquisition speeds, and comparable 2D images would take several more seconds to obtain.

In 2002, Wojtkowski et al introduced the use of the Fourier domain OCT to image in vivo human retina.(Wojtkowski et al., 2002) However, the machines took too long to obtain and process an image to be clinically useful. A year later, Professor Johannes de

Boer, PhD, and his team at the Massachusets General Hospital Wellman Center for Photomedicine developed a fundamentally new technology called the video-rate spectral domain OCT using the Fourier domain OCT technology to achieve simultaneous ultrahigh resolutions with ultrahigh acquisition speeds. (White et al., 2003)(de Boer et al., 2003b) This first prototype video rate spectral domain OCT machine was able to obtain and display images in effective real-time.

1.4.6.2 Time-domain OCT

An earlier version of this technology, the time domain OCT (TD-OCT), uses a moving reference mirror for measuring the time taken for light to be reflected. The time-domain technology acquires images by evaluating the interference pattern created by the echo time delays of backscattered light from the subjects's retina and those from a moving reference mirror (Knight et al., 2009). This relatively slow, mechanical process limits both the amount of data that can be captured as well as image quality. TD-OCT data is acquired at approximately 400 axial scans, or A-scans, per second and produces an axial resolution of 10 µm.

Figure 11 Schematic representation of time domain optical coherence tomography setup. CCD, charge coupled device. HP-SLD high power superluminescent diode; PC, polarizedation controllers; RSOD, delay line; SL slit lamp.(Chen, 2009)

Figure 11 shows the typical set up in a time domain OCT machine. Light which is emitted from a superluminescent diode (SLD) light source goes through the beam splitter to the eye and a reference mirror. As the light returns from the eye and the reference mirror, the interference pattern is processed by a photodetector whose data is then used to create a 2D image.

1.4.6.3 Fourier-domain OCT

Fourier domain OCT is a new version of the OCT instruments utilising spectral (Fourier) domain technology which is significantly faster and non-mechanical. The scan rate of spectral domain OCT is at least 20,000 axial scans per second, with a 5 µm resolution. It measures multiple wavelengths of reflected light simultaneously across a spectrum, hence the name spectral-domain.

Figure 12: Schematic representation of the spectral domain optical coherence tomography (OCT) setup that was used for in vivo measurements.

ASL, air spaced lens; C, collimator; CCD, charge coupled device; E, eye; HP-SLD, high-power superluminescent diode; LSC, line scan camera; ND, neutral density filter, PC, polarization controllers; RSOD, delay line; SL slit lamp; TG, transmission grating.(Chen, 2009)

The first clinically useful spectral domain machine was described as “video-rate” because it can acquire at least 30 frames per second and results can be viewed as moving and not discrete. The normal eye intergrates each received image over a certain time interval and is not an instantaneous detector. If images are displayed at 30 frames per second, the eye will “see” a continuous motion on the screen. On the other hand, if images are displayed slower, for example, 20 frames per second, our brain will realize that the motion is discrete. (Chen, 2009)

The term “spectral domain OCT” is preferred over “Fourier domain OCT,” because the fundamental difference between time domain and spectral domain OCT is the spectrometer, the technology used to process the light as it comes back from the eye and the reference mirror (Figure 12). The spectrometer is composed of a transmission grating and air-spaced focusing lens. It is more efficient than the photodetector, acting equivalent to thousands of photodetector working in parallel. Although the final image is created using the Fourier transform, hence the term “Fourier domain OCT,” the spectrometer is what ultimately enables ultrahigh resolutions with ultrahigh acquisition speeds.(Chen, 2009)

1.4.6.4 Comparison between Time-Domain and Spectral-Domain OCT in RNFL thickness measurement

Studies done over the last few years to assess the diagnostic performance of SD-OCT suggest that SD-OCT performs similarly to TD-OCT for glaucoma diagnosis, but SD-OCT may be superior for detection of early stage diseases. (Grewal and Tanna, 2013) The RNFL thickness measurement between a TD-OCT and SD-OCT cannot be directly compared. Measurements are generally higher with TD-OCT than with SD-OCT except when the RNFL is very thin, like in severe glaucoma.(Knight et al., 2009) However, overall, sensitivity and specificity were higher with SD-OCT than TD-OCT.(Sung et al., 2009)

1.4.6.5 Patterns of OCT scan

Obtaining OCT scans can be performed in many patterns depending on the purpose of scanning and the machine used (Table 3). [1] Scan patterns used for glaucoma assessment are commonly circular scans of the paripapillary RNFL or radial scans cutting across the optic disc.

Table 3: Scan patterns used in OCT. From [1]

	Zeiss Cirrus	Heidelberg Spectralis	RT-Vue	Topcon 3-D	Canon HS-100	Nidek OCT RS-3000	Bioptogen SD-OCT
3D scans	Macular cube	Volume scan	3D macular MM5	Fast map Box scan	Macula 3D Multi-cross	Macula map	Rectangular volume Mixed volume
Line scans	5-line raster scan 1-line raster scan	7-line raster scan	Line scan HD Line Cross-line HD cross-Line	5- and 9-line raster Line scan Oversampled line scan	Cross	Macula multi Macula line	Linear scan
Radial scans	None	No presets, can be selected	Radial slicer MM6	12-line radial		Macula radial	Radial volume
Mesh scan	None		MM5			Macula multi	

1.4.6.6 Advantages and disadvantages of different scan techniques in glaucoma

1.4.6.6.1 Confocal scanning laser ophthalmoscopy (CSLO)

Confocal scanning laser ophthalmoscopy is a non–invasive technique used traditionally to topographically map out the three dimensional images of the retinal surface in vivo. The commercial name is Heidelberg Retina Tomograph (HRT). There are currently two types used, HRT II and HRT III. Three modules are used: in glaucoma for analysis of the optic disc and peripapillary retinal nerve fibers layer, for the retina in macular disorders and for the cornea.

In glaucoma, HRT scans the retinal surface with a diode laser with a wavelength of 670 nm. It uses the principle of confocality in which only the laser light reflected from the

focal plane, focused at the diaphragm, is allowed to pass and registered by the detector. Any other laser light reflected from planes anterior or posterior to the focal plane and not focused at the diaphragm is eliminated.

The scans are vertical and horizontally oriented, producing a total of 64 sections in the coronary plan, of 384 x 384 pixels each. Further optical sections along the optic nerve (z-axis) will result in a layered three–dimensional image (tomography). The sections are re-assembled and the heights of different sections of the optic disc are calculated. The image acquisition time is between 0.025–0.032 seconds. The scans can be performed through undilated pupils. The integrated software performs a stereometric analysis within the area of the optic disc (drawn manually by the observer in case of HRT Ⅱ and automatically in case of HRT Ⅲ). The results are presented by stereometric parameters and topographic maps of the optic disc surface and the adjacent retina.(Alexandrescu et al., 2010)

The HRT provides numerous stemetric parameters, including disc area, rim area and cup area. Classification indices such as the Moorfields regression analysis and glaucoma probability score, which classify regios as “outside normal limits” are available to discriminate between healthy and glaucomatous discs. It has a large, race specific normative database, sophisticated analuysis software and the ability to monitor quality control during image acquisition. However, topographic measurements are based on a reference plane which is constructed by the user and therefore operator input is required for certain analyses. Furthermore, IOP may influence the HRT measurements. (Vizzeri et al., 2011) Studies have shown that although it has good reproducibility, variability was found to be higer in glaucomatous eyes. (Sihota et al., 2002)

1.4.6.6.2 Scanning laser polarimetry (SLP)

SLP uses the birefringence property of the RNFL which changes the polarization of the light when illuminated, which in turn is proportional to the thickness of the birefringent tissue, allowing objective and quantitative measurement of the RNFL thickness. One of the commercially available SLP instruments is the GDx VCC (variable cornea compensation) and GDx ECC (enhanced corneal compensation).

Images are formed by scanning the beam of a near infrared laser (780 nm) in a raster pattern. It covers an image field 40°horizontally and 20° vertically to include both the parapapillary and macular regions. With the GDx VCC, the method of variable corneal polarization compensation, as described by Zhou and Weinreb,(Zhou and Weinreb, 2002) was automated and replaced the original fixed corneal compensator. The variable corneal compensator consists of 2 identical linear retarders in rotating mounts to allow adjustments of both the retardation and axis of the unit as required. (Medeiros et al., 2004) Although the GDx has been shown to discriminate well between glaucomatous and healthy eyes, (Reus and Lemij, 2004) a major setback is the occurrence of atypical retardation patterns, possibly from poor signal-to-noise ratio from light scattering in the eye.

1.4.6.6.3 Optical Coherence Tomography

Schuman and colleagues was the first to introduce the use of a 3.4 mm circumpapillary RNFL thickness scan as the standard for glaucoma assessment. (Schuman et al., 1996) Scanning the peripapillary RNFL thickness with circular B-scans measuring 3.4mm and centered at the center of the optic disc has been the traditional method of detection and monitoring of glaucoma. The spectralis OCT has an acquisition rate of 40,000 A-lines per second, an axial resolution of 7 μm in tissue, and an 870 nm superluminescent

diode source. It provides an Automatic Real-Time (ART) function with an eye tracking system which can increase image quality. With ART activated, multiple frames of the same scanning location are obtained. This data is then averaged for noise reduction, and eye motion artifacts are reduced.

There are three kinds of scan pattern available for SD-OCT in glaucoma: the radial pattern, the volume scan and the circular pattern. The radial pattern comprised of 24 angularly equidistant 15-degree B-scans cutting ascross the optic nerve head. The circular scan is a 12-degree scan centered at the optic disc to measure the circumpapillary RNFL thickness. It comprised 1536 A scans centered at the optic nerve head, and data were averaged from 16 individual B-scans.(Chauhan et al., 2013)

The ring scan pattern is not without its limitations. Because it scans a localized circular area centered at the optic disc, and because the center of the optic disc is variable in an individual based of the gaze of the eye, and also between individuals, scanning the RNFL in a ring pattern may not be accurate. A few changes have been made to this method after considering new developments in published literature:

1.4.6.6.3.1 Anatomic variation in fovea position relative to the optic nerve head

The foveal position, as determined by clinical fundus images lies below the level of the center of the otic nerve head. Studies have shown that the angle between the fovea and Bruch's membrane opening (BMO) center relative to the horizontal axis defined by the fundus image, termed the fovea-BMO center axis, can vary by as much as 23 degrees between different individuals. (Chauhan and Burgoyne, 2013) Additionally, the positions of the fovea and the optic nerve head may also vary in the same individual due to cyclotorsion. However, the path of theRNFL bundles is constant relative to the fovea-BMO center axis. (Patel et al., 2012)

This may result in variation in positioning of the quadrants and sectors of the peripapillary RNFL as the measurements were done from different anatomic location. Consequently, artificially large differences between individuals in sectoral neuroretinal rim width and peripapillary and macular RNFL thickness is likely to occur. The limits of normal variation in the normative database may be artifially increased and thus decreasing the diagnostic precision of imaging devices. (Chauhan and Burgoyne, 2013)

1.4.6.6.3.2 Determining the optic disc margin with the OCT

The optic disc margin is traditionally defined as the inner edge of the sclera lip or crescent. (Hogan et al., 1971) However, because the termination of the Bruch's membrane at the optic nerve head represents the opening through which retinal ganglion cells axons exit the eye, this anatomic opening, termed the Bruch's membrane opening (BMO), is the true outer border of the neural tissues because axons cannot exit through an intact Bruch's membrane. A study of the optic nerve head using the SD-OCT line scan recently helped re-defined the outer border of the optic disc rim. Chauhan and Burgoyne proposed an anatomically and geometrically accurate SD-OCT-based approach for rim assessment to enhance glaucoma detection. (Chauhan and Burgoyne, 2013)

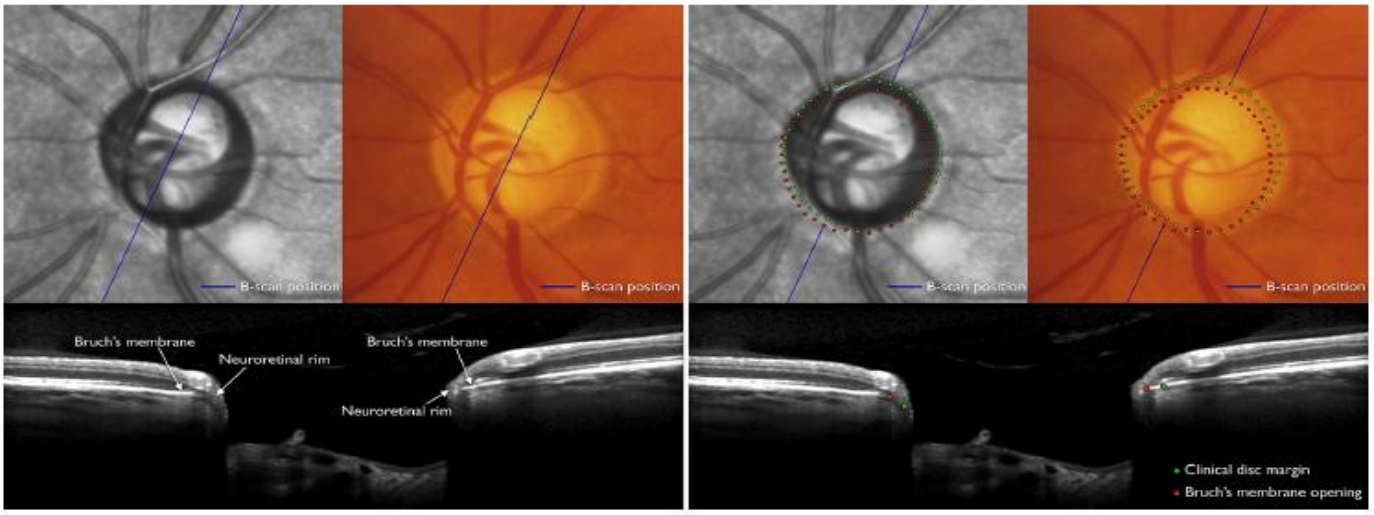

Figure 13: Optic disc appearance with optic disc photography and spectral-domain optical coherence tomography (SD-OCT)

Green dots denotes clinically visible optic disc margin traced in the optic disc photograph and projected to the B scan and the red dots indicates Bruch's membrane opening identified in the B scan and projected to the fundus photograph. The superimposed tracing shows that at the superotemporal quadrant, a clinically invisible overhang of the Bruch's membrane resulted in overestimation of the neuroretinal rim width with disc margin based evaluation, whereas in the inferonasal quadrant, the rim is actually wider than perceived clinically (Chauhan and Burgoyne, 2013).

1.4.6.7 Evolution of scanning technology for identifying glaucoma changes

In 2013, Heidelberg Engineering introduced a new glaucoma module which offers comprehensive analyses for the optic nerve head, retinal nerve fiber layer and posterior pole asymmetry. This new module included the Anatomic Positioning System that accurately places all OCT scans relative to the position of the fovea and Bruch's membrane opening (BMO), both of which serves as anatomic landmarks for individual eye.

1.4.6.8 The Heidelberg Spectralis OCT

The Spectralis OCT (Heidelberg, Germany), is a faster Fourier domain OCT and is combined with other features which allows it to produce precise location of the current and follow-up scans. It produces high definition and fine discriminating scans producing good diagnostic performance in early perimetric glaucoma. (Wu et al., 2012)

The SPECTRALIS system is 100 times faster than TD-OCT and acquires 40,000 A-scans per second. The increased speed and number of scans translates into higher resolution and a better chance of observing disease. (The Heidelberg Engineering website,[2]) By integrating SD-OCT with confocal scanning laser ophthalmoscopy (cSLO), the SPECTRALIS platform is able to produce fundus imaging that reveals new details through multiple perspectives of the retina. These additional plus points may help in redefining diagnosis and treatment of many major eye diseases.

The custom TruTrack™ image alignment software enables real-time simultaneous high speed image acquisition and active eye movement tracking while imaging. With this eye tracking system, the Spectralis platform simultaneously images the eye with two beams of light. One beam captures the image of the retina and maps over 1,000 points to track eye movement, and using the mapped image as a reference, the second beam is directed to the desired location despite blinks or saccadic eye movements. The dual-beam technology lessen eye motion artefact and ensures point-to-point correlations between the OCT and fundus images without post-processing of the data. This allows accurate and repeatable alignment of the OCT and fundus images.

The Heidelberg Noise Reduction ™ system ensures fine image detail by combining multiple images captured in the same location, filters out random speckle noise, and retains only data common to the entire set of images. The result is higher quality images with finer detail. The AutoRescan™ system allows precise follow-up scan placement, adds precision to the RNFL change analysis and minimizes operator variability in follow-up scans. It automatically places the follow-up scans with the detailed retinal map in precisely the same location as the baseline scan. The desired location can then be precisely scanned, eliminating subjective operator placement and

increasing the clinician ability to observe true change over time rather than change from alignment error. In short, the Heidelberg Spectralis OCT system tracks eye movement with simultaneous dual-beam imaging minimizing motion artifact, ensures noise reduction and precisely track changes over time. The result is a point-to-point correlation between the fundus and OCT scans, greater image detail and clarity, and more confident assessment of small changes. (The Heidelberg Engineering website,[2]) (Wu et al., 2010)

1.4.6.9 Quantification of the RNFL for detection and monitoring of glaucoma

Measurement of the retinal nerve fiber (RNFL) thickness has been used adjunctively with other clinical indicators of glaucoma and has been intensely investigated with regards to its sensitivity and reliability in detecting glaucomatous RNFL changes over the last decade. Trying to prove its value in the diagnosis and monitoring of glaucoma was even more enticing given that VF changes occur only after 25 to 35% of RGC loss (Kerrigan–Baumrind et al., 2000). Furthermore, RNFL damage precedes VF changes by up to 6 years (Sommer et al., 1991). RNFL thickness of less than 75µm correlated to clinically significant VF impairment in a study done on patients with optic neuritis. (Costello et al., 2006)

Within the realm of POAG, reduced RNFL thickness has been shown to be a good marker for diagnosing early damage of glaucoma (Budenz et al., 2005)(Medeiros et al., 2004)(Chen and Huang, 2005)(Wu et al., 2012) and glaucoma suspect eyes.(Pomorska et al., 2012) It doesn't only precede VF loss (Cvenkel and Kontestabile, 2011)(Wollstein et al., 2012), but is also reliable and reproducible (Langenegger et al., 2011)'(Mansoori et al., 2011) with up to 98% sensitivity and 87% specificity, (Wu et al., 2012) allowing

early intervention to prevent VF loss from glaucoma. The OCT measures the RNFL thickness with high speed acquisition and high repeatability (Langenegger et al., 2011)(Mansoori et al., 2011), enabling more frequent assessment and better trend analysis.

1.4.6.10 Quantification and measurement of the macula thickness in glaucoma detection and monitoring

The macula has been shown to become atrophic in glaucoma as demonstrated by reduction in macula thickness as measured by imaging modalities. (Zeimer et al., 1998) As a result, measurement of the macula thickness was studied to determine any early changes in preperimetric glaucoma. Diagnostic accuracy was shown to be much improved with the analysis of the inner layers of the macula, arbitralily termed as the "Ganglion Cell Complex" which is readily viewed with high definition spectral domain OCT.(Kotera et al., 2011) The Ganglion cell complex was shown to be better in diagnostic accuracy and repeatability than the total macular thickness. (Tan et al., 2009)The ganglion cell layer (Figure 14) in particular was compared with the peripapillary RNFL and optic nerve head measurements in detection of preperimetric glaucoma. The global volume loss and superior ganglion cell complex thickness showed the largest area under the receiver operating characteristic curve values (AROC) which was 0.84 in each parameter, and this was comparable to the average peripapillary RNFL AROC value (0.89) and the horizontal CDR value (0.85). (Na et al., 2013) Furthermore, statistically significant structural relationship was shown to exist between sections of the macular thickness with its corresponding location on the Humphrey VF analyser. (Boling et al., 2012)

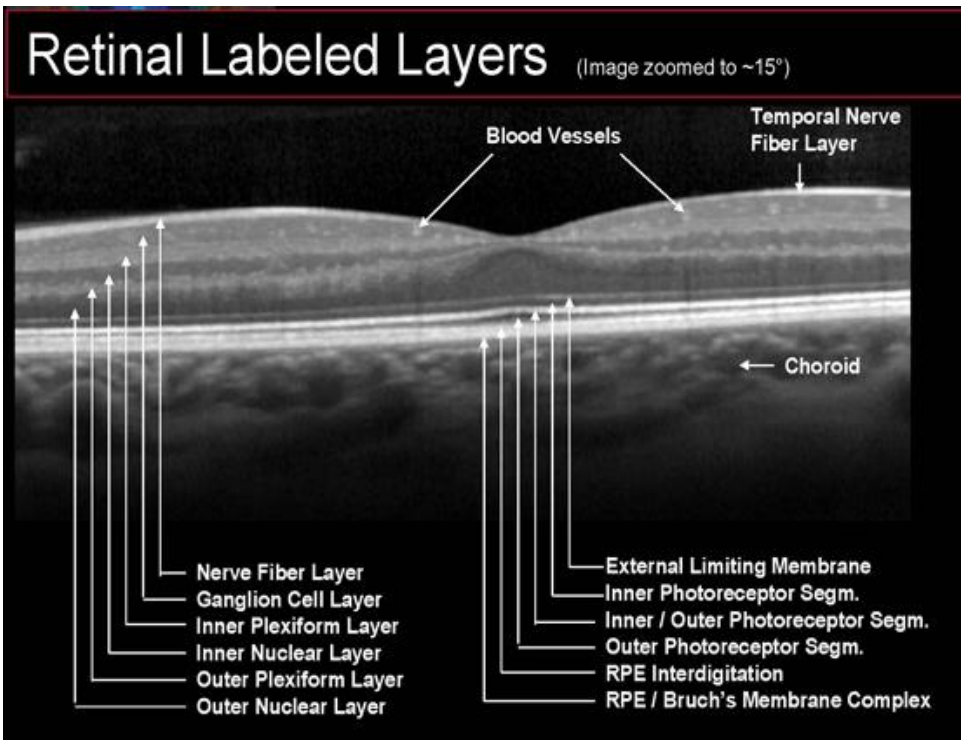

Figure 14: The retinal layers at the macula as imaged by the Heidelberg Spectralis OCT. From the Heidelberg engineering website, [2]

Localised macular thickness changes was also demonstrated in eyes with glaucoma and regional VF defect, resulting in the proposition that macular symmetry testing may also represent a novel method for glaucoma diagnosis. (Bagga et al., 2005)

1.4.6.11 Measurement and interpretation of the RNFL thickness with the Heidelberg Spectralis OCT

After dilatation of the pupils, the patient is seated in front of the OCT machine, facing the operator. The chin is placed on the chin rest and the eyes levelled at the correct position. The patient is instructed to fix on a green target. A circular shaped scan beam is projected onto the patient's retina and placed so that the center of the ring is situated at the center of the optic disc. The system acquires 40, 000 A scans per second. RNFL thickness is measured at each point along the circle scan and the thickness is given as a mean thickness along the circle in any given quadrant.

The software aligns the images resulting real-time simultaneous high speed image acquisition and active eye movement tracking while imaging. The platform simultaneously images the eye with two beams of light. One beam captures the image of the retina and maps over 1,000 points to track eye movement, and using the mapped image as a reference, the second beam is directed to the desired location despite blinks or saccadic eye movements. The dual-beam technology lessen eye motion artefact and ensures point-to-point correlations between the OCT and fundus images without post-processing of the data. This allows accurate and repeatable alignment of the OCT and fundus images.

The software then places lines, based on the reflectivity, on the internal limiting membrane and the ganglion cell layer, which corresponds to the RNFL thickness. The average of the thicknesses was then calculated according to the 4 quadrants: inferior, superior, nasal and temporal, and the sub-qudrants superotemporal, superonasal, inferotemporal and inferonasal, and also the global thickness.

The optic nerve head can also be scanned using a block scan, giving a 3-dimensional image of the optic nerve head and gives the volume of the RNFL in the scanned area.

When using the OCT for glaucoma monitoring, the circular scan is preferred as it provides a more meaningful representation of the ganglion cell loss in the retina. The software will calculate the average RNFL thickness for

1. the overall global thickness (360 °)
2. the 4 quadrants: superior (S), inferior (I), nasal (N), and temporal (T), each 90°
3. the four sub-sectors
    a. Temporal-superior (TS) 45°-90°
    b. Nasal-superior (NS) 90° −135°
    c. Nasal-inferior (NI) 225° −270°
    d. Temporal-inferior (TI) 270° −315°

Utilising the “spotlight display” (Normative Database in SD-OCT: A status report. 2012, [4]) (Lumbroso and Rispoli, 2012)(Leung et al., 2010a) , colour coding is used to classify the global, quadrants and sub sectors:

1. Green denotes the healthy top 5% to 95% of RNFL values and reported as “Within Normal Limits”;
2. Yellow represents borderline measurement between 1% and 5% and reported as “Borderline”
3. Red indicates abnormal values of readings between 0% and 1% of the population and reported as “Outside Normal Limits”.

Figure 15 demonstrates an example of a printout seen in POAG. The printout consists of grey scale photographs of both optic discs with a 3.4 mm circular scanning area around it, a greyscale depiction of the layers of the retina around the optic disc, the mean RNFL thickness in different quadrants and the global RNFL thickness. These values were compared with the inbuilt normative database and colour coded accordingly.

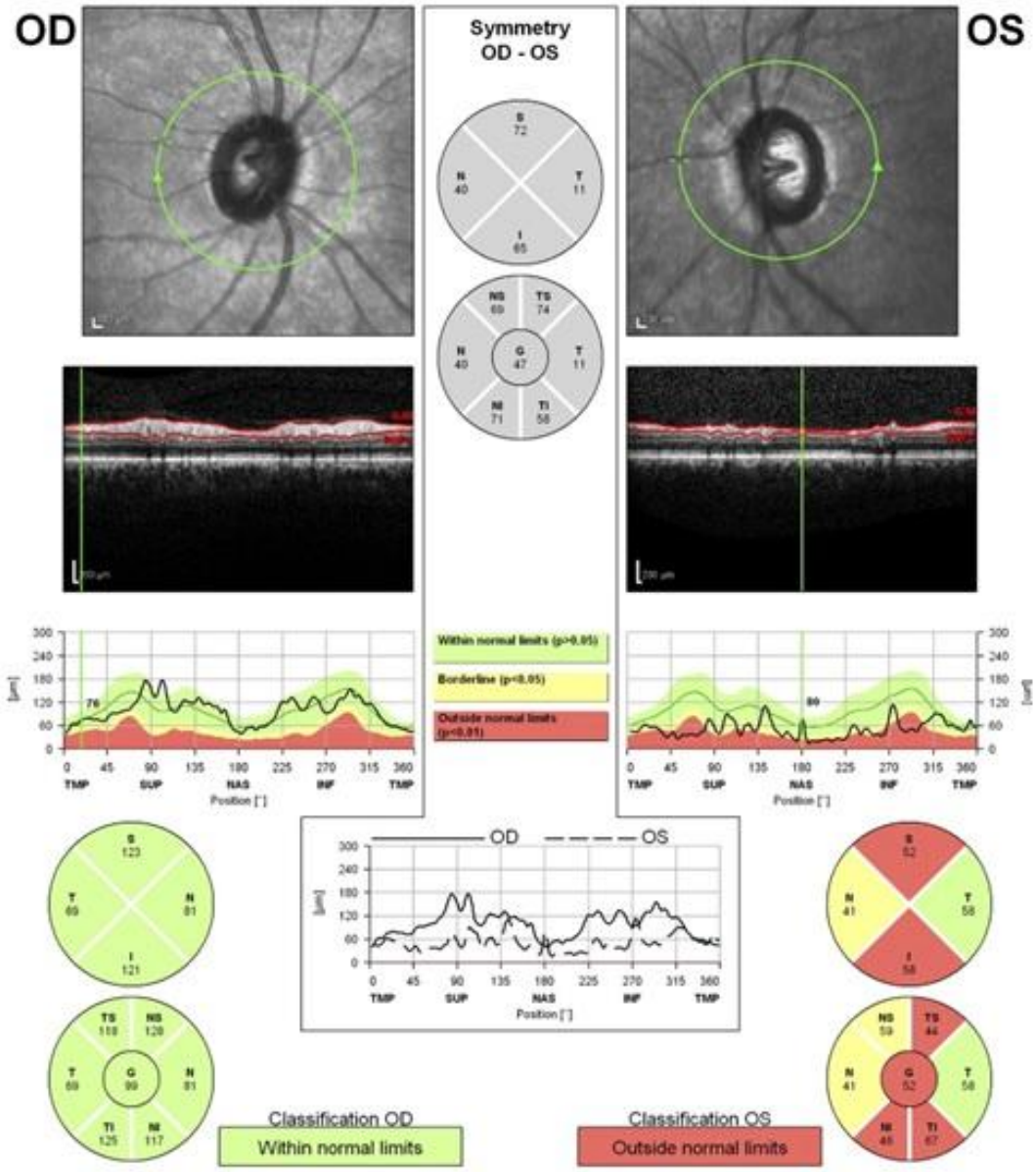

Figure 15: An example of the OCT printout showing the different quadrants and the global RNFL thickness.

The right eye showed normal values of RNFL thickness colour coded green. The left eye showed RNFL thinning due to glaucoma. The superior and inferior quadrant RNFL thickness is less than the thickness seen in 1% of the population (colour coded red) and the nasal quadrant RNFL thickness falls below the thickness seen between 1% and 5% of the population (colour coded yellow). From (Wu et al., 2012)

1.4.6.12 The RNFL normative database

The RNFL normative database is used to quatitavely compare the RNFL measured in the human retina to a database. The current normative database of the RNFL for the Spectralis™ HRA+OCT was derived from 201 subjects of Caucasian origin in Germany which included 111 males and 90 females with a mean ± standard deviation age of 48.2 ± 14.5 years (range from 18 to 78 years). (Access data FDA website, [3]) It received FDA clearance in October 2010. The subjects had no history of glaucoma, normal IOP, normal VF and normal optic disc appearance among others. The subjects had a thorough history and physical examination carried out by two ophthalmologists to determine the "normality" of the eyes. (Normative Database in SD-OCT: A Status Report 2012,[4])

For each subject in the normative database, RNFL thickness was measured at each point along the circle scan. The mean RNFL thickness was then calculated along the whole circle scan (global) and within sectors of the circle scan (temporal, temporal-superior, temporal –inferior, nasal, nasal-superior, nasal-inferior). From these measurements, the age-adjusted percentiles of the database sample of the 201 healthy Caucasians were determined and form the basis for highlighting a result as being within normal limits (greater than the 5^{th} percentile) or outside normal limits (less than the 1^{st} percentile of the database sample). The meaning of the nth percentile is that n percent of normal Caucasian subjects from the database sample have an RNFL thickness of less than or equal to this value.

The results of the RNFL measurement were compiled to form a normative database of RNFL thickness. The database was limited by a sample size of 201 subjects (1 case in the <20 years age group and 13 cases in the >70 years age group), Caucasian ethnicity

and subjects with refractive errors ranging from +5 diopters to -7 diopters. Therefore, any RNFL thickness measurement made with the Spectralis HRA+OCT is compared to the normative database and age-adjustment is performed and percentile limits of the normal distribution are computed.

Below are two examples of the RNFL values of the 1st and 5th percentile at ages 45 and 65 years, given in micrometers.

Table 4: The 1st and 5th percentile values of the retinal nerve fiber layer in from individuals aged 45 years from the normative database. (Access data FDA website, [3])

	1st percentile (95% CI)	5th percentile (95% CI)
Global	76.0 (73.2-78.2)	82.1 (79.9-83.9)
Temporal	46.9 (42.8-49.5)	54.9 (51.7-57.0)
Temporal-superior	96.3 (90.8-100.0)	107.4 (103.1-110.4)
Temporal-inferior	99.1 (92.7-103.1)	111.6 (106.6-115.0)
Nasal	38.3 (34.0-42.0)	48.1 (44.6-51.0)
Nasal-superior	57.8 (52.0-62.6)	70.7 (66.1-74.6)
Nasal-inferior	53.6 (46.7-59.2)	68.8 (63.4-73.3)

Table 5: the 1st and 5th percentile values of the retinal nerve fiber layer in individuals aged 65 years from the normative database. (Access data FDA website, [3])

	1st percentile	5th percentile
Global	74.5 (71.7-76.7)	80.6 (78.4-82.4)
Temporal	43.9 (39.8-46.5)	52.0 (48.8-54.1)
Temporal-superior	93.0 (87.6-96.8)	104.1 (99.8-107.2)
Temporal-inferior	94.6 (88.2-98.6)	107.1 (102.1-110.4)
Nasal	38.3 (34.0-42.0)	48.1 (44.6-51.0)
Nasal-superior	57.8 (52.0-62.6)	70.7 (66.1-74.6)
Nasal-inferior	51.9 (45.0-57.5)	67.2 (61.7-71.7)

1.4.6.13 The use of OCT in uveitic glaucoma

The use of the OCT to detect and monitor glaucoma has been studied in primary glaucomas and primary ocular hypertension. The study of the same usage in uveitic glaucoma may provide valuable information and may pave the way to better understand and tailor the use of this sensitive and reproducible tool in detecting early glaucomatous changes in uveitis. However, the accuracy and benefit of this instrument in uveitic glaucoma needs to be assessed against the effect of uveitis such as disc swelling and diffuse retinitis and choroiditis, like birdshot choroidoretinitis, onto the RNFL thickness. The occurrence of CMO might influence the accuracy of the peripapillary RNFL measurement as macula and surrounding tissue leakages may also give rise to subclinical RNFL swelling resulting in a falsely thicker RNFL measurement. Other studies have shown an increase in thickness of ocular structures with acute exacerbation of uveitis and this may well include the RNFL. (Ozdamar et al., 2010) (Moreno-Arrones et al., 2010)(Traill et al., 2007)

In clinical studies, optic disc cupping in young adults has been reported to be reversible alongside improvement of VF and stereometric parameters with IOP control following trabeculectomy. (Swinnen et al., 2010) Similar changes have been reported in primary congenital glaucomas. (Wu et al., 2002) This is more commonly seen in children less than 1 year of age.(Meirelles et al., 2008) However OCT measurement of the RNFL and macular thickness has been shown to decline with progression of glaucomatous damage seen on stereographs in children. (El-Dairi et al., 2009)(Hess et al., 2005) RNFL thickness measured using imaging tools such as the OCT could be a potential tool to detect early glaucomatous changes in this special group of children as VF loss often occurs late and could be irreversible.

1.5 Management of raised IOP in uveitis

The management of IOP elevation in uveitis is targeted at two crucial aspects, maintaining patients on optimum dose of anti-inflmmatory drugs to attain uveitic quiescence, and sufficient IOP control.

1.5.1 Medical management

The initial treatment of IOP elevation, either primary or secondary in nature like in uveitis, usually starts with topical hypotensive agents. The agent chosen should have excellent IOP-lowering effect and minimal local or systemic side effects. Presently, there are five main categories of drugs used for lowering IOP (Table 6). The selection of which agents to use depends partly on the mechanism of action of each drug because an adjunctive agent with a complementary mechanism of action may enhance the IOP lowering effect with more consistent IOP reduction. (Whitson, 2007) The American Academy of Ophthalmology recommends a 20-30% reduction in IOP from baseline in patients with mild disease and ≥40% reduction for those with advanced disease. [5] This target pressure however, should be dynamic and adjusted over time should the patients' condition change.

1.5.2 Topical Hypotensive Agents

1.5.2.1 Beta blocker

As in the treatment of other types of IOP elevation, beta blockers are still the commonest and the first line of treatment for IOP elevation in uveitis. They are used either as monotherapy or in combination with other topical hypotensive agents. The IOP-lowering effect comes from their ability to reduce aqueous production,(Coakes

and Brubaker, 1978) but due to their lack of effect on nocturnal aqueous humor production, these agents are less efficacious nocturnally compaired to day time. (Liu et al., 2004) The average IOP reduction reached has been reported to be between 20-35%. (Zimmerman and Kaufman, 1977) About 20% of patients needed more than one IOP-lowering medication which included alpha-agonist and carbonic anhydrase inhibitors (Sallam et al., 2009).

Table 6: Agents used for glaucoma therapy (Whitson, 2007)

Class/drug	Typical dosage
α-adrenergic agonists	
Apraclonidine 0.5,1.0%	b.i.d or t.i.d
Brimonidine 0.2%	b.i.d or t.i.d
Brimonidine P 0.15, 0.1%	b.i.d or t.i.d
β-blocker	
Non-selective	
Carteolol 1.0%	b.i.d
Levobunolol 0.25,0.5%	b.i.d
Metipranolol 0.3%	b.i.d
Timolol 0.25, 0.5%	b.i.d
Timolol GFS 0.25, 0.5%	Once daily
Selective	
Betaxolol 0.25, 0.5%	b.i.d
Carbonic Anhydrase inhibitors	
Systemic	
Acetazolamide 125, 250 mg	q.i.d
Acetazolamide sustained-release 500mg	b.i.d
Methazolamide 25, 50 mg	b.i.d or t.i.d
Topical	
Brinzolamide 1.0%	b.i.d or t.i.d
Dorzolamide 2.0%	b.i.d or t.i.d
Cholinergics	
Pilocarpine solution 0.5, 1.0, 2.0, 4.0, 6.0%	q.i.d
Pilocarpine gel 4.0%	QHS
Carbachol 0.75, 1.5, 3.0%	t.i.d
Achothophate iodide 0.25%	b.i.d
Prostaglandin analogs	
Bimatoprost 0.03%	QHS
Latanoprost 0.005%	QHS
Travoprost 0.004%	QHS
Travoprost Z 0.004%	QHS

QHS: At bedtime

1.5.2.2 Alpha agonist

Alpha-agonist is often used in conjunction with other IOP lowering medication. It lowers the IOP by reducing production and increasing outflow of aqueous humor. (Toris et al., 1995) A few case series has reported anterior uveitis and conjunctivis induced by brimonidine tartarate (Alphagan) in patients without any history of uveitis(Nguyen et al., 2008)(Byles et al., 2000). However among uveitic patients, the use of IOP lowering medication has not been shown to induce or exacerbate uveitis (Heinz et al., 2009). Apraclonidine hydrochloride (Iopidine) is a more favourable agent to use in uveitis as it has been reported to result in a tremendous drop in IOP by 50.3% in a patient with Posner-Schlossman attack although the effect is not as dramatic in POAG (Hong and Song, 1993).

1.5.2.3 Carbonic Anhydrase Inhibitor

Carbonic Anhydrase Inhibitors (CAIs) are available topically and systemically. They lower the IOP by reducing aqueous humor production. Dorzolamide has been reported to result in a mean IOP reduction of 18-22%. (Strahlman et al., 1995) In a large retrospective study involving 1736 adults and 261 children with uveitis, topical CAI has also been reported to be the commonest agent used for IOP elevation (Heinz et al., 2009) . Despite that, 65% of adults and 44% of children needed systemic CAI at least temporarily to control the IOP.

1.5.2.4 Systemic Carbonic Anhydrase Inhibitor

Acetazolamide (Diamox) is the commonest systemic CAI used in ophthalmology. It acts by reducing the production of aqueous humor. It is commonly used for short term management of accelerated IOP when topical hypotensive agents are insufficient.

Doses of up to 1 gram a day is given in 2 to 4 divided doses. Precautions are maintained that patients are to increase their fluid intake as acetazolamide is known to cause dehydration among other side effects such as paresthesias, altered taste, electrolyte imbalances, hearing dysfunction and tinnitus, kidney stone formation and anorexia.

Acetazolamide is normally the final medical treatment given for IOP control. The addition of oral CAI has been shown to provide an additional 30% IOP reduction in children with primary glaucoma already on topical CAI. (Sabri and Levin, 2006) Dependancy or inadequate IOP control with acetazolamide often results in glaucoma surgery. In patients who finally require glaucoma surgery, acetazolamide is frequently stopped in the immediate postoperative period to prevent from hypotony, a common problem in uveitic eyes because of reduced aqueous production from a ciliary body that has been subjected to recurrent inflammation.

1.5.2.5 Prostaglandin analogues

The prostaglandin analogues are lipophilic molecules derived from arachidonic acid which is a 20-carbon chain structure, a precursor for other eicosanoids including the leukotrienes and the tromboxanes. (Whitson, 2007) They lower the IOP by enhancing the uveo-scleral outflow. (Toris et al., 1993) Although previously, the use of prostaglandin analogues was suspected of inciting inflammation in glaucoma patients to the extent that its use has been contraindicated in uveitic glaucoma, the risk of inducing an episode of uveitis is low. (Sallam et al., 2009) Some studies have suggested similar efficacy of prostaglandin analogue to a fixed combination of dorzolamide and timolol, (Markomichelakis et al., 2009) despite concerns that there might be lower

efficacy of prostaglandin analouges in a condition where prostaglandins are already present in the eye released during uveitic exacerbations. The use of topical prostaglandin analogues in uveitic eyes has been shown to significantly reduce the IOP without inciting an increased risk of CMO or anterior uveitis (Chang et al., 2008),(Sallam et al., 2009)

1.5.3 Neuroprotectives

Apart from IOP lowering medication, neuroprotective agents have been investigated to decelerate glaucoma progression. Many compounds such as betaxolol, brimonidine, anti-oxidants such as vitamin E and coenzyme Q, and gingko biloba extracts have been reported to be able to protect the retina against free radical damage and lipid peroxidation. (Quaranta et al., 2003), (Chida et al., 1999) Treatment with calcium channel blockers has also been shown to decrease glaucoma progression. (Koseki et al., 2008)

Among the challenges of neuroprotective studies is the lack of human data. (Danesh-Meyer, 2011) In a phase III clinical trial, Memantine (an N-methyl-D-aspartate receptor function), commonly used to treat Alzheimers Disease, failed to demonstrate efficacy against placebo. (Allergen Reports Fourth Quarter Operating Results, [6]) Melatonin is the latest neuro-protective agent compound studied in glaucoma. Although it showed some promising results (Rosenstein et al., 2010)(Sande et al., 2008)(Belforte et al., 2010)(Serle et al., 2004), it's efficacy and safety in treating UG has yet to be elucidated.

1.5.4 Laser treatment

While laser treatment has been widely used in primary glaucomas, only few reports have been made on their use in uveitis. Although laser peripheral iridotomies have

been widely used to break acute angle closure attack, its use for acute angle closure secondary to a seccluded pupil in uveitis will fail to break the attack in more than 50% of cases. (Spencer et al., 2001) It may even endanger the patient by delaying the inevitable move to surgical iridectomy with synechiolysis in patients whom iris bombe may be so severe that the peripheral iris is physically adherent to the peripheral cornea and successful iridotomy will be impossible. Although there have been isolated reports of a benefit from argon laser iridoplasty in uveitic acute angle-closure glaucoma,(Mansouri and Ravinet, 2009) this cannot be advocated as part of the normal approach to treatment as it neither breaks the synechiae which secclude the pupil and cause the attack in the first place, nor does it provide a bypass in the form of an iridectomy. In addition, if the iris is adherent to peripheral cornea, laser iridoplasty would risk further damaging the corneal endothelium already compromised in the area of adhesion. Likewise, argon laser trabeculoplasty does not have a role in eyes with uveitis, presumably due to pre-existing angle damage from recurrent uveitis (Robin and Pollack, 1983).

1.5.5 Surgical management

Only a limited number of patients with UG can be sufficiently controlled with topical and systemic anti-glaucoma therapy alone. The need for glaucoma surgery is significantly higher in children with up to 60% of children on maximum tolerated medical therapy (MTMT) requiring various glaucoma procedures compared to 35% of adults. (Heinz et al., 2009)

One difficulty in comparing success rates between trials is the variable definitions of success. This has now been addressed by a common-standard definition of IOP success in glaucoma surgery by the World Glaucoma Association Guidelines on Design and

reporting of Glaucoma Surgical Trials (Guideline Development Group, 2009). Among other things, the guideline recommends that IOP measurement be measured with a calibrated Goldmann Applanation Tonometer, ocular hypotensive medications be identified by class or generic name, the use of standard automated perimetry as described in several large randomized clinical trials be used until an international consensus can be developed for a single perimetric standard to be used in all future studies, and that visual acuity be determined using the best corrected visual acuity with the standard Snellen charts or with previously published acuity charts, such as the Early Treatment of Diabetic Retinopathy Study (ETDRS). Furthermore, the guideline advocated that IOP reduction is the principle end-point of glaucoma surgical trials, pre- and post-operative numbers of medications should be enumerated as the total number of classes of hypotensive drugs being used, graphical representation of success should clearly illustrate the number of patients still in the trial at a particular time-point, and a survivor curve plus a scatter plot is the minimum requirement for presentation of trial outcomes data. The definition of baseline, or reference IOP may be recorded as the IOP before medication was started, the IOP after washout of medication, or the IOP on the patients's full medical regimen just before surgery (usually the MTMT). There was no consensus as to which of the definitions are the most appropriate, but for practical purposes, it has been agreed that treated IOP just before surgery should be used as this level is considered to be the best that medical treatment can achieve. IOP success should be reported with a number of alternative upper limits (i.e, ≤ 21, 18, 15 and 12 mmHg) and with a lower limit (i.e, 6 mmHg). Failure should be defined as an IOP level measured above the upper limit or below the lower limit on two consecutive study visits and success should be defined as whether or not the above definitions of IOP has been achieved without (complete success) or

with ocular hypotensive medications (qualified success). In future this may assist in the harmonisation of study methodology allowing easier comparison of surgical trial results. However, despite the differences in definition of success, IOP reduction achieved via glaucoma surgery has significantly reduced the incidence and rate of VF progression. (Bhardwaj et al., 2013)

1.5.5.1 Trabeculectomy

Trabeculectomy is the surgical procedure of choice in uveitic eyes without previous intraocular surgery and in the absence of other risk factors for trabeculectomy failure such as anterior segment neovascularisation. (Kok and Barton, 2002) It involves creating a bypass for outflow of aqueous humor from the anterior chamber via an internal osteum and a sclera flap into the subconjunctival space forming a bleb (Figure 16). It is often performed with the use of antimetabolite augmentation such as mitomycin C (MMC) or 5 Fluorouracil (5FU) to minimise fibrosis and subsequent surgical failure.

The success rate of trabeculectomy with MMC has been reported to be approximately 90% at 1 year and 79% at 2 years in one retrospective study comparing 21 uveitic and 30 non-uveitic patients. Here success is defined as IOP ≤ 30% of the baseline with post-operative IOP lowering medication or 5FU injection (Noble et al., 2007).

The use of intraoperative 5FU in trabeculectomy gives a slightly lower overall success rate (both with and without postoperative IOP lowering medication) which was 82% at 2 years and 67% at 5 years. Here, complete success was defined as IOP ≤ 20 mmHg without hypotensive agents and partial success was with hypotensive agents. Failure was more commonly seen and occurred earlier in patients of black ethnic origin. No

deleterious effect on uveitis control was reported as a result of the surgical intervention (Towler et al., 2000).

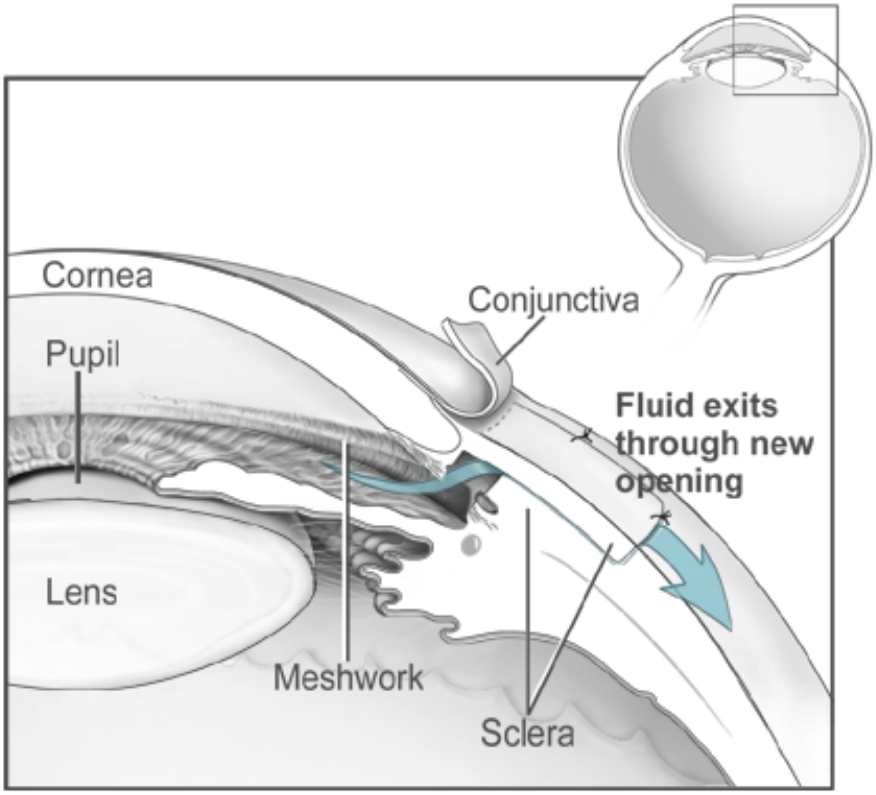

Figure 16: A schematic depiction of trabeculectomy. From the National Eye Institute, National Institute of Health [7].

Comparable success rates have been reported among eyes with UG and POAG undergoing trabeculectomy with MMC. In a retrospective case series involving 53 UG and 80 POAG eyes, after an average follow-up of 5.4 years, success rates (IOP ≤ 15 mmHg) of 57% and 54% were reported in UG and POAG respectively without IOP lowering medication. The success rates increased by 10% in both groups with the use of hypotensive agents. However, postoperative inflammation resulted in loss of IOP control and post-operative hypotony more frequently seen in the UG group (Kaburaki et al., 2009).

Even with adjunctive antiproliferative use, increased inflammatory cells and fibroblast result in significant inflammatory response and excessive fibrosis after trabeculectomy leading to early or latent bleb failure. However, the use of MMC should be used with caution in eyes with chronic uveitis as they may already have significant scleral thinning which may result in intraocular drug penetration leading to ciliary body toxicity. Nonetheless, in eyes after trabeculectomy, particularly with MMC, one should not assume that hypotony is due exclusively to hyposecretion as the most likely cause of hypotony in these cases is overdrainage through the trabeculectomy. Hypotony hyposecretion should only be concluded after the sclera flap and conjunctiva has been resutured tightly shut, absence of leakage has been confirmed with fluorescein testing over the scleral flap, and the hypotony has been found to persist.(Din et al., 2012)

The complications of anti-proliferative agents usage are many, which include corneal epithelial defects with 5FU, late bleb leaks and bleb related endophthalmitis with MMC (Anand and Khan, 2009). To avoid these complications and risk of failure from excessive scarring and fibrosis, shunting devices have been used as a primary surgical procedure for IOP control in certain uveitic patients.

1.5.5.2 Glaucoma drainage devices

There are two types of shunting devices or more commonly known as glaucoma drainage device implants (GDI): valved (such as Ahmed) and non-valved (such as Molteno and Baerveldt). The valved devices is said to allow better IOP control without postoperative hypotony as aqueous is only drained when the IOP reaches a certain amount of pressure. The risk of severe hypotony and suprachoroidal haemorrhage in uveitis is exceptionally high. Therefore, to avoid postoperative hypotony, the lumen of tubes in non-valved devices is usually occluded intraoperatively, either by external

ligature (using absorbable or non absorbable suture which can be lasered later) or internal occlusion with non absorbable sutures (Figure 17). (Nguyen, 2004) The occlusion is removed once a capsule has formed around the plate of the implant, which normally takes up to 3 months. To avoid accelerated IOP in the immediate postoperative period because of this ligature, some authors advocated fenestration of the tube with a small needle just anterior to the ligature. (Schwartz et al., 2006).

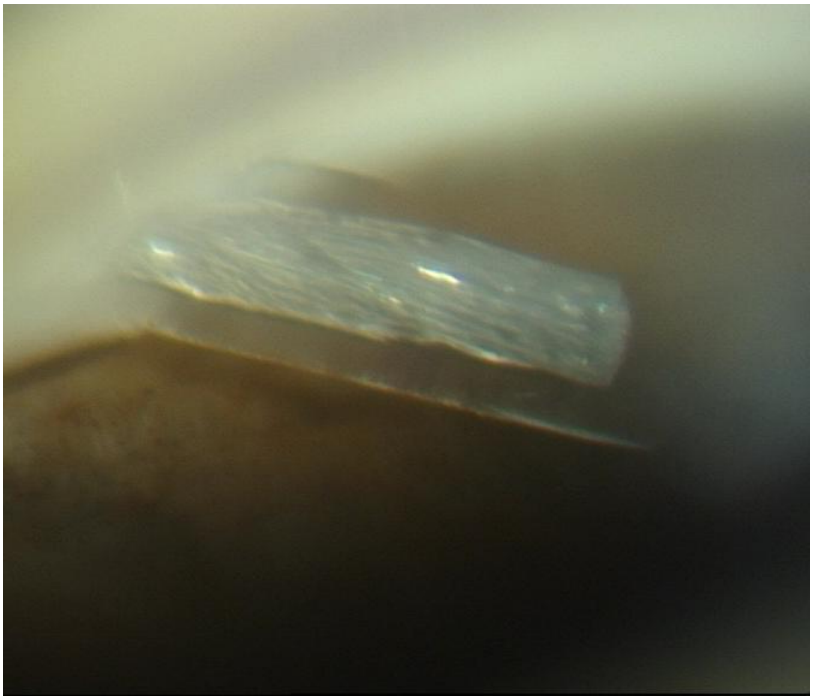

Figure 17: A tube in the anterior chamber occluded with an intraluminal 3-0 nylon supramid suture. (Din et al., 2012)

Evaluation of success rates in these devices is complicated by the varied definition of success across studies. In one long-term prospective case series of 41 Molteno implants in 35 patients with uveitis after a mean follow-up period of 20 year, IOP control of <22mmHg was achieved in 87% of patients at 5 years and 77% at 10 years after surgery (Molteno et al., 2001).

Figure 18: The Baerveldt glaucoma implant shown in three sizes, from (Ceballos and Parrish)

In another retrospective non-comparative case series on the outcome of the Baerveldt Glaucoma Implant in uveitic glaucoma (Figure 18), the cumulative success rates were 95.8% at 3 months and remained at 91.7% up to 24 months. The definition of success used was IOP between 5 and 21mmHg with or without IOP lowering medications and without requirement for further glaucoma surgery, loss of light perception or phthisis. The commonest complication seen in these patients were choroidal effusion and hypotony (Ceballos et al., 2002a). Concerns have remained that in uveitis, because of low levels of aqueous production in some patients, smaller sized implants should be used, but this has not been adequately studied prospectively.

The Ahmed Glaucoma Valve (Figure 19) has a different survival profile in UG. The overall success rate was approximately 70% with the cumulative probability of success rate of 94.4%, 88.9% and 60% at 1 year, 18 months and 2 years respectively. Here, surgical success rate was defined as IOP between 4 and 21 mmHg without loss of light perception and visually devastating complications at the last postoperative examination. The mean IOP reduction achieved was 48% reduction or 17.3 mmHg from the mean baseline IOP of 33.3 mmHg. (Ozdal et al., 2006)

Figure 19: The Ahmed Valve from [8]

Because the Baerveldt implant has a large surface area and no flow resistor, a number of authors have preferred the Ahmed valve. A comparative study between the two

implants revealed that patients that received Ahmed valve required more glaucoma medications and develop later onset failure; and those who received the Baerveldt implant were more likely to develop early postoperative hypotony-related complications and failure. (Tsai et al., 2006)

Favourable outcomes have been observed in eyes receiving Retisert implantation combined with glaucoma tube shunt placement in a single surgical session in eyes receiving MTMT. It has been shown to decrease uveitis recurrences, improve visual acuity and decrease IOP without significant adverse effect (Malone et al., 2010).

2 Chapter 2: Materials and methods

2.1 Aim

This study was designed to fulfill the following objectives:

1. To determine whether we can use the Spectralis OCT to help in the diagnosis of glaucoma in uveitic eyes with raised IOP.
2. To evaluate the factors that influences the RNFL thickness in uveitic eyes
3. To determine the risk factors for raised IOP and glaucoma in adults and children
4. To determine whether there is any progression of RNFL thinning over time in uveitic eyes with raised IOP
5. To evaluate the surgical outcome of each eye in bilateral glaucoma surgery in bilateral uveitic eyes with raised IOP

2.2 General materials and methods

This is a retrospective non-interventional case series of patients attending a tertiary referral uveitis clinic in Moorfields Eye Hospital between May 2010 and November 2012. Clinical data were collected from medical records of the patients. Available OCT scans of the RNFL were also collected and correlated with the patients' clinical data.

2.2.1 Study population

The eyes of eligible patients were divided into four groups according to the category depicted in Figure 20 : Control (normal contralateral eyes of patients with unilateral uveitis), Normotensive uveitis (Uv-N), Hypertensive uveitis (Uv-H) and Glaucomatous uveitis (Uv-G) according to the definitions on section 2.3.

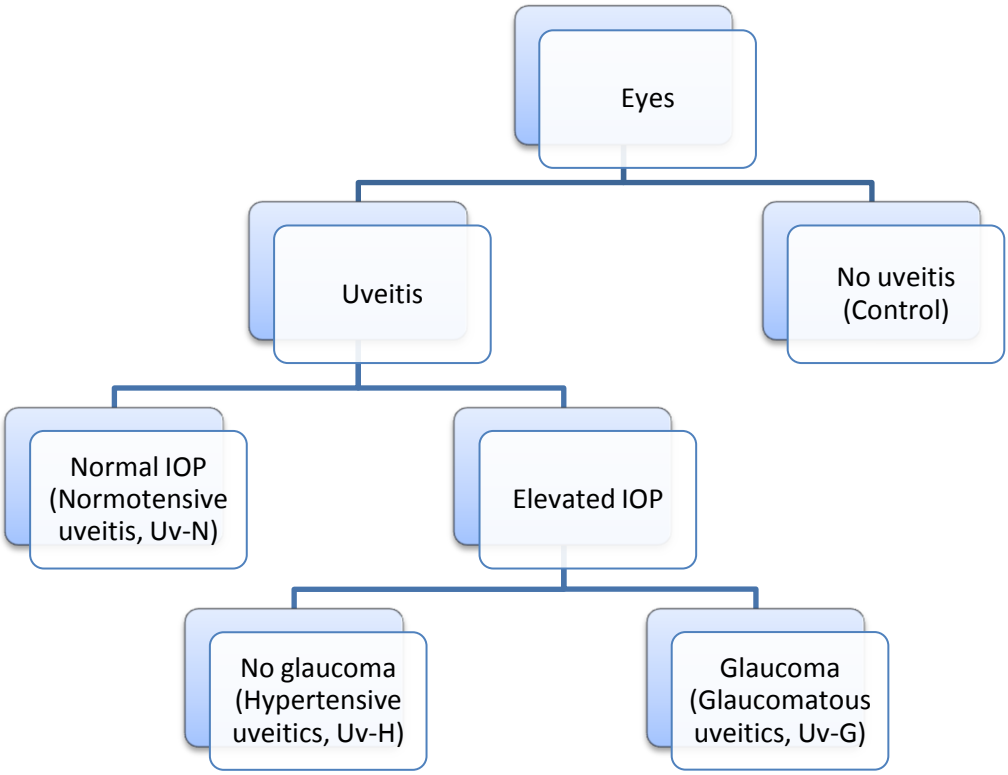

Figure 20: Classification of the study eyes.

2.2.2 Data Collection

The patients' medical records were examined to determine, among others, the age, gender, the anatomical type of uveitis and the type of uveitis based on aetiology, the treatment of both uveitis and raised IOP, duration of follow-up, the onset of IOP elevation, the IOP at 6 months and 1, 2, 3, 4, and 5 years after surgery and at the final visit for the study in Chapter 5, the peak IOP, the aetiology of raised IOP which was categorised into either steroid-induced or uveitic-induced, optic disc appearance by clinical examination and Humphrey VF findings (mean deviation, pattern standard deviation and glaucoma hemifield test) where available.

The information was recorded onto a standard proforma and tabulated into an Excel spreadsheet. The patients' details were entered into an electronic database and each

patient was allocated a study number. The patients' details were anonymised and the primary key was then kept in a locked secure access filing cabinet.

The IOP readings were measured using the Goldmann's Applanation Tonometer. Visual acuity was recorded as the best corrected visual acuity (BCVA) using the Snellen chart with the use of pinholes or the patients' spectacles when used.

2.2.3 Inclusion criteria

Inclusion criteria for patients in Chapter 3 and 4 were a diagnosis of uveitis, history of raised IOP of more than 21 mmHg on two separate occasions, and available peripapillary RNFL scans measured by the Spectralis™ HRA+OCT (Heidelberg Engineering, Germany). Additional inclusion criteria will be mentioned in the respective chapters. The scans were performed as part of the patients' clinical follow-up management.

2.2.4 Exclusion criteria

Exclusion criteria were patients with multiple sclerosis, patients with missing or incomplete data, eyes with frank corneal edema or eyes with other forms of optic neuropathy.

When evaluating the RNFL, eyes with disc swelling, gross retinal changes such as diffuse macular or retinal scars and choroidal neovascular membrane, previous laser retinopexy or vitrectomy, poor quality scans (a Q score of less than 15 as recommended by the manufacturer) or eccentrically located scans were excluded. Eyes with previous laser retinopexy were excluded because laser therapy ablates the retina and therefore may have an effect on the RNFL measurement. Eyes with previous

vitrectomy on the other hand, may have experienced significant IOP fluctuation intraoperatively and immediately postoperatively which may have an impact on the RNFL thickness and were therefore excluded. Eyes with diffuse macular or retinal scars were excluded because we feel that the retinal scars may cause changes to the RNFL thickness in a way not attributable to raised IOP or glaucoma.

2.2.5 Ethical approval

The Research Governance Committee of Moorfields Eye Hospital approved the data collection (protocol LIGS 10201, Causes of Visual Loss in Uveitis). This study adhered to the tenets of the Declaration of Helsinki.

2.3 Definitions

The following definitions were used:

1. Normal (Normal): the normal contralateral eyes of patients with unilateral uveitis.
2. Normotensive Uveitis (Uv-N): Eyes with uveitis and normal optic disc, and no previous history of IOP elevation.
3. Hypertensive Uveitis (Uv-H): Eyes with uveitis and a history of elevated IOP of 21 mmHg or greater, on at least 2 separate occasions, but clinically normal optic disc and/or VFs. (Sallam et al., 2009)
4. Glaucomatous Uveitis (Uv-G): Eyes with uveitis and a history of IOP elevation greater than 21 mmHg on 2 or more occasions with the presence of glaucomatous optic neuropathy, with or without glaucomatous VF changes. This is based on the criteria outlined that the diagnosis of secondary glaucoma

can be done based on the presence of optic neuropathy alone, in the presence of a second ocular pathology. (Foster et al., 2002)

5. Glaucomatous disc changes were diagnosed by the presence of a vertical cup to disc ratio (CDR) of >0.7, (Foster et al., 2002) focal rim notching, rim thinning or rim excavation.(Bowd et al., 2001)
6. Glaucomatous VF: Glaucoma Hemifield test graded as “outside normal limits” and the presence of a cluster of three contiguous points at the 5% level on the pattern deviation plot, using the threshold test strategy with the 24-2 test pattern of the Ziess-Humphrey field analyser .(Foster et al., 2002)(Bowd et al., 2001)
7. Steroid induced IOP elevation: uveitic eyes with IOP elevation ≥ 6 mmHg from pre steroid treatment pressure or IOP elevations > 21 mmHg on at least 2 separate occasions related to any kind of steroid treatment at any time during the follow-up period.(Ren, 2009) (Sallam et al., 2009)
8. Uveitis-induced IOP elevation: uveitic eyes with IOP elevation IOP > 21 mmHg in an actively inflamed eye prior to steroid treatment.
9. Active uveitis: Active uveitis relates to any evidence of ongoing disease activity determined by the presence of inflammatory cells in the anterior or posterior segment with or without CMO.
10. The peak IOP: referred to the highest IOP reading ever recorded during the entire follow-up.
11. Uveitis was classified as anterior, intermediate, or posterior/panuveitis according to the Standardized Uveitic Nomenclature (SUN) classification.(Jabs et al., 2005)

12. Uveitis was defined as acute if the uveitis activity lasted for less than 3 months and chronic if it lasted more than 3 months. (Jabs et al., 2005)
13. Impaired vision was defined as BCVA between 6/15 (20/50) and 6/36 (20/120) and poor vision was defined as BCVA of 6/60 (20/200) or poorer. (Jabs et al., 2005)
14. The number of topical IOP-lowering medications refers to the number of medications according to the classification of the medications.

2.4 Acquisition of the Spectralis OCT scans

All patients were scanned using the commercially available Spectralis™ HRA+OCT (Heidelberg Engineering, Germany). This instrument uses a wavelength of 820 nm in the near infrared spectrum in the SLO mode which comes from a super luminescent diode with a wavelength of 870 nm. Infrared images and OCT scans at the rate of 40,000 A-Scans/sec of the dual laser scanning systems are acquired simultaneously. Sixteen consecutive circular B-scans with a diameter of 3.4-mm diameter centered at the optic disc were automatically averaged to reduce speckle noise. An online tracking system compensated for eye movements. The retinal vessels within the RNFL were considered to be part of the RNFL. (Bendschneider et al., 2010)

The signal strength (range, 0–40) of each scan was reviewed, and scans with signal strength of less than 15 (as suggested by the manufacturer) were excluded from the analysis.(Wu et al., 2010) In addition, criteria for determining adequate scan quality were as follows: a clear fundus image with good optic disc and scan circle visibility before and during image acquisition, RNFL visible and without interruptions, and a continuous scan pattern without missing or blank areas.

The software in the OCT machine compared the RNFL thickness of the patients with the inbuilt normative database of the Spectralis™ HRA+OCT and represents the mean RNFL thickness using a colour coded percentile scale as described in section 1.4.6.11.

2.5 Statistical Analysis

Data was analysed using Stata version 10 (Intercooled) (StataCorp, College Station, TX). Normality of the data was determined by plotting the normal quantile plot.

All categorical variables were compared using Chi-square test. For data count of less tha 5 in any subgroup, Fisher's Exact Test was used to compare proportions. Student's T test and Mann-Whitney test were used to compare means in parametric and non-parametric data respectively. One-Way ANOVA with Bonferroni correction was used to compare means in more than 2 groups and the Kruskal Wallis test was used for comparing nonparametric values in more than 2 groups. Multivariate Linear and Logistic Regression was used to determine the factors affecting the RNFL thickness and risk factors for RNFL defects, raised IOP and glaucoma. Pearson correlation coefficient was calculated to assess correlation between two variables. Positive and negative correlation coefficients indicate positive and negative correlation respectively, and zero indicates absence of correlation. Coefficient values from 0 to 0.25 indicate little or no correlation, from 0.25 to 0.50 fair correlation, from 0.50 to 0.75 moderate to good correlation, and from 0.75 to 1.00 very good to excellent correlation.(Colton, 1974) A p-value of less than 0.05 was considered significant. Results are described as mean and standard deviation unless stated otherwise.

2.5.1 Area under the receiver operating curve

The Area under the Receiver Operating Curve (AROC) is a statistical analytical method to determine the discriminating power of an instrument/method to differentiate the presence of a certain disease in any given condition.(Hanley and McNeil, 1982) We included the Uv-H and Uv-G eyes in this calculation to determine the discriminating power of each quadrant to differentiate the two conditions.

AROC were calculated for RNFL thickness in each quadrant to determine their ability to discriminate the two groups of eyes. Data on the OCT result (whether Normal or borderline/abnormal), the eye group (Uv-H and Uv-G) and the RNFL values of the different quadrants around the optic nerve was used to produce the AROC values for each quadrant. These AROC values denote the respective quadrants' ability to differentiate whether an eye is Uv-H or Uv-G based on the OCT result (normal or borderline/abnormal). An AROC of 1 represents perfect discrimination, whereas an area of 0.5 represents chance discrepancy. (Mansoori et al., 2010) The interpretation of AROC values are as follows: 0.9-1= excellent, 0.8-0.89= good, 0.7-0.79 = fair, 0.6-0.69 = poor, and 0.50-0.59= fail. [9]

2.5.2 Linear Mixed Model Analysis

Linear Mixed Model analysis was used in this study to evaluate longitudinal data of the RNFL thickness over time in Chapter 3 and 4, and changes in the IOP, visual acuity and CDR over time in Chapter 5.

In Chapter 3 and 4, the RNFL thickness were clustered within each patient and the eyes respective groups (Control, Uv-N, Uv-H or Uv-G) and in Chapter 5, the parameters were clustered within each patient and groups of first or second eyes.

3 Chapter 3: IOP elevation and glaucoma in adult uveitis patients and evaluation of the retinal nerve fiber layer with the Spectralis OCT.

3.1 Introduction

Raised IOP in uveitis is among the commonest causes of secondary glaucoma in clinical practice. Glaucoma in uveitis was ranked as the third commonest cause of visual loss in uveitis after cataract and CMO.(Rothova et al., 1996) (Yeo et al., 2013) However, while visual loss from the first two causes is potentially reversible, glaucomatous visual loss is permanent. Although inflammation itself may cause raised IOP, corticosteroid treatment is also responsible for raised IOP in about 60% of patients.(Sallam et al., 2009)

The means to detect glaucoma early prior to VF changes has been intensely investigated over the past decade especially in primary glaucomas. (Arnalich-Montiel et al., 2006)(Hwang and Kim, 2012)(Cellini et al., 2012) Peripapillary Retinal Nerve Fiber Layer (RNFL) measurement is one of the subjects of interest for this purpose. (Cvenkel and Kontestabile, 2011) Previous studies has demonstrated the Spectralis OCT (Heidelberg Engineering, Germany) to be a good diagnostic tool for detection of early perimetric changes and excellent for moderately advanced perimetric changes induced by glaucoma. (Wu et al., 2012)

Uveitis has been reported to cause thickening of ocular structures in acute exacerbations such as the cornea in Behcet's uveitis (Ozdamar et al., 2010) although other studies reported the contrary in acute anterior uveitis. (Turan-Vural et al., 2012)

Thickening of the macula in anterior uveitis has been demonstrated on the OCT in the absence of clinically detectable CMO, suggesting that the inflammation is not actually confined to the anterior segment despite the clinical appearance. (Moreno-Arrones et al., 2009)' (Traill et al., 2007) If the same increase in thickness can be seen in the peripapillary RNFL, it may suggest that the normative database of the peripapillary RNFL thickness on the OCT used to screen for glaucomatous changes might not be applicable to uveitic patients, as it may produce false negative results during screening should the normative curve be shifted to the right.

Using the current normative database, the RNFL thickness has been shown to correlate well with VF indices in POAG.(Cvenkel and Kontestabile, 2011) Approximately 17% of RNFL loss may result in detectable VF loss. (Wollstein et al., 2012) Therefore measurement of the RNFL with the OCT may be a good adjunctive tool to detect and monitor glaucomatous changes together with sound clinical evaluation and judgement. (Jones and Rhee, 2006)' (Hwang and Kim, 2012)' (Mansoori et al., 2010)

Detection of glaucomatous disc and VF changes in uveitis may be affected by uveitic changes on the disc and VFs. For example, conventional Humphrey VF tests are affected by diffuse retinal changes such as that seen in birdshot choroidoretinopathy (Gordon et al., 2007), multifocal choroiditis (Reddy et al., 1996) and CMO.(Taylor et al., 2012) Disc swelling from the inflammatory process may also obscure optic disc assessment for glaucomatous changes. Therefore, measurement of the RNFL thickness with the OCT, although an attractive objective option for glaucoma detection in uveitis, must be assessed against the effect of inflammation on the RNFL before considering its use for glaucoma detection in uveitic patients.

3.2 Aim

In this study, we first assessed the distribution of RNFL thicknesses in eyes with uveitis both active and quiescent but with no history of IOP elevation, to see whether these were comparable to measurements obtained from non-uveitic eyes and whether we could use the existing normative database to determine the presence of RNFL thinning in hypertensive uveitic eyes. Secondly, we assessed the effect of uveitis on the RNFL. We then determined any RNFL changes related to raised IOP in glaucomatous uveitic eyes (positive controls) and ascertained whether those changes were also present in non glaucomatous hypertensive uveitic eyes. By doing so, we hope to identify a subset of uveitic eyes with raised IOP but undiagnosed RNFL damage and therefore at risk of visual loss from glaucoma. We then performed logistic and linear regression analyses to determine the risk factors for the development of RNFL defects and factors influencing the RNFL thickness. Areas under the receiver operating curves (AROC) were calculated to assess the discriminating power of each quadrant of the RNFL in differentiating between hypertensive uveitic eyes and glaucomatous uveitic eyes. We also assessed the risk factors for IOP elevation and glaucoma in these eyes.

3.3 Methods

The methods have been described in the general materials and methods section in Chapter 2. When assessing the RNFL thickness, eyes with poor scan quality, eccentric scans, large peripapillary scars and previous vitrectomy or laser retinopexy were excluded.

3.4 Statistical Analysis

The statistical analysis has been described in Chapter 2.

3.5 Results

3.5.1 Patients Demography

Three hundred and forty four adult patients were identified. Two patients were excluded for missing data and three patients were excluded for having multiple sclerosis with optic nerve involvement. Out of the remaining 339 patients, four eyes were excluded for other types of optic neuropathy (optic disc pit, normal tension glaucoma, primary open angle glaucoma, non-arteritic anterior ischaemic optic neuropathy) and three eyes were excluded for non-uveitic related conditions (trauma, scleritis, statuory night blindness) Therefore, we included 671 eyes of 339 patients in the analysis. The mean age of the patients was 50.4 ±14.8 years (range 18-90 years). The male to female ratio was 1:1.4.

Eighty-six eyes did not have uveitis, and the remaining 585 eyes consisted of 229 eyes (39.1%) with anterior uveitis, 230 eyes (39.3%) with intermediate uveitis abd 126 eyes (21.0%) with posterior uveitis.

Table 7 describes the distribution of patients with specific systemic association of the uveitis.

Table 7: Distribution of eyes according to the types of uveitis.

Systemic disease	Number of eyes
Normal Eyes	86
Behcet's Disease	6
Birdshot choroidoretinopathy	5
Fuch's heterochromic iridocyclitis	6
Herpetic uveitis	13
HLAB27 related uveitis	27
Juvenile idiopathic arthritis	5
Multifocal choroiditis	3
Possner Schlossman	9
Sarcoidosis	63
Systemic lupus erythematosis	3
Sympathetic ophthalmia	1
Infection (toxoplasmosis, tuberculosis)	8
Vogt koyanagi harada syndrome	18
Wegeners granulomatosis	3
Idiopathic	415
Total	671

3.5.2 IOP elevation and glaucoma in uveitis

The eyes were divided into 86 Control and 585 with uveitis, which were further categorized into Un-N (n=195), Uv-H (n=269) and Uv-G (n=121) based on the above criteria. The incidence of IOP elevation among uveitic eyes was 30%/person-year. The prevalence of raised IOP in eyes with uveitis (Uv-H and Uv-G eyes) was 66.7 % (390 of 585 eyes), and 20.7% (121 of 585 eyes) of them had clinical signs of glaucoma. Table 1 describes the clinical characteristics of the different groups of eyes. The proportions of males with elevated IOP (Uv-H and Uv-G) was higher in males (74.3%) compared to females (60.8%), p=0.003.

Table 8: Demographic characteristics of the eyes in Uv-N, Uv-H and Uv-G groups.

	Uv-N (n=195)	Uv-H (n=269)	Uv-G (n=121)	p 1	p 2	p 3
Age (years),mean ± SD	50.1 ±14.5	48.4 ±14.5	56.4 ±15.7	<0.001§	0.28¶	<0.001¶
Female, no. of eyes (%)	131 (67.2)	139 (51.7)	61 (50.4)	0.001 β	0.001β	0.8 β
Males, no. of eyes (%)	64 (32.8)	130 (48.3)	60 (49.6)			
Mean Spherical equivalent, D (SD)	-0.6 (1.6)	-1.1 (2.0)	-0.7 (1.9)	0.3§		
VF mean deviation, dB	-1.82	-2.39	-5.57	<0.001¥	0.57€	<0.001€
VF pattern standard deviation, dB	1.9	1.72	4.23	<0.001¥	0.2€	<0.001€
Duration of follow-up (year), mean	6.1	7.2	9.6	<0.001¥	0.2€	0.006€
Type of uveitis						
Anterior uveitis	54 (27.7)	112(41.6)	63(52.0)			
Intermediate uveitis	91 (46.7)	107(39.8)	32(26.4)			
Post/panuveitis	50 (25.6)	50 (18.6)	26(21.5)	<0.001β	0.007β	0.05 β
Mean peak IOP , SD	NA	35.5 (9.0)	40.0 (10.5)	NA	NA	<0.001‡
Mechanism of IOP elevation	NA	177	46 (55.3%)	NA	NA	
Steroid induced, n (%of eyes)		(72.8%)				
Uveitis induced, n (%eyes)	NA	66 (27.2%)	57(44.7%)			0.001 β

D= Diopter, dB=decibel, IOP= intraocular pressure, SD= standard deviation, NA=Not applicable, ‡= t-test, β= chi square test, §= ANOVA, ¥= Kruskal Wallis test, €= Mann Whitney test, ¶ = ANOVA with Bonferroni correction, p1= p value among Uv-N, Uv-H and Uv-G groups, p2 = p value between Uv-N and Uv-H groups, p3= p value between Uv-H and Uv-G groups.

3.5.2.1 *Risk factors for raised IOP and glaucoma in uveitic eyes*

To isolate risk factors for raised IOP (Uv-H vs. Uv-N) we examined the following clinical properties: age, gender, mean duration of follow-up and type of uveitis. Only two were found to be significant in a multivariate logistic regression analysis (Table 9). Males were twice as likely to develop hypertensive uveitis as females (OR 2.3, 95% CI 1.4-3.6; p=0.001). The risk of hypertensive uveitis in anterior uveitis was increased two fold compared to other types of uveitis (OR=1.95, 95% CI 1.02-3.74, p=0.045)

Table 9: Multivariate logistic regression for assessing risk factors for IOP elevation.

Variable	Odds Ratio	Standard Error	p	95% Confidence Interval
Age	0.98	0.008	0.051	0.97-1.0
Gender	2.3	0.54	0.001	1.4-3.6
Duration of follow-up	1.02	0.02	0.38	0.98-1.06
Anterior uveitis*	1.95	0.65	0.045	1.02-3.74
Intermediate uveitis*	0.7	0.2	0.225	0.4-1.2

***Posterior/panuveitis was made the reference group for the variable uveitis type.**

A chi square test examining association between uveitis type and gender revealed significantly more males had anterior uveitis than intermediate or posterior/panuveitis compared to females, p=0.024, (Table 10). Further analysis revealed the proportions of eyes with raised IOP was higher in these systemic associations of uveitis (number in brackets are number of Uv-N vs Uv-H eyes): Fuch's iritis (1 vs 7), Possner Schlossman (0 vs 9), herpetic uveitis (2 vs 11), HLAB7 related uveitis (8 vs 19), JIA (1 vs 4). A Fisher's exact test examining the above diseases with gender revealed male gender was significantly associated with Posner Schlossman syndrome and HLAB7 related uveitis, p=0.046.

Table 10: Gender distribution across anatomical types of uveitis.

Gender	Anterior uveitis	Intermediate uveitis	Posterior/panuveitis	p
Female, no. of eyes (%)	111 (48.5%)	134 (58.3%)	86 (68.3%)	
Male, no of eyes (%)	118 (51.5%)	96 (41.7%)	40 (31.7%)	0.001

When examining the risks factors for glaucoma from hypertensive uveitis (Uv-G vs. Uv-H), we found that older age (56.4 years vs 48.4 years respectively, p<0.001), longer duration of follow-up (9.6 vs 7.2 years, p=0.002), higher peak IOP (40.0 vs 35.5 mmHg, p<0.001) and uveitis-induced rather than steroid-induced raised IOP (54.6% vs 45.4%, p=0.001) were significant risk factors for glaucoma. Gender and the type of uveitis were not significant risk factors.

3.5.2.2 Prognosis of steroid-induced and uveitis-induced IOP elevation.

To determine the prognosis of steroid-induced compared to uveitis-induced IOP elevation, we compared the clinical features of eyes with steroid-induced and uveitis-induced IOP elevation.

The mean maximum IOP in eyes with steroid-induced and uveitis-induced IOP elevation were 34.35 mmHg and 41.1 mmHg respectively, p<0.001. Univariate linear regression showed that the increase in maximum IOP for eyes with uveitis-induced IOP elevation was, on average 6.7 mmHg higher (OR 6.7, 95% CI 4.6-8.8) p<0.001, when compared to steroid-induced IOP elevation. The mean age of patients with steroid-induced IOP elevation was also younger compared to uveitis-induced IOP elevation (48.3 vs 56.2 years, p<0.001).

A univariate logistic regression showed that the risk of glaucoma in uveitic-induced IOP elevation was increased 2.3 fold compared to steroid-induced IOP elevation (OR: 2.26, 95% CI 1.37-3.74, p=0.002). However, after adjusting for age and maximum IOP in a multivariate logistic regression, we found that age and maximum IOP were significant factors for glaucoma, and the mechanism of IOP elevation (steroid-induced or uveitis-induced) was no longer significant (Table 11).

Table 11: Multivariate analysis to determine the risk of steroid-induced and uveitis-induced IOP elevation for glaucoma

Variable	Odds Ratio	p	95% Confidence Interval
Age	1.04	<0.001	1.02-1.07
Steroid induced IOP elevation	0.83	0.59	0.44-1.6
Maximum IOP	1.06	<0.001	1.03-1.09

3.5.2.3 Treatment of raised IOP

Uv-G eyes received a mean of 3.1 glaucoma drops compared to Uv-H eyes (2.6 drops, p<0.001). Oral Acetazolamide was also used in 29 % of eyes in Uv-G compared to 21.6 % of Uv-H eyes, although this was not statistically significant. Almost a quarter (22.6%) of Uv-G eyes had to undergo either trabeculectomy or glaucoma drainage devices implantation for further IOP control as compared to 5.2% of Uv-H eyes (p<0.001).

3.5.3 RNFL thickness in uveitis

3.5.3.1 RNFL thickness in normotensive uveitic eyes

Thirty five patients had no OCT scans done and was therefore excluded from the following analysis. Of the 309 patients who had OCT scans, 70 eyes were excluded for

poor quality scans either from dense vitritis, dense cataract, corneal scar or vitreous haemorrhage (29 eyes), eccentric scans (6 eyes) or presence of disc swelling (6 eyes), large peripapillary retinal scars or choroidal neovascularisation (15 eyes) and previous vitrectomy or laser retinopexy (14 eyes). Eyes with previous vitrectomy were excluded because the eyes may have experienced significant IOP fluctuations intra-operatively and immediately post-operatively. Eyes which had undergone laser retinopexy were excluded as this ablates the retina and may have an effect on the RNFL thickness. Retinal scars may affect the RNFL in a way not attributable to glaucoma which was the subject of this study.Therefore we included 531 eyes of 309 patients in this analysis. These eyes were further divided into 73 normal eyes, 136 Uv-N, 231 Uv-H and 91 Uv-G according to the same definition used before.

We first examined the characteristics of the RNFL in normotensive uveitic eyes and determined whether the normative database provided with the Spectralis OCT is applicable to them. To do this, we utilised 136 Uv-N eyes and compared this to 73 normal other eyes (Control).

The mean global RNFL was significantly thicker in Uv-N (106.5 ± 21.1 μm) compared to Control eyes (96.0 ± 8.6 μm, $p<0.001$, Table 12). This increase in thickness was significant in all quadrants (Figure 21). As opposed to the Control eyes; RNFL in the temporal quadrant (85.0 ±22.4μm) was thicker than the nasal quadrant (82.1 ±24.8μm) of the Uv-N eyes.

Table 12: Comparison of RNFL thickness in different quadrants between the Control and Uv-N eyes.

RNFL thickness	Control (n=73)	Uv-N (n=136)	
	Mean ±SD (µm)		p
Global	96.0 ± 8.6	106.5 ± 21.1	<0.001
Inferior	122.3 ± 15.0	134.8 ± 27.4	<0.001
Superior	116.6 ± 13.6	123.9 ± 29.1	0.04
Nasal	73.9 ± 15.5	82.1 ± 24.8	0.01
Temporal	70.8 ± 10.3	85.2 ± 22.4	<0.001
Nasosuperior	103.4 ± 19.7	111.3 ± 32.2	0.06
Temperosuperior	129.8 ± 14.0	137.6 ± 31.6	0.05
Temperoinferior	137.1 ± 18.0	150.5 ± 31.0	<0.001
Nasoinferior	107.8 ± 22.5	118.7 ± 34.0	0.014

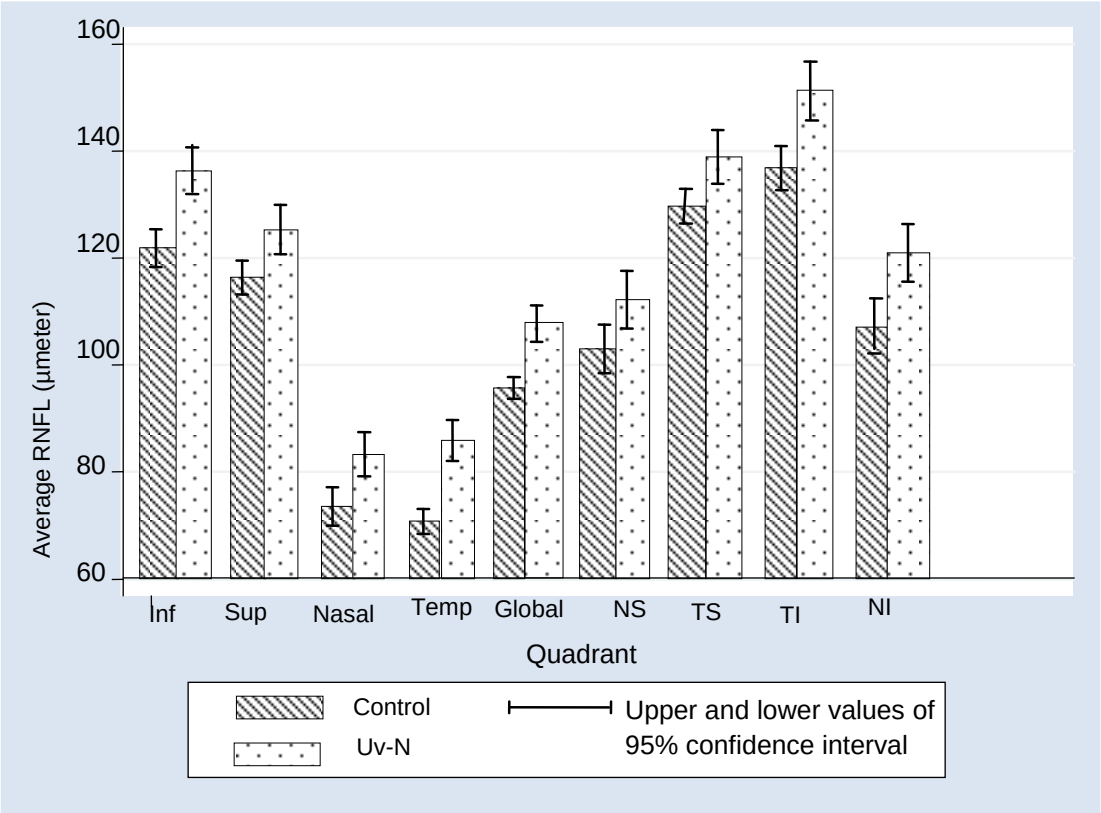

Figure 21: Comparison of the RNFL thickness in Uv-N and Control eyes in each quadrant.

Inf= Inferior, Sup= Superior, Temp =Temporal, NS= Nasosuperior, TS= Temperosuperior, TI= Temperoinferior, NI= Nasoinferior.

Furthermore, within the Uv-N group, eyes with active uveitis during OCT scanning had thicker mean global RNFL (118.1 ± 23.3 µm) when compared to quiescent eyes (103.3 ± 21.2 µm, p=0.006) in the absence of clinically apparent disc swelling. The mean global RNFL thickness in quiescent Uv-N eyes (103.6 ± 18.8) were also thicker than Control eyes (96.0 ± 8.6, p<0.001. All actively inflamed eyes at the time of OCT scanning will be excluded hereafter.

One-way ANOVA test showed a significant difference in the RNFL thickness between different types of uveitis, p< 0.001. The mean global RNFL thickness in all types of uveitis is increased as compared to the Control eyes. A Benferroni correction demonstrated that this increase was significant between control eyes and eyes with intermediate uveitis (p<0.001) (Figure 22).

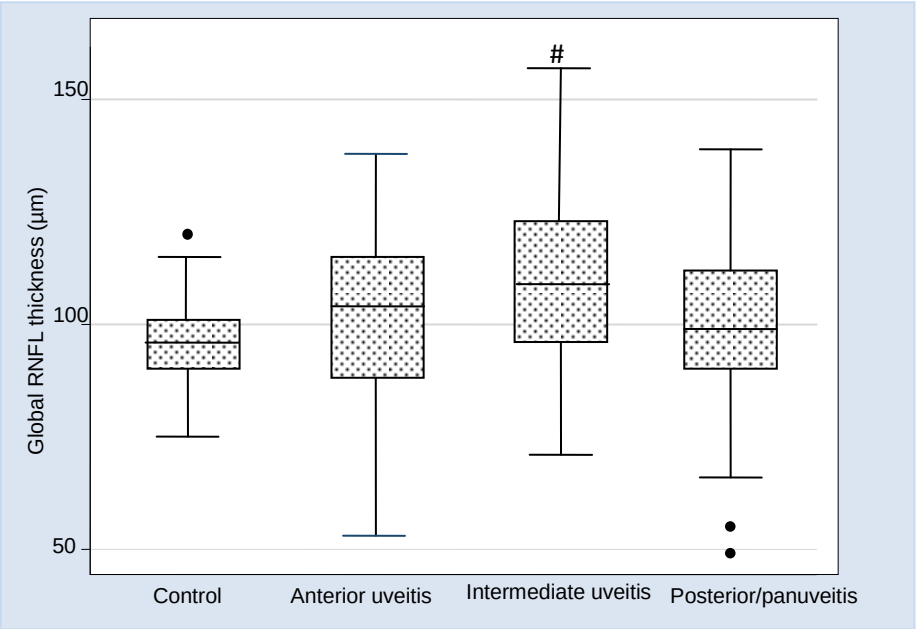

Figure 22: Comparison of the global RNFL thickness in Control eyes and the different types of uveitis in quiescent eyes of the Uv-N group.

 # =Global RNFL thickness of intermediate uveitis eyes compared to control eyes, p<0.001

3.5.3.2 Is the normative database of the Spectralis OCT applicable to uveitic eyes?

Next, we determined whether the inbuilt normative database provided with the Spectralis OCT is applicable to uveitic eyes and can be referred to. To do this, we utilised 114 quiescent Uv-N eyes and compared this to the Control eyes.

The histogram in Figure 23 shows the distribution of the global RNFL thickness of quiescent Uv-N eyes compared to the Control group. Because the mean RNFL in the Uv-N eyes was greater, one would expect the distribution of the RNFL values to be shifted to the right and therefore screening for RNFL defects should be done in comparison to a database comprised of uveitic eyes whereby the 5th percentile is set at a higher value to avoid false negatives. However, this was not the case as the 5th percentile values of quiescent Uv-N eyes and Control eyes were not much different. For example, the 5th percentile value used as the cut off point to divide normal and borderline global RNFL thickness was 82µm and 78µm for Control and quiescent Uv-N eyes respectively. Eventhough the distribution of RNFL values in the Uv-N group appears more spread, it still maintains the lower 1st and 5th centile while the 95th and 99th centile may be shifted to the right.

We therefore concluded that the inbuilt normative database should still be referred to when screening for RNFL defects in uveitic eyes.

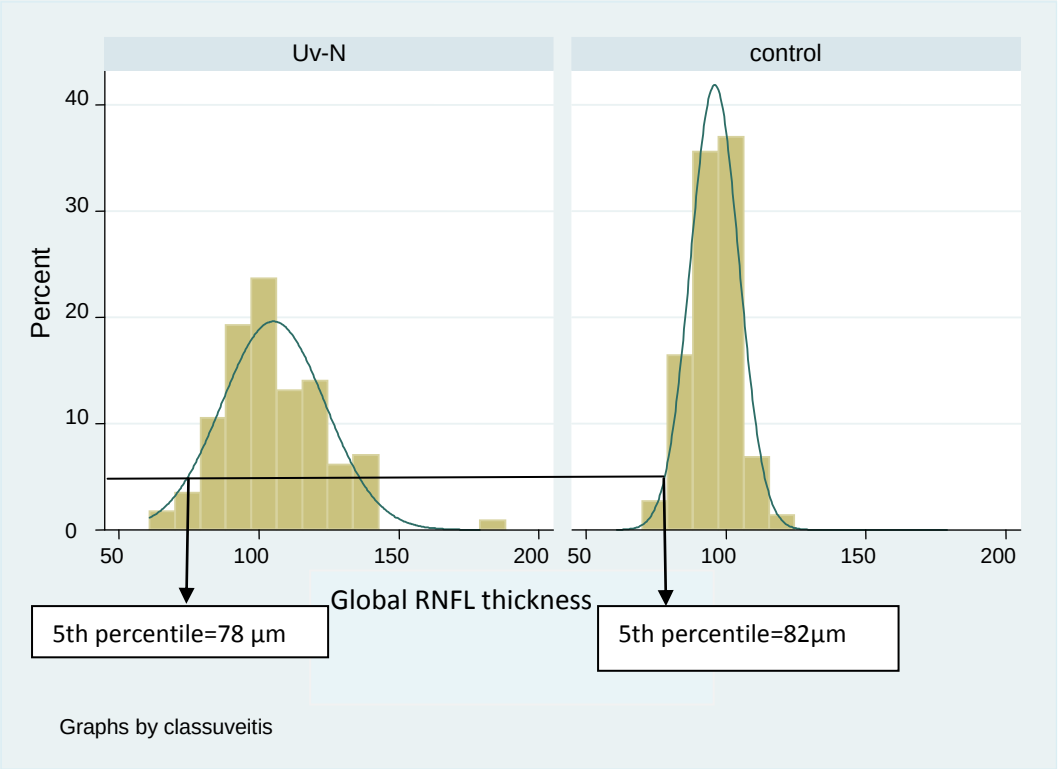

Figure 23: Histogram of the global RNFL showing the percentages of global RNFL thickness and the 5th percentile value for quiescent eyes of the Uv-N and Control group.

3.5.3.3 Factors influencing the RNFL thickness

We performed a multivariate linear regression to evaluate the influence of age, gender, uveitis activity and the type of uveitis on the global RNFL thickness in Uv-N eyes (both active and quiescent). Only factors with a $p<0.05$ on univariate regression analysis were included in this model.

After adjusting for the other factors, for every 10 years increase in age, RNFL thickness decreased by an average of 3.6 µm (OR-0.36, SE 0.2, 95% CI=-0.68-0.03; p=0.032). Eyes with active uveitis during OCT scanning had an increase in global RNFL by 11.8 µm (OR 11.8, SE 4.9, 95% CI=1.9-21.7, p=0.02) as compared to quiescent eyes (Table 13). The R^2 value for this model was 0.264. Intermediate uveitis causes an increase in global RNFL

by 15 µm compared to anterior and posterior/panuveitis. The other factors were not statistically significant.

Table 13: Multivariate linear regression examining factors associated with the mean global RNFL thickness

Variable	Regression coefficient	Standard error	p	95% Confidence interval	R sq
Age	-0.36	0.16	0.032	-0.68 - -0.03	0.27
Gender	-0.35	4.7	0.94	-9.8 - 9.1	
Anterior* uveitis	3.0	6.8	0.66	-10.5 – 16.7	
Intermediate uveitis*	14.7	5.9	0.02	2.8 – 26.5	
Active uveitis	11.8	5.0	0.02	1.9-21.7	

* Posterior/panuveitis was made the reference group for the variable uveitis type

The scatter plot in Figure 24 compares the RNFL thickness between quiescent Uv-N eyes and Control eyes with age. Although the mean RNFL in quiescent Uv-N eyes was thicker when compared to the Control eyes, the regression line is steeper indicating a faster loss of RNFL as age increased. As opposed to the average RNFL loss in Uv-N eyes (3.5 µm for every 10 years increase in age), the average RNFL reduction in Normal eyes was 1.69 µm for every 10 years of increase in age, p=0.03, 95% CI –0.32 - -0.01.

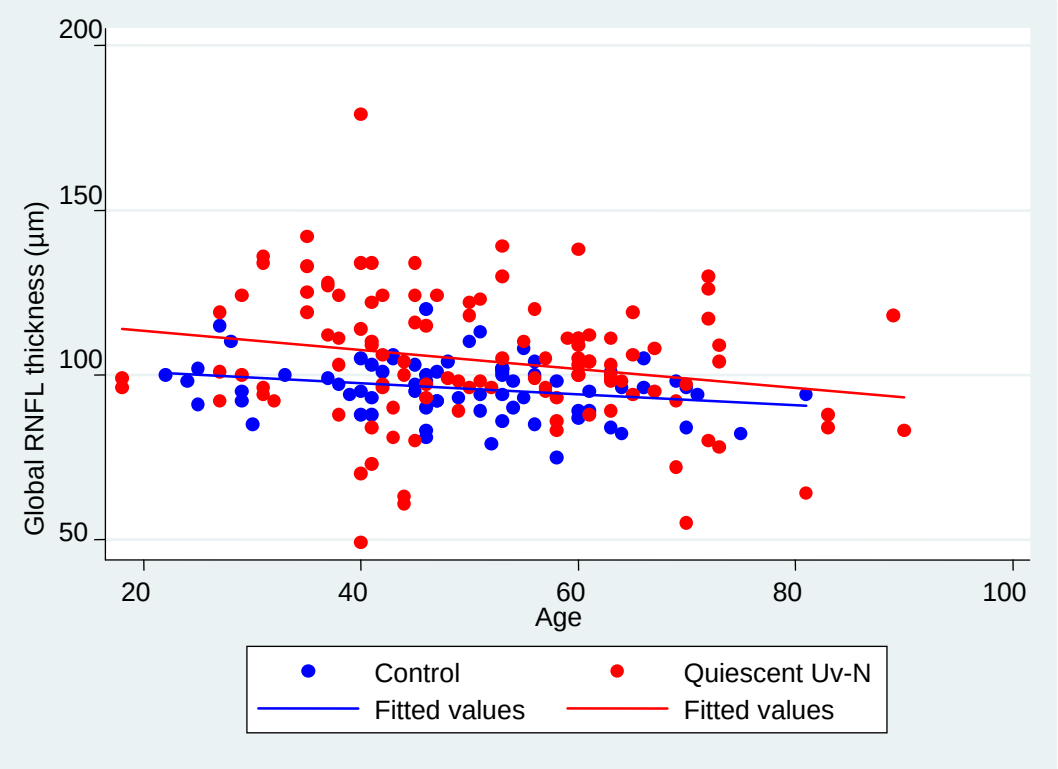

Figure 24: Scatter plot comparing the global RNFL thickness and age among quiescent Uv-N eyes and Control eyes.

3.5.3.4 RNFL thickness in hypertensive uveitic eyes.

We examined the RNFL thickness in quiescent Uv-G eyes which act as the positive controls and compared them to quiescent Uv-N eyes, to determine any RNFL changes so that we can then look for them in the Uv-H group.

The mean global RNFL was significantly thinner in quiescent Uv-G compared to quiescent Uv-N eyes (81.3 ± 26 µm vs 103.6±18.8µm respectively, p<0.001), affecting the superior, (87.3±27.4µm vs 120.8±25.7 µm, p<0.001), inferior (93.3 ± 35.5µm vs 131.8 ± 26.7 µm, p<0.001) and nasal quadrants (66.3±24.7µm vs 78.8±20.7µm, p<0.001). However, there was no statistically significant difference in the temporal quadrant (77.7±35.4 µm vs 83.1±21.5µm, p=0.18).

We then compared the Uv-H and Uv-N eyes. The inferior quadrant was significantly thinner in Uv-H than Uv-N eyes (126.3 ± 20.6 µm vs 131.9 ± 27.6 µm respectively, p=0.04). There was no significant difference in the global as well as the rest of the quadrants. (Table 14)

Table 14: Comparison of RNFL thickness between the Uv-N and Uv-H eyes.

RNFL thickness	Quiescent Uv-N (n=136)	Quiescent Uv-H (n=231)	
	Mean ±SD (µm)		p
Global	103.6±18.8	101.4±14.6	0.24
Inferior	***131.8 ± 26.7***	***126.2 ± 20.5***	***0.04***
Superior	120.8±25.7	119.5±21.3	0.64
Nasal	78.8±20.7	79.6±19.7	0.74
Temporal	83.1±21.5	80.1±18.4	0.20
Nasosuperior	109.1±28.9	106.6±25.2	0.43
Temperosuperior	133.7±28.8	131.6±22.0	0.47
Temperoinferior	146.8±30.2	141.5±22.8	0.08
Nasoinferior	116.3±33.5	111.5±27.5	0.17

3.5.3.5 Can the OCT detect RNFL damage in Uv-H eyes

Within the quiescent Uv-H eyes, 41 Uv-H eyes (21.7%) was classified as "Borderline" or "Outside Normal Limits" by the OCT and a further 148 Uv-H eyes (78.3%) were classified as "Within Normal Limits". The "Borderline/Outside Normal Limits" group had at least one quadrant of thickness falling below the 5th percentile of the normative database and deemed to have an RNFL defect on OCT.

The first compared to the latter group belonged to older patients (54.2 ± 11.0 vs 47.8 ± 14.1 years respectively, p=0.008), had higher mean peak IOP (38.7 ± 10.8 vs 34.6 ± 8.4 mmHg, p=0.01) and a higher proportion with uveitis-induced than steroid-induced raised IOP (33.3% vs 17.0%, p=0.015) (Table 15). There was no difference in the duration of follow-up between the two groups. Gender and the type of uveitis were not risk factors for RNFL defect.

Table 15: Analysis of eyes with quiescent Uv-H grouped according to the results of the OCT scan.

	Normal OCT	Borderline/Abnormal OCT	p
No of eyes (%)	148 (78.3)	41 (21.7)	
Mean Global RNFL (SD)	105.6 (12.9)	86.2 (9.8)	<0.001
Mean age, SD	47.8(14.1)	54.2 (11.0)	0.008
Female, no of eyes (%)	79(79.8)	20(20.2)	0.27
Male, no of eyes (%)	69 (76.7)	21 (23.3)	
Type of uveitis, no of eyes (%)			
Ant uveitis	60 (75.0)	20 (25.0)	
Int uveitis	62 (83.8)	12 (16.2)	
Post uveitis /panuveitis	26 (74.3)	9 (25.7)	0.34
Mean duration of follow-up(SD), years	6.8 (5.2)	7.9 (7.2)	0.3
Mean maximum IOP (SD), mmHg	34.6 (8.4)	38.7 (10.8)	0.01
Mechanism of IOP elevation			
Steroid induced, n (%of eyes)	109(83.2)	22(17.0)	
Uveitis induced,n (%eyes)	34(66.7)	17(33.3)	0.015

We then determined whether these risk factors for having “Borderline/Outside normal limits” OCT results among the Uv-H eyes were similar to the risk factors for glaucoma.

To do this, we compared the clinical factors between quiescent "Borderline/Outside Normal Limits"Uv-H eyes with quiescent Uv-G eyes.

Table 16 compares the clinical features of Uv-H eyes with "Borderline/Outside Normal Limits"and Uv-G. There was no difference in terms of age, gender, maximum IOP or the types of uveitis. Uv-G eyes had a longer duration of follow-up compared to Uv-H eyes with "Borderline/Outside Normal Limits", although not statistically significant. This may suggest that given time, these Uv-H eyes will likely go on to develop clinical signs of glaucomatous disc and VF changes.

Table 16: Clinical features of Uv-H and borderline/abnormal OCT eyes and Uv-G eyes

	Quiescent Uv-H with abnormal OCT	Quiescent Uv-G	p
No of eyes	41	85	
Mean Global RNFL (SD)	86.0 (9.7)	82.1 (27.1)	0.37
Mean age , SD	54.2 (11)	56.6 (14.6)	0.34
Female, n (%eyes)	20 (30)	47 (70)	
Male, n(%eyes)	21 (35.6)	38 (64.4)	0.47
Type of uveitis (no of eyes)			
Ant uveitis	20 (32.3%)	42 (67.7%)	
Int uveitis	12 (31.6%)	26 (68.4%)	
Post uveitis /panuveitis	9 (34.6%)	17 (65.4%)	0.07
Mean duration of follow-up (years), SD	8.0 (7.1)	10.4 (9.6)	0.17
Mean maximum IOP , SD	38.6 (10.7)	40.1 (10.9)	0.45
Mechanism of IOP elevation			
Steroid induced, no. of eyes (%)	22 (34.9%)	41 (65.1%)	
Uveitis induced, no. of eyes (%)	17(31.5%)	37 (68.5%)	0.69

3.5.3.6 Risk factors for the RNFL defect seen in Uv-H eyes.

We compared Uv-H eyes flagged as "Within Normal Limits" (deemed no RNFL defect) and "Borderline/Outside Normal Limits" (with RNFL defect) and performed a multivariate logistic regression analysis to explore the effect of age, duration of follow-up, peak IOP and aetiology of raised IOP on the risk of an RNFL defect on OCT in Uv-H eyes (Table 17). After adjusting for the other factors, for every increase in 1 mmHg of peak IOP, the risk of an RNFL defect was increased by 6% (OR 1.06, 95% CI 1.01-1.11, p=0.03) . Furthermore, for every 1 year increase in age, the risk of an RNFL defect increased by 3% (OR 1.03, 95%CI 1.01 -1.07, p=0.01).

Table 17: Logistic regression analysis of the risk factors for RNFL defect in Uv-H eyes.

	Odds Ratio	SE	p	95% Confidence Interval
Age	1.03	0.014	0.013	1.01 -1.07
Duration of follow-up	1.01	0.033	0.87	0.94-1.07
Maximum IOP	1.06	0.024	0.011	1.01-1.11
Uveitis-induced IOP elevation	0.81	0.36	0.6	0.35-1.87

Comparison of the RNFL thickness between the quiescent Uv-H with "borderline/outside normal limits" and quiescent Uv-G eyes showed that the RNFL in the inferior and superior quadrant were significantly thicker in the Uv-H eyes. This suggested that the superior and inferior quadrants were still the least to be affected by glaucomatous damage in Uv-H eyes as they are still significantly thicker in the Uv-H eyes. (Table 18)

Table 18: Mean RNFL thickness in different quadrants between quiescent Uv-H with abnormal OCT, and quiescent Uv-G eyes.

RNFL thickness	Mean ±SD (µm)		p
	Uv-H+ abnormal OCT(n=41)	Uv-G (n=85)	
Global	86.0±9.8	82.1±26.3	0.25
Inferior	***108.6±17.1***	***93.3±35.5***	***0.01***
Superior	***101.8±24.2***	***87.2±27.4***	***0.004***
Nasal	62.4±19.1	66.3±24.7	0.37
Temporal	73.8±19.0	77.7±35.4	0.51
NS	89.4±24.4	78.0±27.9	0.03
TS	110.3±17	96.6±34.3	0.03
TI	123.8±21.3	100.6±43.1	0.001
NI	93.8±27.5	86.1±33.2	0.19

3.5.3.7 The diagnostic ability of the OCT to differentiate Uv-H and Uv-G eyes

We utilised the Uv-H and Uv-G eyes to calculate the AROC of RNFL thickness in each quadrant to determine the discriminating ability of each quadrant in differentiating Uv-H from Uv-G eyes. The values listed in Table 19 shows that the superior and inferior quadrants have good discriminating ability. The temporal quadrant however, discriminates poorly.

Table 19: Comparison of Area Under the Receiver Opeating Curve (AROC), sentisitivity and specificity between different quadrants to differentiate Uv-G and Uv-H

RNFL parameter	AROC (SE)	Sensitivity (%)	Specificity(%)	95% Confidence Interval
Inferior	0.7465 (0.03)	56.76	92.55	0.741-0.864
Superior	0.7271 (0.03)	54.05	91.36	0.774-0.884
Nasal	0.53 (0.02)	10.96	95.65	0.653-0.781
Temporal	0.54 (0.02)	9.59	98.14	0.519-0.666
Global	0.70 (0.03)	47.22	93.83	0.737-0.863
NS	0.66 (0.03)	38.36	94.44	0.726-0.845
TS	0.76 (0.03)	60.8	90.7	0.76-0.877
TI	0.74 (0.03)	54.8	92.5	0.745-0.868
NI	0.60 (0.03)	25.3	95.1	0.696-0.821

AROC= Area under the receiver operating curve, NS=Nasosuperior, TS= Temperosuperior, TI= Temperoinferior, NI= Nasoinferior

Figure 25 and Figure 26 illustrates the ROC curve of the superior and temporal quadrant respectively. The superior quadrant has a bigger area under the ROC curve which denotes a higher discriminating power to differentiate between Uv-H and Uv-G eyes.

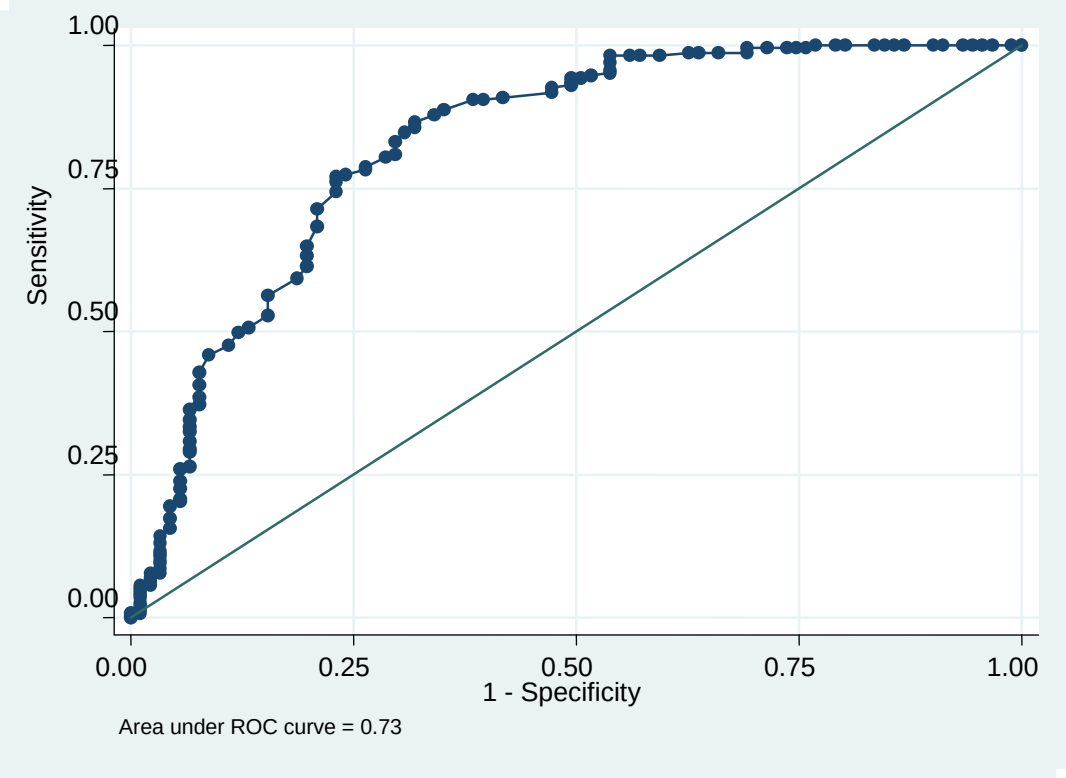

Figure 25: Receiver Operating Curve (ROC) of the superior quadrant.

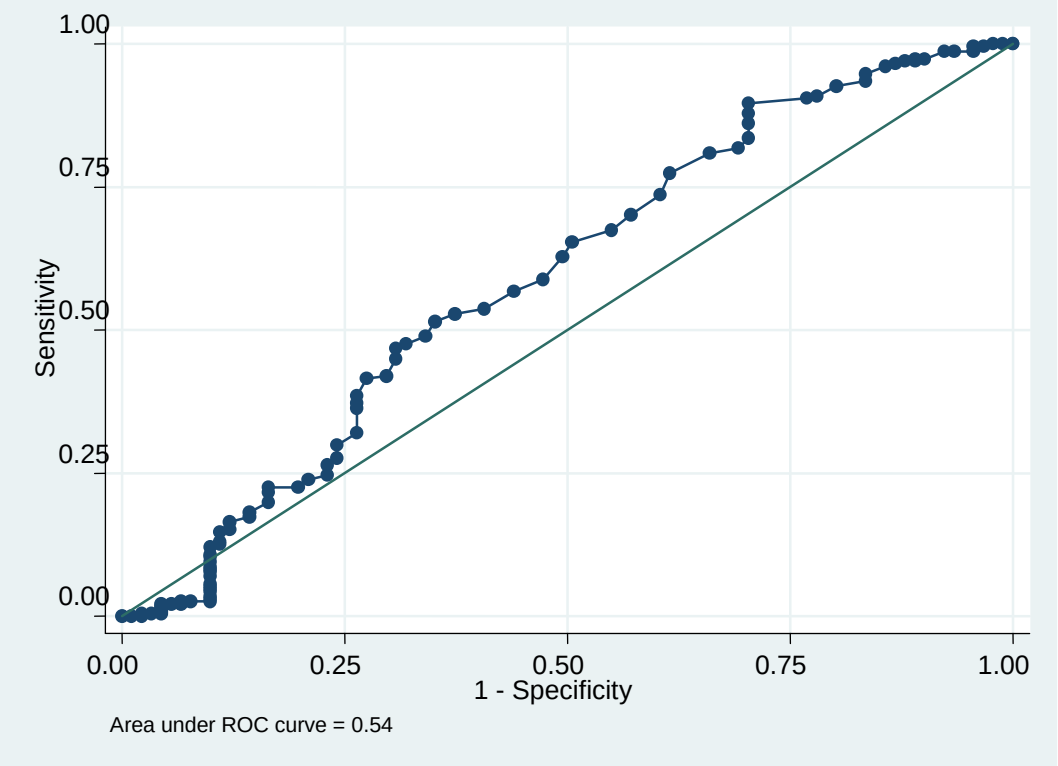

Figure 26: ROC curve of the temporal quadrant.

3.5.3.8 *Correlation between mean deviation of the visual field and the global RNFL thickness*

To determine whether there was any correlation between the mean deviation of the Humphrey VF and the global RNFL, we calculated the Pearson correlation coefficient. There was a fair positive correlation between the global RNFL thickness and the mean deviation of the Humphrey VF, Pearson correlation r=0.30, p<0.001. However, this reaches a plateau after about 75 µm of RNFL thickness after which it does not show any further correlation (Figure 27). This suggests that thinner global RNFL is associated with worsening of the mean deviation on the Humphrey VF.

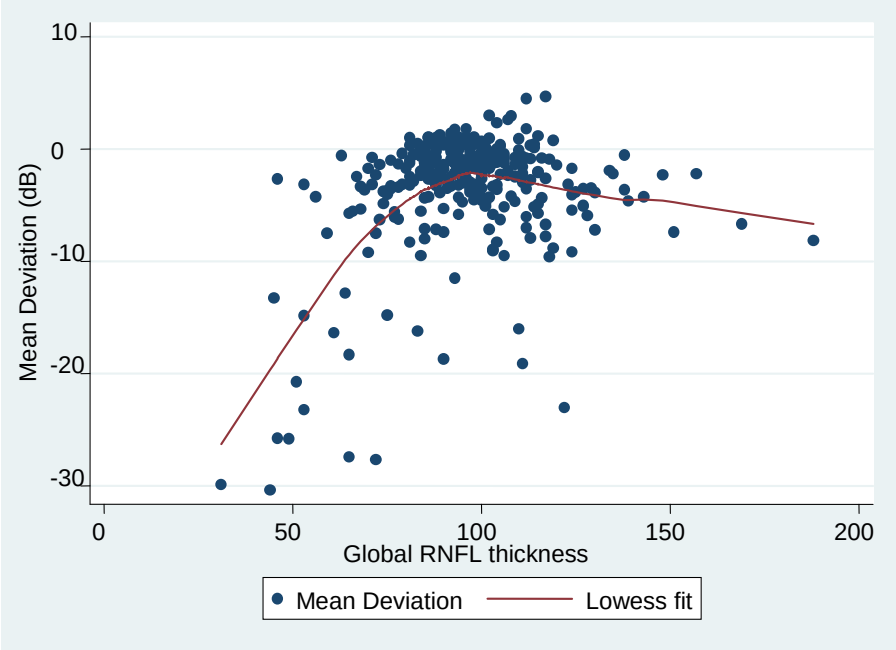

Figure 27: Correlation between Global RNFL and mean deviation of Humphrey Visual Field

3.5.4 Longitudinal changes of the RNFL over time

To determine any significant RNFL changes over time, available RNFL values from 563 quiescent eyes of 302 patients were analysed using linear mixed model analysis. The dependant variable was global RNFL thickness and the independant variable was year

(2010, 2011 and 2012). The RNFL values were nested within each eye of each patient. The interval between each OCT scan was between 8-12 months from each other.

There was a significant reduction of the Global RNFL thickness in the Uv-G group. The RNFL thickness reduced by a mean of -1.8 micrometer per year (Table 20). The rest of the groups did not show significant change in global RNFL thickness over the span of 3 years.

Table 20: Regression coefficient of the change in the global RNFL thickness in each group of eyes in the year 2010-2012

Group	Regression coefficient	Standard error	p	95% Confidence Interval
Uv-G	-1.79	0.74	0.016	-3.25 - -0.34
Uv-H	-0.3	0.57	0.6	-1.4 – 0.8
Uv-N	0.08	0.7	0.9	-1.3 – 1.45
Control	-0.15	0.47	0.75	-1.07 – 0.77

Figure 28 shows the distribution of the global RNFL thickness within each group of eyes over the span of 3 years. While the RNFL in the Uv-N and Uv-H group showed thicker RNFL, the Uv-G group consistently showed thinner RNFL compared to the control group.

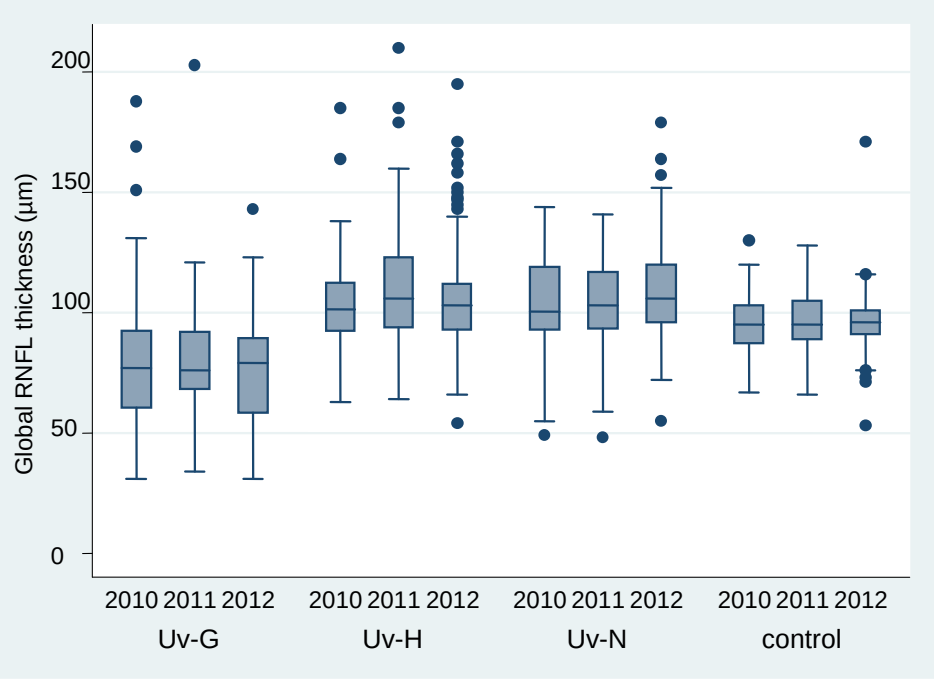

Figure 28: Composite graph box showing the distribution of the global RNFL thickness in different groups over the span of 3 years.

Next, we examined each quadrant of the quiescent Uv-G eyes to see which quadrant had significant change in RNFL thickness. Apart from the superior quadrant which showed borderline changes, the rest of the quadrants did not show any significant changes in RNFL thickness (Table 21).

Table 21: Regression coefficient describing change in the RNFL thickness of different quadrants in the quiescent Uv-G group.

Quadrant	Regression coefficient	Standard error	p	95% confidence interval
Inferior	-1.28	1.46	0.38	-4.14 – 1.56
Superior	-2.07	1.07	0.053	-4.017- -0.03
Nasal	-1.63	1.06	0.12	-3.7 – 0.44
Temporal	-2.65	1.4	0.055	-5.36 – 0.058
Nasosuperior	-2.42	1.32	0.066	-5.0 – 0.16
Temperosuperior	-1.85	1.23	0.13	-4.24 – 0.53
Temperoinferior	0.46	1.7	0.78	-2.8 – 3.8
Nasoinferior	-3.17	1.82	0.08	-6.7-0.4

3.5.5 Measurement of macula thickness in uveitic eyes with glaucoma

We went on the see whether any macular changes can also be seen in Uv-G eyes. Full macula thickness was taken and divided into several sections (Figure 29):

1. the center 1 mm (center)
2. the next inner 3 mm which was divided into
    a. inner superior (InnS)
    b. inner nasal (InnN)
    c. inner inferior (InnI)
    d. inner temporal (InnT)
3. the next outer 6 mm which was divided into
    a. outer superior (OutS)
    b. outer nasal (OutN)
    c. outer inferior (OutI)
    d. outer temporal (OutT)

We compared the full thickness of the macula in each section between the Uv-N, Uv-H and Uv-G eyes. Only macular scans without cystoids macula edema changes ware included in this analysis.

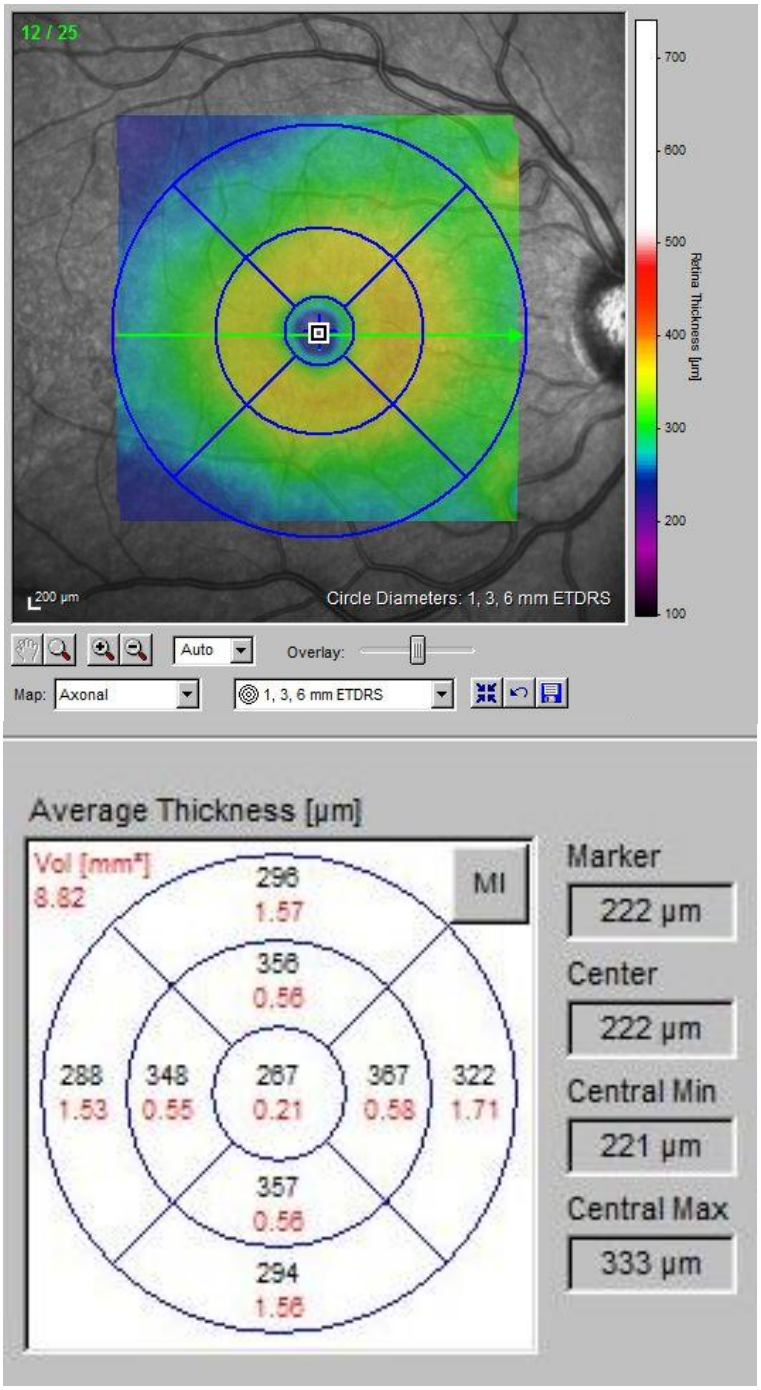

Figure 29: The divisions of macular thickness.

Table 22 shows the mean thickness of the macular in different sections. ANOVA analysis revealed that there was significant difference in macula thickness between the different groups of eyes. The difference was statisticall significant between Uv-G eyes and both Uv-N and Uv-H eyes, whereas there is no difference in thickness between the Uv-N and Uv-H eyes except for the outer superior section.

Table 22: Mean macular thickness on different sections of the macula

Macula section	Uv-N Mean ±SD (µm)	Uv-H Mean ±SD (µm)	Uv-G Mean ±SD (µm)	p	p2	p3	p4
Central	282.7±32.8	282.8±33.5	272.6±38.0	0.02	0.9	0.06	0.04
Inner inferor	344.4±27.2	344.3±24.7	323.7±30.0	<0.001	0.9	<0.001	<0.001
Inner superior	349.5±23.7	348.7±23.9	328.4±29.2	<0.001	0.8	<0.001	<0.001
Inner nasal	351.9±25.7	350.4±26.1	332.8±30.0	<0.001	0.6	<0.001	<0.001
Inner temporal	334.8±22.5	334.6±22.3	315.4±29.1	<0.001	0.9	<0.001	<0.001
Outer inferior	303.1±20.3	297.0±23.8	277.7±24.1	<0.001	0.2	<0.001	0.004
Outer superior	313.5±21.8	304±19.7	288.5±22.6	<0.001	0.02	<0.001	0.005
Outer nasal	321.9±24.1	321.9±27.0	303.4±26.0	<0.001	0.9	<0.001	<0.001
Outer temporal	291.7±20.9	291.2 ±22.8	280.3±32.8	0.005	0.8	0.01	0.01

p= p from ANOVA comparing all groups of eyes, p2= p from t-test between Uv-N&Uv-H, p3= p from t-test between Uv-N&Uv-G, p4= p from t-test between Uv-H & Uv-G

3.6 Discussion

This study involved relatively young patients (mean age 50.4 years) which was to be expected as uveitis tends to affect young individuals. (Durrani et al., 2004) The study population also consisted of slightly more females than males, consistent with the gender predilection reported previously.(Gritz and Wong, 2004) Anterior and intermediate uveitis predominate the type of uveitis, followed by posterior and panuveitis. There were various diseases associated with uveitis in this population of patients, reflecting the multitude of diseases seen in a tertiary referral uveitis clinic. Sarcoidosis and HLA B27 related uveitis were the two commonest disease associations. This study was performed in a tertiary referral uveitis clinic and therefore it probably represents some of the more severe uveitis observed. However the results may still be applicable to many uveitis specialists throughout the world.

This study aims at evaluating whether the RNFL measurement can be used to detect and monitor glaucoma progression in uveitis as an adjunct to other means of diagnosis by identifying RNFL defects in uveitic eyes with elevated IOP. We have found that in quiescent Uv-H eyes, the OCT has detected RNFL defect attributed to raise IOP.

The findings of this study are summarized as follows:

1. The prevalence of raised IOP and glaucoma in our study was 66.7% and 20.7% respectively
2. Risk factors for IOP elevation (Uv-H and Uv-G) were male gender and anterior uveitis.
3. Risk factors for glaucoma among Uv-H eyes were older age, longer duration of follow-up, higher maximum IOP and uveitis-induced IOP elevation.

4. Eyes with uveitis-induced IOP elevation had higher maximum IOP and were more at risk of glaucoma than steroid-induced IOP elevation
5. Steroid induced IOP elevation occurred in younger patients than uveitis-induced IOP elevation.
6. Significantly more IOP lowering drops were used in Uv-G compared to Uv-H eyes. Uv-G eyes which received oral acetazolamide were also 10% more than Uv-H eyes; with almost a quarter of the Uv-G eyes eventually had to undergo surgery for further IOP control.
7. Eyes with active inflammation had significantly thicker RNFL and this increase was seen more in intermediate uveitis than anterior uveitis, which was in turn thicker than posterior/panuveitis.
8. The normative database in the spectralis software is still applicable to uveitic eyes as a reference value.
9. Uv-G compared to Uv-N eyes had significant RNFL thinning in all except the temporal quadrant.
10. Uv-H compared to Uv-N eyes showed significant RNFL thinning only in the inferior quadrant
11. About 20% of Uv-H eyes showed an RNFL defect ("borderline/outside normal limits" OCT results) at least in one quadrant of the RNFL. Risk factors for these RNFL defects were older age, higher maximum IOP and uveitis-induced IOP elevation. These eyes also share the same clinical features as the Uv-G eyes (similar in mean age and maximum IOP, distribution in gender and the type of uveitis).

12. There was a significant difference in the RNFL thickness between Uv-H + abnormal OCT and Uv-G in the inferior and superior quadrant, but no significant difference in the nasal and temporal quadrant.
13. The superior and inferior quadrant had the highest AROC value to discriminate between Uv-H and Uv-G eyes.
14. There was a fair correlation between mean deviation in the Humphrey VF and global RNFL thickness.
15. There was a significant global RNFL progression at -1.8 micrometer per year in the Uv-G eyes over a span of 3 years but no significant reduction was detected in the Uv-H and Uv-N eyes.

3.6.1 Risk factors for IOP elevation and glaucoma

The prevalence of raised IOP and glaucoma in our study is almost double than that in a report by Herbert et al (Herbert et al., 2004) which were 41.8% and 9.6% respectively from 342 eyes of 257 uveitic patients. This difference is due to the difference in case selection. We had higher prevalences because patients included in this study had raised IOP and were at a higher risk of glaucoma and therefore required screening with the OCT.

Risk factors for raised IOP identifed in this study were male gender and anterior uveitis. The risk of raised IOP was increased two-fold in anterior uveitis compared to intermediate or posterior uveitis, possibly from the direct effect of inflammation on the trabecular meshwork compromising the aqueous outflow system. Males were also twice as likely to develop hypertensive uveitis as females.

While there are no reports linking gender and risk of raised IOP or steroid responsiveness, there are 2 reports relating male gender as a risk factor for complications and poor visual outcome in JIA-associated uveitis. (Ayuso et al., 2010)(Kalinina Ayuso et al., 2010) There has not been any other report linking gender and raised IOP in non-JIA related uveitis. Of interest, we found a higher proportion of men with anterior uveitis relative to intermediate or posterior/panuveitis, therefore perhaps it is the presence of anterior uveitis that is the true risk factor and not gender. Furthermore, although we found males were significantly associated with Possner Schlossman syndrome and HLAB27-related uveitis, both of which commonly causes anterior uveitis, but due to the small number of cases in some of the subtypes, we were unable to explore the relationship of IOP and specific aetiologies and focused on anatomical site of inflammation instead.

Older age, higher peak IOP and uveitis-induced raised IOP were risk factors identified for glaucoma and RNFL defect. Our observation that male gender and the type of uveitis was no longer a risk factor for glaucoma may be explained by the fact that glaucoma develops over time and severe IOP elevation may be a more significant factor than gender or type of uveitis. While there are studies reporting no difference in the risk of glaucoma among different types of uveitis,(Neri et al., 2004) the findings in a few large studies established anterior uveitis as the commonest cause for uveitic glaucoma (Bodaghi et al., 2001)(Hwang et al., 2013), which is consistent with the overall distribution of uveitis. (McCannel et al., 1996) We found anterior uveitis to be a significant risk factor for IOP elevation but we were unable to find any significant association with glaucoma, possibly due to the equal distribution of anterior and intermediate uveitis in our study.

Our analysis found that eyes with steroid-induced IOP elevation were less likely to have developed glaucoma compared to uveitis-induced IOP elevation. They had lower maximum IOP, belonged to a younger age group and less likely to develop RNFL defects when compared with uveitic-induced IOP elevation. Herbert et al and Sallam et al also reported that corticosteroid-induced IOP elevation had a more favourable outcome than non-corticosteroid-induced IOP elevation. (Herbert et al., 2004) (Sallam et al., 2009)

We aggressively manage hypertensive uveitic eyes to keep the IOP under 21 mmHg but when glaucomatous changes occur in Uv-G eyes, we aim for a target pressure of 12-14 mmHg. Therefore, more pressure lowering drops were used and more Uv-G eyes underwent glaucoma surgery compared to Uv-H eyes. This study suggests that once RNFL changes have occured in Uv-H eyes, these patients already have nerve damage and therefore these eyes should be more aggressively managed to reduce the IOP down to 12-14mmHg just like we do manage the IOP in POAG.

3.6.2 Evaluation of the RNFL

The mean global RNFL thickness of 96.0 ± 9.0 µm in our control eyes agrees favourably with previously studied normal eyes which was 97.2 ± 9.7 µm (Baleanu et al., 2009) (Leung et al., 2010c), and we compared this to our Uv-N eyes. We found the RNFL to be thicker in Uv-N eyes regardless of the type of uveitis when compared to Control eyes. The increase in thickness was especially seen in actively inflamed than quiescent eyes. These findings not only support previous reports of increased thickness of ocular tissues in exacerbations of acute uveitis,(Moreno-Arrones et al., 2010)'(Traill et al., 2007) but also suggest that monitoring for RNFL changes in uveitic eyes should be done during quiescence. While some studies have found increased thickness of the

RNFL in eyes with anterior uveitis (Shulman et al., 2012)(Castellano et al., 2009)(Wexler et al., 2012) we found that this is also the case in other types of uveitis.

The RNFL in quiescent Uv-N eyes were also found to be thicker than control eyes. This could be related to the period required for the RNFL to return to baseline thickness after cessation of uveitis activity. Although treatment with corticosteroid has been shown to reduce macula thickening in acute anterior uveitis, (Castellano et al., 2009) other studies reported that resolution of macula thickening by OCT occurred in only 55% of patients at 6 months after resolution of symptoms and signs of acute anterior uveitis. (Traill et al., 2007) Nevertheless, to minimise the effect of uveitis on the RNFL, we excluded actively inflamed eyes in the subsequent analysis.

We initially thought that the increase in mean global RNFL thickness in Uv-N eyes might affect the reference value for screening of RNFL defect in hypertensive uveitic eyes, assuming that the cut-off point for normality should be increased as well. However, the distribution of the RNFL values is wider than non-uveitic eyes resulting in lower 5th percentile values in these uveitic eyes which will actually mask the true positives in these eyes. It is therefore still valid to use the normative values provided by the manufacturer as reference.

The pattern of RNFL thickness in the control eyes follows the ISNT rule, (Jonas et al., 1988a) (Harizman et al., 2006) which state that the RNFL is thickest in the inferior quadrant followed by the superior, nasal and last of all, the temporal quadrant. Our Uv-N eyes however, showed a reversal of the nasal and temporal quadrant, with the temporal quadrant being thicker than the nasal quadrant. This may be explained by the fact that the macula, which is in direct continuation with the temporal quadrant of the peripapillary RNFL, has a propensity to thicken in uveitis even in the absence of

clinically apparent CMO. (Traill et al., 2007) This leads to the suggestion that macula edema in uveitis is not an all-or-none phenomenon and clinically evident CMO may simply represent the severe spectrum of macula changes commonly occurring in uveitis. (Traill et al., 2007) Even in anterior uveitis without clinically apparent CMO, the macula has been found to be thickened.(Moreno-Arrones et al., 2010) (Traill et al., 2007) This may explain the thickening seen in the temporal quadrant of the peripapillary RNFL in our study involving all types of uveitis.

Furthermore, unlike in POAG where the RNFL was found to be significantly decreased in all quadrants,(Hwang and Kim, 2012) we found that the temporal quadrant seems to be spared in our Uv-G eyes, again possibly explained by the inclination of the macula to be thickened which translates into thickening of the temporal quadrant. Consequently, while significant RNFL thinning is seen in the temporal quadrant in primary ocular hypertension (Mansoori et al., 2010), we found instead, significant thinning in the inferior quadrant in hypertensive uveitis. Therefore, we propose that RNFL thinning affecting the inferior quadrant may suggest an early glaucomatous change in uveitic eyes.

When examining individual Uv-H eyes, approximately 20% of them had an RNFL defect detected on OCT. They share the same clinical features with Uv-G eyes whereby they belonged to an older age group, had higher peak IOP, longer duration of follow-up and had uveitic-induced raised IOP. This suggests that if the Uv-H eyes with an RNFL defect on OCT were followed up for longer, they would also develop glaucomatous disc changes and VF loss. It also supports previous reports that more hypertensive non-corticosteroid responders went on to develop glaucoma than corticosteroid responders. (Sallam et al., 2009)'(Herbert et al., 2004)

We found the best discriminating ability to differentiate Uv-G and Uv-H eyes lies in the superior and inferior quadrant based on the highest AROC values yielded. Although these values were less than the reported AROC values in POAG, due to the effect of uveitis, the quadrants agree with previous studies performed on non-uveitic patients. Studies on non-uveitic eyes reported the inferior quadrant RNFL thickness had the largest AROC (0.93) to distinguish between ocular hypertension and glaucoma. The temporal quadrant, on the other hand, had the largest AROC to discriminate normal and ocular hypertension eyes, although with poor discrimination (0.65) (Mansoori et al., 2010). Studies on POAG found the superior quadrant with the highest AROC in differentiating control and glaucoma eyes. (Hwang and Kim, 2012) Our study found a fair discriminative power to distinguish Uv-H and Uv-G eyes in the superior and inferior quadrant with an AROC value of 0.83 and 0.80 respectively. The temporal quadrant had the lowest AROC value (0.59) in differentiating Uv-H and Uv-G presumably due to a thicker temporal quadrant of the peripapillary RNFL in uveitis.

The superior and inferior poles of the otic nerve head are most vulnerable to glaucomatous damage. It transcends a larger portion of the superior and inferior retinal areas carrying more densely packed axons of the retinal ganglion cells around the optic nerve (Figure 6). These two areas were also postulated to be the watershed areas at the junction of the vascular supply from adjacent ciliary vessels. (Hayreh, 2001) Furthermore, ultrastructural examination of the lamina cribrosa shows that the pores in the superotemporal and inferotemporal areas are larger and therefore more vulnerable to compression.(Quigley and Addicks, 1981) These findings may explain the higher AROC values of the superior and inferior quadrant in differentiating glaucoma from non-glaucoma eyes as the axons here are more susceptible to damage. Likewise,

the significant rate of progression found in the superior quadrant among Uv-G eyes could also be accounted for.

Significant global RNFL progression was detected in our Uv-G eyes but not in other groups of eyes. This progression was significantly seen in the superior quadrant. Studies on POAG found that RNFL progression at the rate of -0.33 micrometer per year were seen over a span of at least 3 years and the progression was most commonly seen in the inferotemporal meridian.(Leung et al., 2012) Our study found a higher rate of progression at -1.8 micrometer per year. The rate of progression was highest in the temporal (-2.65 µm per year) and the superior quadrant (-2.07 µm per year), although at borderline significance. A possible explanation to the rapid progression in the temporal quadrant may be reflective on the occurrence and resolution of CMO with treatment and not actually due to glaucoma.

Contrary to the RNFL thickness, the macular thickness showed significant reduction in the Uv-G group in all sections of the macula when compared to both Uv-H and Uv-N eyes. The macular thickness between the Uv-H and Uv-N eyes on the other hand, was similar in all sections. Our findings agree with other studies done on non-uveitic glaucomatous eyes which showed significant macular thinning seen in glaucomatous eyes, although macular thickness in our study was taken as the full thickness instead of just the inner ganglion cell complex. (Tan et al., 2009) (Kotera et al., 2011) It is possible that because of this reason, we failed to show any difference in macular thickness between the Uv-H and Uv-N eyes, as found in other studies. (Na et al., 2013)(Nakano et al., 2011)(Nakatani et al., 2011)

RNFL loss detected on OCT only correlates with VF loss on VF testing after approximately 17% loss or when the RNFL thickness is less than 75.3 µm.(Wollstein et

al., 2012) We found a fair positive correlation between the mean deviation of the Humphrey VF and the global RNFL thickness. Worsening of mean deviation was seen with reduction of RNFL thickness. However, the correlation was no longer seen after approximately 75 µm of RNFL thickness.

3.7 Summary

In summary, the OCT may provide evidence of RNFL damage in hypertensive uveitic eyes and it may be used to screen for glaucomatous RNFL thinning. However, it should be done during quiescence as this reduces the masking effect of RNFL thickening associated with active uveitis. RNFL thinning seen in the inferior quadrant should raise the possibility of progression to glaucoma in hypertensive uveitic eyes.

The use of the OCT to detect and monitor RNFL changes in uveitic eyes has to be used with caution as there are both the effect of increase thickness from uveitis and decrease thickness from elevated IOP. However, when RNFL thinning is detected and associated with IOP elevation in uveitic eyes it indicates a higher risk of progression to glaucoma. Identification of the subgroup of patients at higher risk of glaucoma may help in planning a more agreessive approach for IOP control.

4 Chapter 4: IOP elevation in children with uveitis and its effect on the RNFL

4.1 Introduction

Uveitis in children is a potentially blinding condition and may result in a devastating visual outcome. (Rothova et al., 1996) It causes significant ocular morbidity with severe vision loss found in 25-33% of cases. (Zierhut et al., 2005) The estimates from population based incidence and prevalence studies reported that childhood uveitis is 5 to 10 fold lower than in adults. (Cunningham, 2000) The distribution of anatomical types of uveitis also differs from that in adults, with posterior uveitis being slightly commoner than anterior uveitis. However, the anatomical distribution varies between reports from a tertiary or primary based ophthalmological setting, and also different geographical areas. (Cunningham, 2000)

Intraocular pressure (IOP) elevation in childhood uveitis is a challenging problem and an important risk factor for glaucoma and irreversible visual loss. (Thorne et al., 2007) IOP elevation and glaucoma are among the commonest visually threatening complications of childhood uveitis, together with cataract and CMO. (Rothova et al., 1996)(Woreta et al., 2007)(Cunningham, 2000) It can be very difficult to treat given that these children are twice as likely to respond to corticosteroids with twice as severe IOP elevation as in adults. (Kwok et al., 1997)(Sijssens et al., 2006)(Sallam et al., 2009) Additionally, unlike other conditions, corticosteroid therapy for uveitis often requires prolonged treatment with topical or systemic corticosteroid. In cases where sight threatening inflammation is insufficiently controlled with corticosteroids; or

when steroid-induced IOP elevation is a problem, immunosuppressive agents such as mycophenolate mofetil, methotrexate and azathioprine are used with the prednisone.(Gregory et al., 2013) Biologics are usually reserved for those who failed conventional therapy for cost and access issues. (Heo et al., 2012)

4.1.1 JIA-related uveitis and IOP elevation

Juvenile Idiopathic Arthritis (JIA) is the commonest childhood rheumatic disease in the United States and Europe and the commonest identifiable systemic association of uveitis with chronic iridocyclitis accounting for 4-33% of uveitic cases seen in a tertiary care setting. (Kump et al., 2006) ANA positive girls with early onset oligoarthritis are at greatest risk for uveitis (Kotaniemi et al., 2003)

JIA-related ocular hypertension and glaucoma has been frequently reported, affecting approximately 25-42% of children with JIA. (Sijssens et al., 2006)(Foster et al., 2000)(Paroli et al., 2003) It has been reported that there was no difference in the risk of IOP elevation but secondary glaucoma was more often noted in JIA compared to non-JIA-related uveitis after a follow-up period of 5 years. The presence of ANA in the blood was significantly associated with secondary glaucoma in JIA-related uveitis. (Sijssens et al., 2006) However, non-JIA related uveitis is less common and, consequently, there is much less published data on ocular hypertension and glaucoma in this group of children.

4.1.2 Non-JIA-related uveitis and IOP elevation

Non-JIA-related uveitis is a very heterogenous group of disease entities. Different aetiologies, even within an anatomic category of uveitis, will have different levels of risk for glaucoma. An overall prevalence of 10.3% of secondary glaucoma or ocular

hypertension was reported in a case review of 261 children from a single tertiary uveitis referral center. (Heinz et al., 2009)

There are a number of diagnostic and therapeutic challenges in children with uveitis in general (Table 23). (Cunningham, 2000) Among other things, children might not be recognized to have uveitis until a parent or teacher notices eye redness, leukocoria, strabismus or difficulty at school which causes delayed presentation as children could not describe the onset and characteristics of their visual symptoms, and it is often difficult to perform a complete eye examination, particularly in very young, preverbal patients. Unilateral loss of vision is often reported late. Additionally, controlling inflammation may be more difficult in young children, which may result in development of vision-threatening complications such as cataract, band keratopathy, glaucoma and cystoid macula edema.

Table 23 : Special considerations in children with uveitis, (Cunningham, 2000)

Diagnosis
Delayed diagnoses **Children may be preverbal or asymptomatic** **The uveitis may be unrecognized or is misdiagnosed**
Unique presentation **Children may present with leukocoria or strabismus, or have difficulty with routine activities at home or at school.** **Anterior uveitis may occur without pain, redness or phtophobia; so-called 'white iritis'**
Difficult examination **Children can be more difficult to examine than adults. Complete**

examination is essential, however, and often requires examination under anaesthesia (EUA).
Different diagnoses
Children can develop an otherwise uncommon masquerade syndromes, such as retinoblastoma, leukaemia, juvenile xanthogranuloma, and retinitis pigmentosa.
Children can develop relatively uique forms of uveitis, such as juvenile idiopathic arthritis (JIA) and Kawasaki's disease.
Children tend to develop a disproportionate amount of infectious posterior uveitis.
In older children, infectious causes of posterior uveitis include toxoplasmic retinochoroiditis, oclar toxocariasis and metastatic bacterial endophthalmitis.
In infants, congenital Toxoplasmosis, Rubella Cytomegalovirus, and Herpes simplex virus (TORCH syndromes) may cause retinitis.
Children can develop relatively unique clinical forms of otherwise common disorders. In young children, for example, sarcoidosis is more often associated with arthritis and a rash, and less frequently with pulmonary involvement.
Different normative values on laboratory testing
Serum angiotensin-converting enzyme (ACE) level is often physiologically elevated in children. Lysozyme is usually preferred over ACE in young patients to help support the diagnosis of sarcoidosis.
Management

More frequent complications   **Cataract, glaucoma, and cystoid macular edema.**
Unique complications   **Amblyopia, strabismus and band keratopathy**
Different side effects of therapy   **Corticosteroid-induced growth retardation.**   **An increased risk of corticosteroid-induced ocular hypertension.**   **An increased risk of corticosteroid-induced cataract**
Different surgical considerations   **Intraocular lens placement after cataract surgery may be more difficult than in adults.**   **Trabeculectomy may be more likely to fail than in adults.**

Consequently, detecting and monitoring glaucomatous changes in these children poses additional challenges as conventional methods may be affected by multiple additional factors. Notwithstanding any problems with measuring IOP, Humphrey VF testing, already a great challenge in adult uveitics(Taylor et al., 2011), is often unreliable in children.(Srinivasan et al., 2013) Severe uveitis may cause optic disc swelling, masking glaucomatous optic disc assessment. The plasticity of glaucomatous disc changes in children (Wu et al., 2002)(Swinnen et al., 2010) further complicates the assessment.

As a result, there has been a great interest in newer methods of detecting and monitoring GON. Thinning of the peripapillary RNFL is associated with glaucoma and its measurement has been recommended as an adjunct to other means of glaucoma

detection in primary glaucomas in the last decade (Budenz et al., 2005), (Medeiros et al., 2004), (Chen and Huang, 2005) Measurement of the RNFL with the OCT is relatively quick and easy to perform in children, apart from being reliable and reproducible, which allows serial assessment of RNFL thickness.

4.2 Aim

In this part of the study we aimed to identify the risk factors for IOP elevation and glaucoma, and evaluate the course of raised IOP and treatment outcome in children with non-JIA related uveitis. We also wanted to investigate whether measurement of the RNFL using the Spectralis OCT can be a useful adjunctive tool to help in detection and monitoring of glaucomatous optic disc changes and also to determine any correlation with the children's clinical data to identify risk factors for RNFL loss.

4.3 Methods

Parts of the methods have been described in chapter 2. Additional methodologies are as follows:

We included all children with varying types of uveitis attending a single consultant tertiary referral paediatric uveitis clinic at Moorfields Eye Hospital seen between May 2010 and October 2012. Only patients with the onset of ocular inflammation not due to JIA before the age of 16 years were included. IOP readings were taken with the Goldmann's Applanation Tonometry or the Tono-Pen® (Medtronic Ophthalmics, Minneapolis, MN) in a small minority of uncooperative children.

The children's eyes were divided into 4 groups following the same definition described in chapter 2. Of note, glaucoma was diagnosed solely based on the presence of a

pathologic disc cupping assessed clinically and VF changes were not a criteria to diagnose glaucoma. (Foster et al., 2002) Eyes with raised IOP included both Uv-H and Uv-G eyes. Steroid responders were a subset of eyes with raised IOP and refer to steroid-induced IOP elevation.

Steroid responder eyes were further divided into high responders, intermediate responders and low responders according to the definition introduced by Armaly (Armaly, 1965) to demonstrate the severity of steroid responsiveness. High response was defined as a maximum increase in IOP of more than 15 mmHg from pre-treatment IOP, intermediate response when maximum IOP increase was between 6 and 15 mmHg and low response if maximum IOP increase was less than 6 mmHg.

Eyes with non-uveitic conditions such as Coat's disease and Von Hippel Lindau syndrome, extra-ocular inflammation such as scleritis and vernal keratoconjunctivitis and patients with missing or incomplete notes were excluded. When assessing the RNFL thickness, eyes with prior laser retinopexy or vitrectomy, poor-quality OCT images that prevent evaluation and quantification of the RNFL, optic disc swelling and large macular or retinal scars were excluded for the same reasons identified in Chapter 2.

In our practice, uveitic eyes with elevated IOP of more than 28 mmHg without optic disc changes i.e no overt signs of glaucoma, will be started on topical hypotensive agents first, usually a single agent and changed or added accordingly depending on the response to the first drug. In the event that maximum topical hypotensive agents alone were insufficient to attain a satisfactory IOP of less than 21 mmHg, systemic carbonic anhydrase inhibitors (CAI) may be started at a dose of 20-40 mg/kg per day given in 2 to 4 divided doses. Glaucoma surgery will be performed in eyes which were

either dependant on systemic CAI or had poorly controlled IOP whilst on systemic CAI with or without glaucomatous disc changes. This would either be trabeculectomy with antimetabolite, or implantation of glaucoma drainage devices such as Baerveldt, Molteno or Ahmed valve. Glaucoma drainage devices may be implanted primarily in eyes at higher risk of failure such as in aphakia, pseudophakia, previous failed trabeculectomy or previous vitreoretinal surgery.(Sung and Barton, 2004) Eyes with glaucomatous disc or VF changes will be aggressively managed to achieve a target IOP of 12-14 mmHg.

Data was analysed using Stata version 10 (Intercooled) (StataCorp, College Station, TX). Incidence rates of raised IOP were calculated as the number of events divided by the number of eyes at risk. (Thorne et al., 2007) Other analyses were as described in chapter 2.

4.4 Results

4.4.1 General characteristics

From a total of 118 children who attended the clinic, 15 patients were excluded for JIA (n=5), non-uveitic condition such as Stargardts macular dystrophy, Von Hippel Lindau disease and trauma (n=4), non-intraocular inflammation such as vernal conjunctivitis and scleritis (n=3) and missing data (n=3). We therefore included 206 eyes of 103 children. There were 32 normal eyes (control) and 174 eyes with uveitis which was further classified into 108 Uv-N, 41 Uv-H and 25 Uv-G eyes.

There was a slight female preponderance with a male to female ratio of 1:1.2. The mean age at diagnosis of uveitis was 10.5+3.5 years. Sixty-eight eyes (33.0%) had anterior uveitis, 64 eyes (31.07 %) had intermediate uveitis and 42 eyes (20.4%) had

posterior/panuveitis. Table 24 summarizes the demographics of the patients across different groups of eyes.

Table 24: Demographics of the children

Characteristics	Control n = 32	Uv-N n = 108	Uv-H n = 41	Uv-G n = 25	P value
Age, years‡	12.3 ±2.7	12.4±2.8	12.4±3.1	11.4±4.1	0.5
Follow-up period, years‡	NA	2.4±2.5	2.2±2.0	2.8±1.6	0.7
Female, no. of eyes (%)	14 (15.2)	55 (59.8)	15 (16.3)	8 (8.7)	0.2
Male, no. of eyes (%)	18 (15.8)	53 (46.5)	26 (22.8)	17 (14.9)	
Type of uveitis, no. of eyes (%)					0.1
Anterior uveitis	NA	51 (68)	16 (23.5)	5 (7.3)	
Intermediate uveitis	NA	37 (57.8)	17(26.6)	10(15.6)	
Posterior/Panuveitis	NA	24(57.1)	8(19.1)	10(23.8)	
Maximum IOP, mean (SD)	NA	NA	30.1(4.7)	40.9 (6.8)	<0.001
Chronicity, no. of eyes (%)					<0.001§
Acute	NA	54 (83.1)	11 (16.9)	0 (0)	
Chronic	NA	53 (49.1)	30 (27.8)	25 (23.1)	

‡ **Results are given in means and standard deviation,** § **Fisher's exact test**

Uv-G eyes had higher peak IOP compared to Uv-H eyes (40.9 ±6.8mmHg vs 30.1±4.7 mmHg, p<0.001). All eyes with Uv-G (100%) had chronic uveitis compared to 76.2% of eyes with Uv-H had chronic uveitis (Fisher's exact test, p<0.001).There was no difference in age, gender, type of uveitis and duration of follow-up between the groups of eyes (Table 24)

4.4.2 IOP elevation in uveitic eyes

Out of 103 patients, 78 patients (75.7%) had bilateral uveitis. IOP elevation occurred in 40 patients (38.8%) or 66/174 eyes with uveitis (37.9%), which was bilateral in 25 patients (62.5%) and unilateral in 15 patients (37.5%), out of whom 7 patients (46.7%) had unilateral uveitis and 8 patients (53.3%) had bilateral uveitis.

At 6 months of follow-up, the prevalence of IOP elevation was 19.4% (Table 25). This figure dropped slightly at 1 year of follow-up and increased steadily every year until it reached a maximum at 6 years of follow-up.

Table 25: The distribution of patients with IOP elevation according to follow-up years.

Duration of follow-up	Number of patients	Number of patients with elevated IOP, n (%)
6 months	103	20 (19.4)
1 year	93	9 (9.7)
2 years	71	9 (12.7)
3 years	51	6 (11.8)
4 years	31	4 (12.9)
5 years	16	4 (25)
6 years	10	6 (60)

At 6 months after diagnosis of uveitis, 36/174 eyes (20.7%) with uveitis developed IOP elevation. The cumulative percentage increased with follow-up: 48 eyes (27.6%) at 1 year after diagnosis, 58 eyes (33.3%) at 2 years after diagnosis, 60 eyes (34.5%) at 3 years, 62 eyes (35.6%) at 4 years, 64 eyes (36.8%) at 5 years and 66 eyes (41.7%) at 6 years. Figure 30 describes the cumulative probability of IOP elevation in eyes against the time after uveitis diagnosis in months.

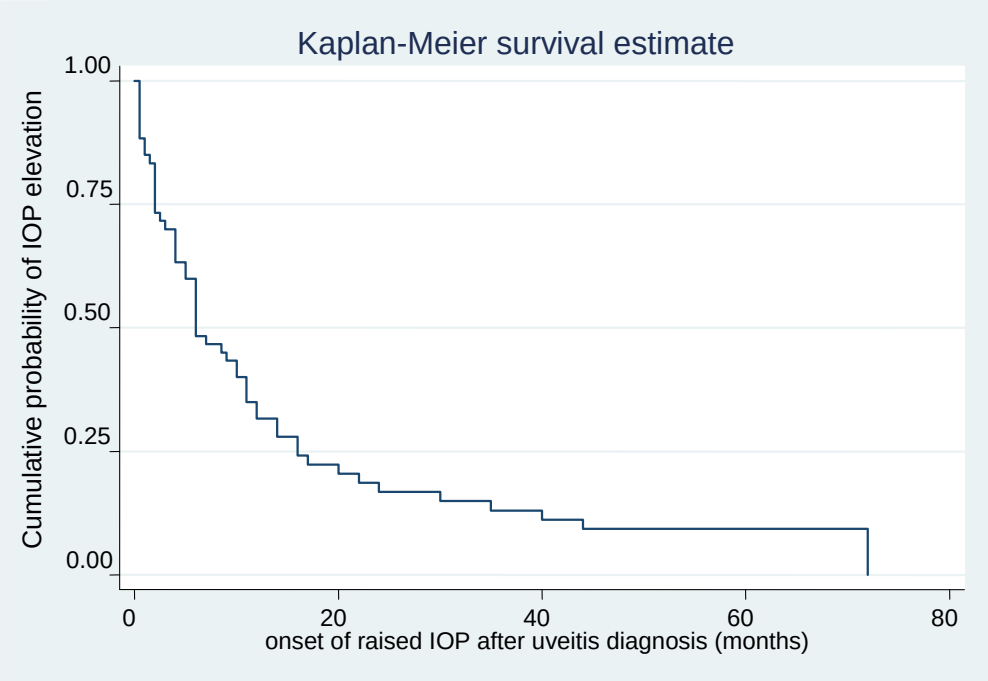

Figure 30: Kaplan Meier graph of the cumulative probability of raised IOP in eyes against time.

The prevalence of raised IOP in eyes with chronic uveitis was significantly higher (55/109 eyes, 50.4%) than with acute uveitis (11/65 eyes, 16.9%, p<0.001). Anterior uveitis formed 58.5 % of the acute uveitis whereas intermediate uveitis formed 43.1% of the chronic uveitis, p<0.001. The distribution of uveitis according to chronicity is displayed in Figure 31.

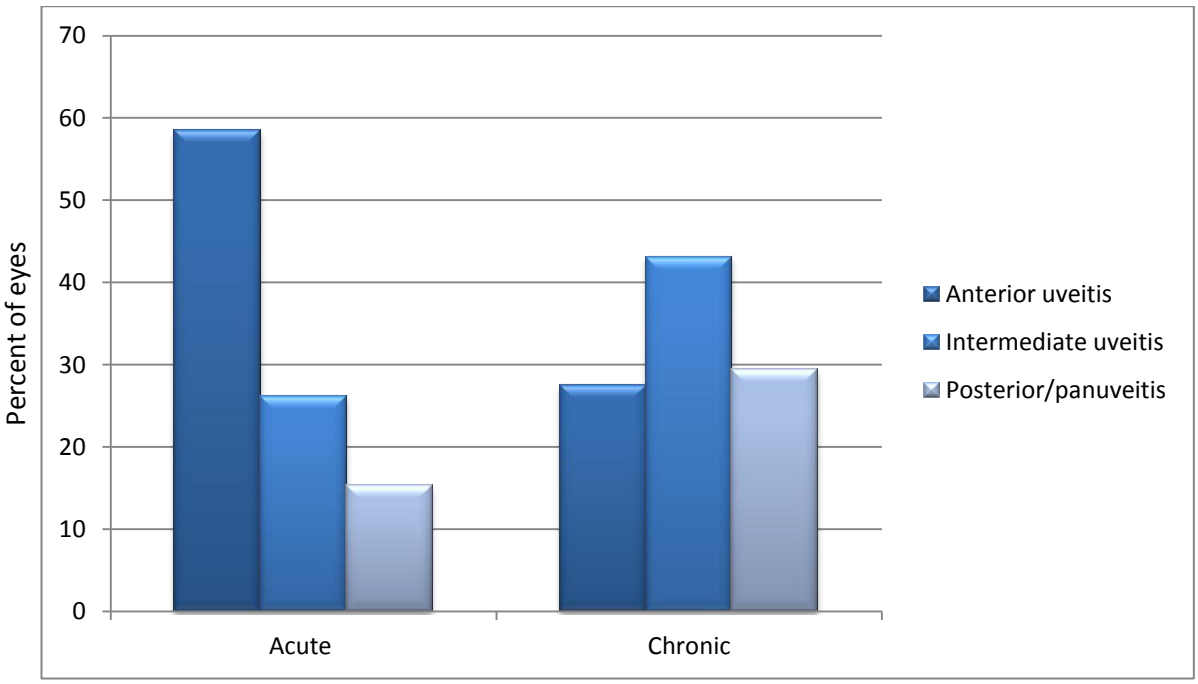

Figure 31: Distribution of types of uveitis according to chronicity

Consistent with the chronic course followed by about 40% of eyes with intermediate uveitis, the onset of IOP elevation started in the later stage of the disease but the prevalence continue to increase over time in intermediate uveitis (Figure 32). On the other hand, the onset of raised IOP occurs earlier in anterior and posterior/panuveitis.

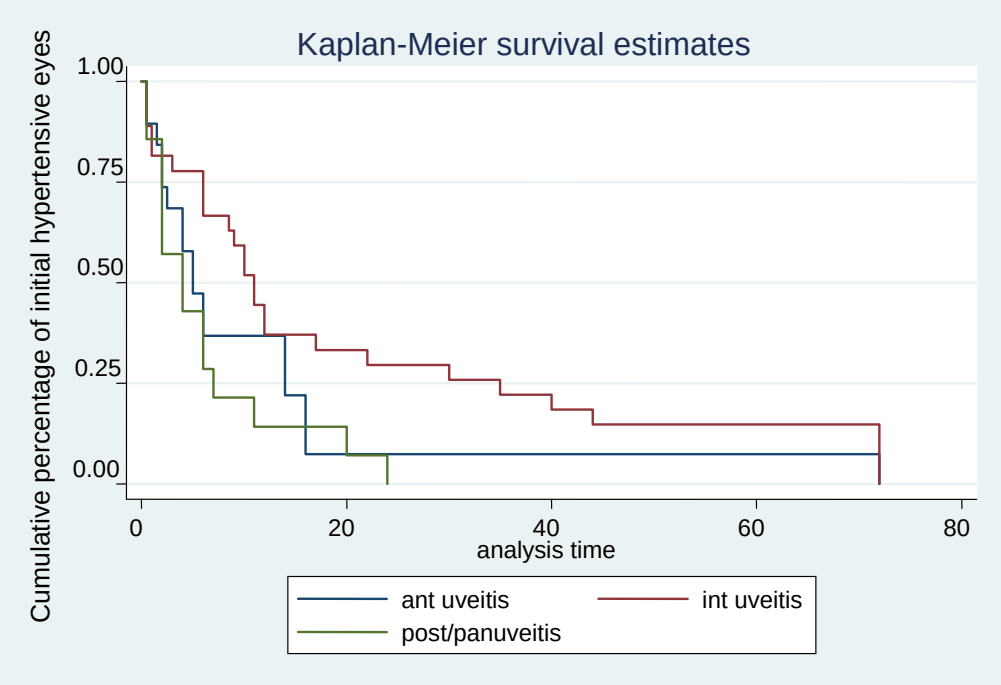

Figure 32: Kaplan Meier graph of the cumulative percentage of eyes with initial IOP elevation with time in different types of uveitis

4.4.3 Risk factors of IOP elevation and glaucoma

To determine the risk factors for IOP elevation (in Uv-H and Uv-G eyes), we performed a multivariate logistic regression against Uv-N eyes for the following factors: the type of uveitis, duration of follow-up, chronicity, age and gender.

Male gender and chronic uveitis were found to be significantly associated with elevated IOP. After adjusting for the other factors, there was a 9 fold increase in the risk of elevated IOP in chronic uveitis and males were 5.5 times more likely to have elevated IOP compared to females (Table 26) A chi square test did not detect any association between male gender and chronic uevitis (p=0.3) or types of uveitis (p=0.063).

Table 26: Multivariate logistic regression examining risk factors for elevated IOP (Uv-N vs Uv-H + Uv-G).

Variable	Odds ratio	Standard error	p	95% confidence interval
Age	1.04	0.1	0.6	0.87 – 1.25
Gender	***5.51***	***3.1***	***0.002***	***1.85 – 16.4***
Duration of follow-up	0.9	0.12	0.43	0.68 – 1.18
Chronicity	***9.28***	***6.4***	***0.001***	***2.4 -36.1***
Anterior uveitis*	0.85	0.57	0.8	0.23 – 3.19
Intermediate uveitis *	0.85	0.63	0.82	0.2 – 3.6

***Anterior and intermediate uveitis was compared with posterior/panuveitis as the reference group.**

However, when assessing risk factors for glaucoma (Uv-H and Uv-G), chronicity predicts for glaucoma in 100% of eyes i.e all Uv-G eyes had chronic uveitis, and therefore was dropped from the analysis. Analysis of the remaining factors found higher peak IOP to be a significant risk factor for the development of glaucoma. After adjusting for all the other factors, for every 1 mmHg increase in maximum IOP, the risk of glaucoma increased by 40% (OR 1.4, p=0.003, 95% CI 1.12 – 1.7, Table 27).

Table 27: Multivariare logistic regression of risk factors for glaucoma (Uv-H and Uv-G).

Variable	Odds ratio	Standard error	p	95% confidence interval
Age	0.82	0.17	0.34	0.55 – 1.23
Male gender	0.35	0.47	0.43	0.02 – 4.8
Maximum IOP	***1.4***	***0.15***	***0.003***	***1.12 – 1.7***
Anterior uveitis*	0.09	0.17	0.2	0.003 – 3.02
Intermediate uveitis*	0.14	0.18	0.125	0.01 – 1.73
Duration of follow-up	1.15	0.43	0.71	0.54 – 2.4

***Anterior and intermediate uveitis were compared with posterior/panuveitis as the reference group, Chronicity was dropped from the calculation as it predicts glaucoma perfectly.**

4.4.4 Treatment regime and visual outcome of IOP elevation

Out of the 66 eyes with raised IOP, 13 eyes (19.7%) received no treatment at the onset of raised IOP as the IOP was less than 28 mmHg, 17 (25.6%) eyes received monotherapy, either beta blocker (12 eyes), topical CAI (4 eyes) in asthmatic patients or a prostaglandin analogue (1 eye) in severe IOP rise, and 36 eyes (54.5%) received more than one hypotensive agents. In 13 eyes that did not receive hypotensive treatment, stronger steroids (Dexamethasone or Prednisolone acetate) were switched to a weaker compound (Rimexolone). Out of those, only 3 eyes (23.1%) had no further increase in IOP. The remaining eyes (76.9%) required additional topical hypotensive agents at the next follow-up visit. In eyes where prostaglandin was used, no eyes showed increased inflammation post treatment. Nineteen of 43 patients who had IOP elevation (44.2%) received oral CAI at least temporarily resulting in a mean IOP reduction of 9.4 mmHg (range 8-16mmHg) from the IOP whilst on topical agents alone.

Slightly more than three quarters (78.3%) of Uv-G eyes needed oral CAI together with topical agents for additional IOP control compared to 15.2% of Uv-H eyes. Nineteen out of 25 Uv-G eyes (76%) underwent glaucoma surgery, either trabeculectomy with antimetabolite or implantation of a glaucoma drainage device, due to systemic CAI dependency or insufficient IOP control whilst on MTMT. None of the Uv-H eyes required glaucoma surgery.

Out of all eyes with uveitis, 20/179 eyes (11.2%) had final VA worse than 20/50 (6/15 in Snellen) which consisted of 7 Uv-G (35%), 1 Uv-H (5%) and 12 Uv-N eyes (60%), p=0.03. Among the seven Uv-G eyes, only 1 eye had poor VA from a pale glaucomatous disc alone. Visual impairment in the remaining Uv-G eyes was caused by a combination

of glaucomatous disc and other pathologies such as macular scar, CMO and incomplete aphakia correction after vitreolensectomy.

4.4.5 Steroid induced IOP elevation.

Among the eyes with raised IOP, 5 eyes had uveitis-induced IOP elevation and 61 eyes had steroid-induced IOP elevation. The mean peak IOP in eyes with uveitis-induced was higher compared to steroid-induced IOP elevation although not statistically significant (37.4 mmHg vs 34.6 mmHg, p=0.4). Consequently, uveitis-induced IOP elevation eyes were 3 times more likely to require oral acetazolamide compared to eyes with steroid-induced IOP elevation although again this failed to reach statistical significance (p=0.261) because of the small number of eyes with uveitic-induced IOP elevation.

The prevalence of a steroid response among all eyes treated with steroids either topically, systemically or with injections was 35.1% (61/174 eyes). The median duration of onset of raised IOP was 6 months after starting steroids (range: 2 weeks to 72 months). There was no correlation between the level of IOP elevation with the onset of IOP elevation after diagnosed with uveitis (Pearson correlation coeffcient, r=-0.0986, p=0.5, Figure 33)

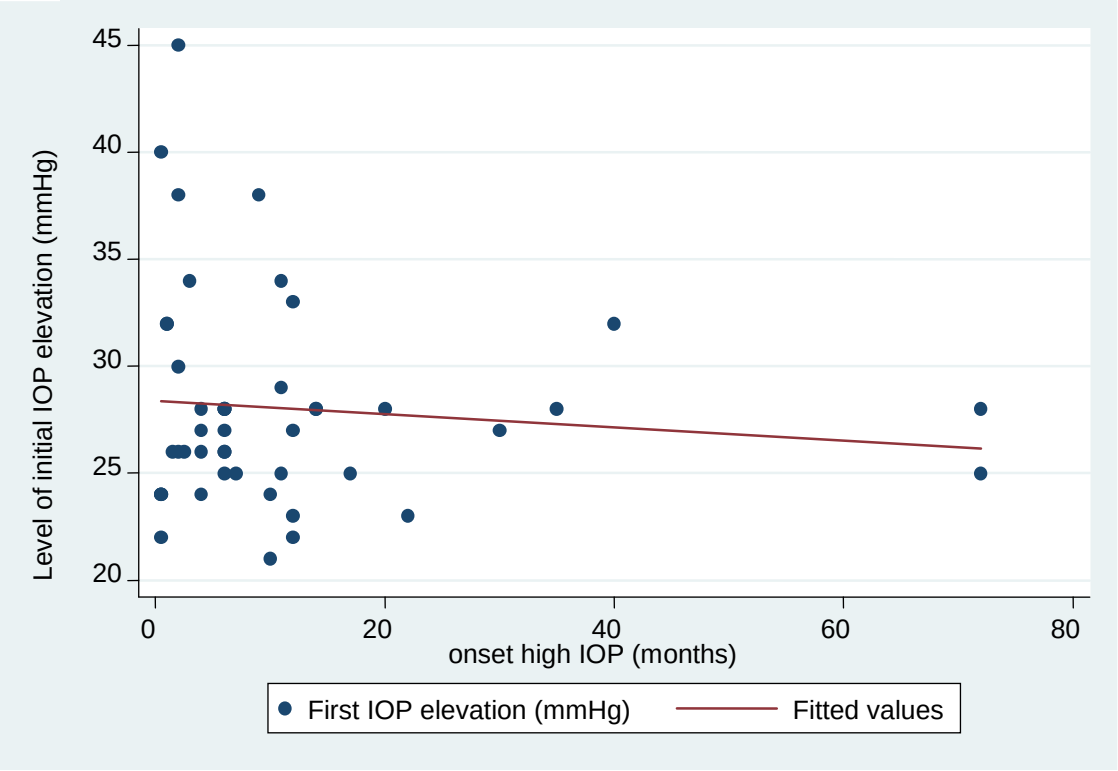

Figure 33: Scatter plot describing the correlation between the level of IOP elevation and the onset of IOP elevation.

The mean peak IOP was 34 mmHg (range: 22 mmHg to 56 mmHg) with 4 eyes (6.6%) reaching a peak IOP of 50 mmHg or more, 12 eyes (19.7%) between 40 mmHg and 49 mmHg and a further 28 eyes (45.9%) had peak IOP of 30 – 39 mmHg). Forty-two of the 61 eyes (68.8%) were high responders, 17 eyes were intermediate responders (27.9%) and only 2 eye (3.3%)was a low responder.

Chronic uveitis compared to acute uveitis was a significant risk factor for SR (83.8 % vs 16.1%, OR 8.4, p<0.001, 95% CI 2.4-29.0) after adjusting for the duration of follow-up. The risk of a steroid response in chronic uveitis was 8 fold higher than acute uveitis.

High responders compared to intermediate responders were associated with younger age group and lower IOP at presentation. Regional steroid injection was the only uveitis treatment associated with a high response compared to intermediate response

(Table 28) . Sixteen high responder eyes (38.1%) had to undergo glaucoma surgery while none of the intermediate responders underwent glaucoma surgery. Gender and the type of uveitis were not significant risk factors for high responders.

Table 28: Clinical data of high and intermediate steroid responders.

Characteristics	Types of steroid response		P value
	High responders, n=42	Intermediate responders, n=17	
Age(years)§	11.4±3.8	13.5±2	0.04
IOP at presentation(mmHg) §	13.1±3	16.5±4.8	0.001
Peak IOP(mmHg) §	37.4±7.2	28.4±4.7	<0.001
Type of uveitis treatment			
Immunosuppressive agents	25 (58%)	11 (55%)	0.8
Steroid injection	18(42%)	3 (15%)	0.04
Oral prednisolone	32 (72.7%)	12 (27.3%)	0.2
Topical steroids	42 (76%)	20 (60%)	0.2
Reason for glaucoma surgery			
Uncontrolled IOP on systemic CAI	5	NA	
Uncontrolled IOP with glaucomatous disc	10	NA	
Controlled IOP but systemic CAI dependant	3	NA	

§ Results are given in mean and standard deviation, n=number of eyes, NA= not applicable, CAI=carbonic anhydrase inhibitor, IOP=intraocular pressure

4.4.6 Peripapillary RNFL in uveitic eyes

Available OCT scans of the peripapillary RNFL were analysed to determine any evidence of RNFL thinning in hypertensive uveitis eyes with and without glaucomatous disc changes.

Ninety-nine out of 103 children (198 eyes) had OCT scans of the RNFL. Of these, 45 eyes were excluded for disc swelling (27 eyes), poor scan quality due to cataract or severe vitritis (6 eyes), previous vitrectomy and/or laser retinopexy (8 eyes) and large or diffuse retinal or macular scars from toxoplasmosis or multifocal choroiditis (4 eyes).

The remaining 153 eyes were divided into 27 Control, 76 Uv-N, 31 Uv-H and 19 Uv-G eyes following the same definitions as before.

4.4.6.1 The effect of uveitis on the RNFL

Among the Uv-N eyes, there was a significant difference in mean global RNFL thickness between anterior uveitis (105.3 ± 12.7 µm), intermediate uveitis (119.0 ± 22.8) and posterior/panuveitis (113.3 ± 19.7), p= 0.02. A post hoc Bonferroni correction revealed the difference was significant between eyes with anterior uveitis and intermediate uveitis (p=0.016). The global RNFL in Uv-N eyes with active inflammation at the time of OCT scan was also significantly thicker than quiescent eyes (118.7 ±18.6 µm vs 104.8±14.7 µm respectively, p=0.003). The mean global RNFL in quiescent Uv-N eyes were also significantly thicker than control eyes (96.6 ± 8.1µm, p<0.001). To minimise the effect of active uveitis on the RNFL, eyes with active uveitis were excluded from further RNFL analysis unless stated otherwise.

4.4.6.2 The effect of elevated IOP on the RNFL in uveitic eyes

First, we compared the Uv-G eyes which act as a positive control with the Uv-N eyes to determine any RNFL changes that have occurred so that we can look for these in the Uv-H eyes. Comparison of RNFL thickness between quiescent Uv-G and Uv-N eyes revealed significant thinning only in the inferior quadrant alone (Table 29).

Table 29: Comparison of RNFL thickness between Uv-N and Uv-G.

Quadrant	Uv-N	Uv-G	
	Mean ±SD (µm)		p
Global	109.1 ± 18.3	100.9 ± 22.6	0.185
Inferior	***142.1 ± 32.0***	***121.3 ± 28.9***	***0.043***
Superior	128.8 ± 17.2	116.1 ± 36.4	0.07
Nasal	84.2 ± 24.4	81.5 ± 24.7	0.73
Temporal	81.2 ± 20.8	84.3 ± 15.6	0.63
Nasosuperior	118.4 ± 27.1	103.7± 32.3	0.1
Temperosuperior	140.0 ± 16.2	128.9± 42.7	0.13
Temperoinferior	158.0 ± 36.9	141.4 ± 34.3	0.16
Nasoinferior	124.4 ± 38.8	101.75 ± 30.0	0.06

Comparison of the RNFL thickness between quiescent Uv-N and Uv-H eyes however, found no significant difference in RNFL thickness in all quadrants.

We then compared the RNFL thickness between quiescent Uv-H and Uv-G eyes. Although there was no significant difference in the global and the 4 major quadrants (inferior, superior, nasal and temporal quadrants, we found significant RNFL thinning of Uv-G eyes in the naso inferior and nasosuperior quadrant (Table 30).

Table 30: Comparison of RNFL thickness between Uv-H and Uv-G eyes.

Quadrant	Uv-H	Uv-G	
	Mean ±SD (µm)		p
Global	114.7 ± 30.3	100.9 ± 22.6	0.2
Inferior	144.3 ± 45.8	121.3 ± 28.9	0.14
Superior	138.2 ± 32.2	116.1 ± 36.4	0.11
Nasal	97.1 ± 34.8	81.5 ± 24.7	0.2
Temporal	79.3 ± 23.0	84.3 ± 15.6	0.53
Nasosuperior	***134.9 ± 43.5***	***103.7± 32.3***	***0.049***
Temperosuperior	141.4 ± 29.2	128.9± 42.7	0.37
Temperoinferior	146.8 ± 45.9	141.4 ± 34.3	0.74
Nasoinferior	***142.0 ± 51.4***	***101.75 ± 30.0***	***0.024***

4.4.6.3 Factors affecting RNFL thickness

To isolate the factors that affect the RNFL thickness, we performed a multivariate linear regression between all uveitic eyes (Uv-N, Uv-H and Uv-G eyes) with age, the maximum IOP and active uveitis at the time of OCT scan.

After adjusting for age and maximum IOP, active uveitis was significantly associated with an increase in the RNFL thickness in the global (adjusted regression coefficient 23.9, SE= 9.1, p=0.012), inferior (adjusted regression coefficient 35.4, SE= 2.5, p=0.017) and temporal quadrant, (adjusted regression coefficient 28.1, SE= 8.9, p=0.003). Maximum IOP on the other hand was significantly associated with reduction in the RNFL thickness in the nasosuperior (adjusted regression coefficient -1.69, SE= 0.71, p=0.023) and nasoinferior quadrant (adjusted regression coefficient -2.3, SE= 1.1,

p=0.04) after adjusting for age and active uveitis. Age was not associated with any significant change to the RNFL.

4.4.6.4 Longitudinal changes of the RNFL

We performed linear mixed model analysis on 164 eyes of 82 patients to determine any significant changes of the RNFL thickness over a span of 3 years. The dependant variable was global RNFL thickness and the independant variable was year (2010, 2011 and 2012). The RNFL values were nested within each eye of each patient. The interval between each OCT scan was between 8-12 months from each other.

There was no significant change in the global RNFL thickness in all groups of eyes (Table 31).

Table 31: Regression coefficient of the longitudinal global RNFL changes in different groups of eyes within the period between 2010-2012.

Group	Regression coefficient	Standard error	p	95% Confidence Interval
Uv-G	-3.8	2.03	0.058	-7.8 – 0.12
Uv-H	-0.03	2.1	0.9	-4.2 – 4.1
Uv-N	0.33	1.0	0.7	-1.7 – 2.3
Control	-0.23	0.6	0.7	-1.4 – 0.96

However, when examining the individual quadrants in the Uv-G eyes, we found significant RNFL reduction occurring in the superior and temporal quadrants (Table 32). Reduction in the temporal quadrant occurred both in the temperosuperior and temperoinferior sector.

Table 32: Regression coefficient of the Uv-G eyes from the linear mixed model to describe the longitudinal change of different quadrants of RNFL.

Quadrant	Regression coefficient	Standard error	p	95% confidence interval
Inferior	-2.36	2.08	0.26	-6.4 – 1.72
Superior	***-5.4***	***2.4***	***0.026***	***-10.15 – 0.65***
Nasal	-1.45	2.37	0.54	-6.1 – 3.2
Temporal	***-5.6***	***2.7***	***0.036***	***-10.9 - -0.36***
Nasosuperior	-3.94	2.47	0.11	-8.8 – 0.9
Temperosuperior	-7.23	2.62	0.006	-12.4 - -2.1
Temperoinferior	-5.3	2.5	0.035	-10.3 - -0.34
Nasoinferior	1.96	2.2	0.376	-2.4 – 6.3

Within the Uv-H eyes, although there was no significant reduction in the global RNFL, we found a significant reduction in the nasosuperior quadrant (Table 33).

Table 33: Regression coefficients of different quadrants of the RNFL in Uv-H eyes describing longitudinal changes of the RNFL

Quadrant	Regression coefficient	Standard error	p	95% confidence interval
Inferior	1.01	3.4	0.8	-5.7 – 7.8
Superior	-3.1	2.6	0.23	-8.1 – 1.9
Nasal	-0.8	2.73	0.8	-6.1 – 4.5
Temporal	1.7	2.3	0.47	-2.8 – 6.2
Nasosuperior	***-6.5***	***2.6***	***0.01***	***-11.6 - -1.3***
Temperosuperior	-0.1	3.1	0.97	-6.15 – 5.9
Temperoinferior	3.1	3.6	0.38	-3.9 – 10.2
Nasoinferior	1.2	3.1	0.7	-4.8 – 7.2

4.5 Discussion

This study was conducted in a tertiary referral uveitis center and would therefore represent the more severe cases seen in the paediatric uveitis practice as a whole. Non-JIA-related uveitis represents a very heterogenous group of children with varying risks for IOP elevation and glaucoma. Therefore, the prevalence data is more relevant to the patient mix at a tertiary uveitis referral center like Moorfields Eye Hospital than to a general ophthalmological practice setting. The proportion of females was slightly more than males, consistent with the reported gender distribution in most surveys of childhood uveitis. (Cunningham, 2000) There were slightly more eyes with anterior uveitis compared to intermediate uveitis, while posterior/panuveitis formed the remaining 20% of cases. Analysis of the distribution of different types of uveitis varies between centers and geographical areas but overall, anterior uveitis accounts for 30-40% of the uveitis in children, intermediate uveitis accounts for 20 to 10% of cases, whereas posterior uveitis accounts for 40-50% of cases. (Cunningham, 2000) (Zierhut et al., 2005)

Uveitis was bilateral in approximately 76% of our cases, agreeing favourably with previous reports of between 71 to 74% of bilateral cases in children. (Kump et al., 2005)(Sijssens et al., 2006)(Rosenberg et al., 2004) About 40% of our patients developed IOP elevation, out of which 62.5% was bilateral. The highest prevalence of IOP elevation (60%) occurred at 6 years of follow-up. The percentage of IOP elevation at 6 months in our patients was approximately 20%, slightly higher than the 14% reported by Sijssens et al in a study involving JIA and non-JIA-related uveitis children. (Sijssens et al., 2006) However, the percentages thereafter were lower compared to their study reflecting the higher prevalence of raised IOP in chronic JIA-related uveitis

in their study. Approximately 20% of eyes had IOP elevation within 6 months after diagnosis of uveitis and a further 10% occurred after 1 year of uveitis diagnosis.

4.5.1 Risk factors for IOP elevation and glaucoma

Consistent with previous reports, we found the prevalence of raised IOP to be higher in eyes with chronic uveitis. (Herbert et al., 2004) However, other reports did not find any association between IOP elevation and chronicity of uveitis possibly because of their small number of patients with acute uveitis in a study involving a mixture of JIA and non JIA-related childhood uveitis. (Sijssens et al., 2006) Chronic uveitis was not only found to be a significant risk factor for raised IOP, but also responsible for steroid responsiveness and glaucoma, resulting in a 9 fold increase in the risk of raised IOP and a 5 fold increase in steroid response compared to acute uveitis. Additionally, it predicts glaucoma extremely well as all Uv-G eyes had chronic uveitis. This would imply that somehow, the chronicity of the disease alters the eye's response to steroids, or it might be that patients with chronic disease simply use more steroids. Together with chronic uveitis, higher peak IOP was also an important risk factor for glaucoma, with the risk of glaucoma increasing by 40% with every increase of 1 mmHg of peak IOP. While acute uveitis was predominantly anterior type and chronic uveitis was predominantly intermediate, intermediate uveitis was not isolated as a risk factor for IOP elevation probably because the posterior/panuveitis also formed a substantial proportion of eyes with chronic uveitis (Figure 31).

Apart from chronic uveitis, male gender was also a significant risk factor for IOP elevation. The types of uveitis were not associated with the risk of IOP elevation, agreeing with previous reports. (Herbert et al., 2004) (Sijssens et al., 2006) Our data was not able to find any difference in the percentage of IOP elevation across uveitis

types, possibly due to the small sample size or other issues that prevented the confirmation of a statistical evidence. While we found male gender significantly associated with anterior uveitis in adults, we could not find any association between male and any other factors in children to explain the association between male gender and elevated IOP. It is also interesting to note that although the proportion of females with uveitis was slightly more than males, they were not at higher risk for elevated IOP. Additionally, similar to our findings in adult uveitis, male gender did not emerge as a significant risk factor for glaucoma. Perhaps, a future study using only one eye per patient might elucidate the true association between male gender and IOP elevation and glaucoma.

We found approximately 11% of eyes had a final VA poorer than 20/50 (6/15 in Snellen chart), slightly lower than in the report by Edelsten et al who found about 17% of children with uveitis had VA of less than 6/12 in at least one eye. (Edelsten et al., 2003) However, the underlying cause of visual loss in our study was largely not due to glaucoma alone. Macular scar and CMO were among the additional causes of visual loss in these patients.

While secondary glaucoma is among the commonest causes of irreversible visual loss in childhood uveitis (de Boer et al., 2003a) (Rosenberg et al., 2004), visual loss is contributed to by two closely related factors: inflammation and raised IOP. Control of inflammation by itself is necessary to prevent visual loss from chronic uveitic changes such as chronic CMO and cataract. (Loh and Acharya, 2010) However, the use of corticosteroids to control inflammation in chronic uveitis also predisposes to the risk of a steroid response and consequently glaucoma in these young children. In our study,

about a third of the Uv-G eyes had impaired vision with a final best corrected VA of less than 20/50, almost 20% more than in Uv-H eyes.

The prevalence of a steroid response among eyes in our study was 35.1% occurring after a median duration of 6 months. Similar to adults, uveitis-induced IOP elevation had a higher peak IOP compared to steroid-induced IOP elevation and therefore was more likely to require oral acetazomlamide. About a quarter of the steroid responder eyes had maximum IOP elevation of 40 mmHg or more with nearly 70% of eyes fulfilling the criteria of high responder as described by Armaly. (Armaly, 1965) Our finding that chronic uveitis was a significant risk factor for steroid response, after adjusting for the duration of follow-up, could be attributed to chronic angle changes either from chronic use of steroid or chronic uveitis impeding the aqueous humor outflow without closing the angle. We additionally found that younger age, lower IOP at presentation and regional steroid injection were associated with high responder eyes. About 40% of high responders eventually required glaucoma surgery.

Steroid responsiveness is therefore a major obstacle in the management of childhood uveitis. These children often require prolonged treatment with either topical, regional injection or systemic corticosteroid with or without the addition of other immunosuppressive agents. Lam et al reported 33% of children treated with topical 0.1% Dexamethasone four times a day and 18.3% of those who received twice a day dose given as treatment after strabismus surgery were high responders. (Lam et al., 2005) They also found that the hypertensive response was not just dose but also age dependant. However, unlike postoperative strabismus surgery, our children needed a higher dose of steroid for longer periods to control more severe ocular inflammation. Very often it is started as a two hourly dosing and tapered within a minimum of four

weeks. Some children went on to receive prolonged low dose steroids for months to keep the eye quiet. It is of no surprise that we found approximately 70% high responder eyes and nearly 30% intermediate responders with about 6% of the eyes reaching a peak IOP of more than 50 mmHg. The eyes which were high responders belonged to younger patients, had lower presenting IOP and had received regional steroid injection. About 30% of the high responders eventually required glaucoma surgery for additional IOP control. Unlike Lam's study, ours is a retrospective study and topical steroids were not discontinued if the IOP elevation exceeded 30 mmHg because of the danger of rebound uveitic activity. Nevertheless, topical steroids were either tapered or changed to weaker compounds like Rimexolone whilst concurrent pressure lowering drops with or without oral CAI prescribed with close monitoring.

Switching steroids alone (from more potent steroids like Dexamethasone to weaker compounds like Rimexolone) was able to halt further IOP rise in only 23% of eyes in our study. The remaining eyes required additional hypotensive agents either as monotherapy or in combination. Even when the inflammation has been brought under control with either a weaker or stronger steroid, nearly 45% of patients required systemic CAI for IOP control which provided an additional IOP reduction by a mean of 9.4 mmHg. Despite that, three quarters of Uv-G eyes eventually had to undergo glaucoma surgery.

Published data have compared the safety and efficacy of topical Prednisolone against Rimexolone in the treatment of uveitis. (Foster et al., 1996)(Biswas et al., 2004) There were also reports of efficacy and safety of Rimoxelone compared to Fluoromethalone in known steroid responders (Leibowitz et al., 1996) and anecdotal reports of severe IOP elevation with the usage of Rimexolone in uveitis. (Cazabon and Morrell, 2001)

However, a Pubmed search did not reveal any reports of the outcome of switching from Prednisolone or Dexamethasone to Rimexolone in terms of further IOP elevation. We found that by switching to Rimexolone, about 23% of the eyes did not show a further increase in IOP. Other weaker topical steroid like Loteprednol has been shown to be ineffective in severe uveitis and therefore was not largely used in our practice. (Loteprednol Etabonate Study Group,(1999)

The primary treatment for raised IOP in uveitic eyes, like in any other primary glaucoma, is topical hypotensive agents. The addition of oral CAI has been shown to provide an additional 30% IOP reduction in children with primary glaucoma already on topical CAI. (Sabri and Levin, 2006) However, in the context of uveitis, the IOP-lowering effect of these topical agents are highly variable, from no effect at all to the occasional 70-80% reduction effect especially with topical CAI (Sung and Barton, 2004). Furthermore, Heinz et al reported a mere 26% success rate of topical therapy in a retrospective study involving 261 children with secondary glaucoma and ocular hypertension (52% of them had underlying JIA). (Heinz et al., 2009) Forty-four percent of the children on topical therapy received systemic CAI at least temporarily to control the IOP out of which 67% of the children had to undergo glaucoma surgery in the latter course of treatment.

4.5.2 RNFL and IOP elevation in children

This study also found that monitoring of hypertensive uveitic eyes with RNFL thickness measurement may be useful in detecting early RNFL changes. Due to the unavailability of normative database of the RNFL in children, we compared the values among our patients and not with the inbuilt normative database.

Similar to adults, we found the mean global RNFL to be thicker in active uveitis than quiescent uveitic eyes, which was in turn still thicker than control eyes. Intermediate uveitis had thicker global RNFL thickness compared to anterior uveitis. This is probably attributed to the inclination of intermediate uveitis to develop CMO in children (Kump et al). As explained earlier, the occurrence of CMO would not only cause thickening of the macula, but also increased thickness of the RNFL especially in the temporal region.

We postulate that Uv-G eyes began as Uv-H eyes and therefore should demonstrate parallel RNFL findings to the Uv-H eyes. This is in fact the case when we found that while RNFL thinning was detected in the inferior quadrant of Uv-G when compared to Uv-N eyes, RNFL thinning was detected in the nasoinferior quadrant of the Uv-G when compared to Uv-H eyes. Furthermore, higher peak IOP seen in Uv-G eyes was associated with significant RNFL thinning in the nasoinferior as well as nasosuperior quadrant after adjusting for active uveitis and age.

As opposed to adults, RNFL thinning in Uv-G eyes in children showed significant thinning in the inferior quadrant alone. This probably describes the resilience of children's retina to withstand elevated IOP without causing significant RNFL thinning, but it is also possible that it could be masked by the effect of increased RNFL thickness due to uveitis. Consequently, we were unable to detect decreased RNFL in any of the quadrants in Uv-H eyes compared to Uv-N eyes. When comparing Uv-H and Uv-G eyes, we found significant thinning of RNFL in the nasoinferior sector of the Uv-G eyes.

Previous studies have provided evidence that the spectralis OCT is able to provide high definition and fine discriminating scans enabling diagnosis of early perimetric glaucoma. Nadeau et al compared the peripapillary RNFL thickness taken with the Zeiss Stratus OCT between normal, ocular hypertension and primary glaucoma eyes in

children. He found that eyes with glaucoma had significantly thinner RNFL than both normal and eyes with ocular hypertension (Nadeau et al., 2010) in the superior and inferior quadrant. There was no difference found between the normal and ocular hypertension eyes. Other studies reported thinning of the RNFL in all quadrants in Primary Congenital Glaucoma compared to normal eyes.(Srinivasan et al., 2013)

The effect of maximum IOP was not as profound as in adults to cause a significant change in the global RNFL. While active ueitis was found to increase the global, inferior and temporal quadrants, maximum IOP was only associated with thinning in the nasosuperior and nasoinferior sectors.

Because of the retrospective nature of the data, the interval between RNFL measurements was inconsistent and varied between 8-12 months. Unlike in adults where significant change was detected in the global RNFL thickness of the Uv-G eyes, we could not find any significant change in the global RNFL thickness in all groups of eyes, including the Uv-G eyes, over the span of 3 years. However, we could detect a significant reduction in the superior and temporal quadrant of the Uv-G eyes and in the nasosuperior quadrant of the Uv-H eyes.

Ideally, VF testing should be done on all children with raised IOP. However, the reliability of VFs depends largely on the age and maturity of the child. Not all patients have VFs done on them, and among those that do have, the VFs may not be reliable enough for a concrete diagnosis of glaucoma. Furthermore, even if the VFs do show changes, it could be that the changes are due to uveitic effects such as retinal or macula scars and not glaucoma. The absence of adequate VFs performed in these patients may limit the usefulness of the definitions used in this study to be used in future investigations. The findings regarding the diagnostic performance in other

studies were done in primary glaucomas, but in uveitic glaucoma, the aetiology and anatomical types of uveitis might have some effect on the RNFL as well.

4.6 Summary

In conclusion, clinical awareness of the risks of raised IOP and glaucoma in younger children, those with chronic uveitis and higher peak IOP is important. These children are at a higher risk of glaucoma and irreversible visual loss.

We speculate that monitoring of the peripapillary RNFL thickness in uveitic children with raised IOP can be a useful adjunctive tool to help detection of RNFL thinning associated with glaucoma. This finding can be validated through a longitudinal study with serial OCT scans alongside a course of an acute exacerbation of uveitis. Other factors like increased thickness with disease activity could confound serial results. We therefore suggest utilising the OCT for monitoring glaucomatous changes to be done during disease quiescence. The presence of any RNFL thinning in these children warrants aggressive control of IOP and inflammation. It may also support the funding of more expensive, well-tailored immunosuppressive agents or biologic drugs to spare the steroid use. The use of steroid sparing agents may have to be prioritized for these children to prevent visual loss from chronic uveitis or glaucoma.

5 Chapter 5: Glaucoma progression in eyes with uveitis after bilateral glaucoma surgery

5.1 Introduction

Uveitis is bilateral in approximately 75% of patients and up to 40% of them suffered bilateral IOP elevation at some point in the course of the disease. (Sijssens et al., 2006)(Kump et al., 2005) These patients often have chronic uveitis and poor vision if left untreated.(Cabral et al., 1994)

In patients with raised IOP, topical hypotensive agents were able to control the IOP in 26% of patients and an additional 62% required oral CAI such as acetazolamide for additional IOP control. (Heinz et al., 2009) Despite that, in those that are on MTMT, about 35% of adult and 60% of children with glaucoma inevitably need glaucoma surgery, (Heinz et al., 2009) either because of oral CAI dependency or insufficient IOP control. Since IOP elevation in uveitis can be very severe and difficult to treat in some patients, emergency glaucoma surgery, usually trabeculectomy or glaucoma drainage device implantation (GDI) is sometimes performed for IOP control even in the absence of glaucomatous disc changes. (Kok and Barton, 2002) Although medical therapy delays VF loss, greater IOP reduction and less IOP fluctuation often achieved with incisional glaucoma surgery can prevent further VF progression when maximally tolerated medical therapy is insufficient for IOP control.(Caprioli and Coleman, 2008)(Folgar et al., 2010)

Glaucomatous assessment takes into account progression of the optic disc,(Jonas et al., 2000) visual field, (Chauhan et al., 1990) peripapillary retinal nerve fiber bundle

atrophy,(Quigley et al., 1992) and more recently, retinal nerve fiber layer thickness measurement. (Zangwill et al., 2000)(Furuichi et al., 2002)(Leung et al., 2010b)(Grewal and Tanna, 2013) VF progression has been based almost exclusively from Standard Automated Perimetry (SAP) and many studies have used only SAP as a primary functional endpoint. (Chauhan et al., 2008) (Folgar et al., 2010) (Smith et al., 1996)

The Humphrey VF test is one of the most widely performed tests and considered the gold standard for diagnosis and monitoring of glaucoma progression. Progression can be assessed either by event-based analysis using parameters that reflect global or hemifield progression (i.e. whether VF progression has occurred or not) (Advanced Glaucoma Intervention Study 2,(1994), or trend analysis of the rate of disease progression. (Folgar et al., 2010)(Smith et al., 1996)(Chauhan et al., 2008) Trend analysis with point-wise linear progression (PLR) uses the rate of loss in decibels per year (dB/year) to describe localized points that are actively progressing. It has the advantage over event-based analysis for being more accurate in quantifying true disease progression. The use of software programs that perform objective and automated analyses were recommended. (Chauhan et al., 2008)

In the early postoperative period systemic CAI are stopped to prevent post operative hypotony in the operated eye in patients who have had a trabeculaectomy. With this, the second eye (SE) which is dependent on the oral CAI may experience marked IOP elevation. Depending on the interval between the first and second surgery, the SE may suffer glaucoma progression more than the first eye (FE).

We hypothesize that following cessation of oral CAI after glaucoma surgery in the FE, the SE may be exposed to accelerated IOP elevation which may lead to glaucoma progression occurring more in the SE compared to the FE.

5.2 Aims

In this study, we aim to determine the effect of stopping oral acetazolamide on the SE and the IOP rising again before surgery to the SE is undertaken in terms of worsening of VA, VF progression, IOP and increasing CDR in the SE compared to the FE. The variability in the duration between the FE and SE surgery may reflect in complications occurring in the FE. Additionally, we wanted to determine the surgical success of glaucoma surgery in this cohort of patients.

5.3 Methods

A retrospective chart review was conducted among patients attending the uveitis clinic in Moorfields Eye Hospital from May 2010 to Nov 2012. Patients with a diagnosis of bilateral uveitis, who had undergone bilateral glaucoma surgery, either trabeculectomy or GDI with or without antimetabolite augmentation, and a minimum post surgical follow-up of 2 years were included. Exclusion criteria were patients with missing data or inadequate follow-up period.

The preoperative data point refers to the point when the decision for surgery was made, i.e when the patients were on MTMT. Data collected included age, anatomical uveitis type, glaucoma treatment, CDR as reported in the case notes, the BCVA preoperatively and at 1, 2, 3, 4 and 5 years after their respective surgeries and, the highest IOP reading recorded during the entire period before and after surgery (excluding any IOP elevation within 2 month after surgery to account for post-surgical IOP fluctuation) (Iwao et al., 2012), the preoperative IOP prior to their respective surgeries and at 1, 2, 3, 4 and 5 years postoperatively, the status of the lens at the time of surgery, either phakic, pseudophakic or aphakic and Humphrey VF data.

To describe the amount of IOP reduction after surgery, the percentage of IOP reduction between the preoperative IOP (while on MTMT) and at one year postoperatively was calculated. IOP readings were taken using the Goldmann's Applanation Tonometer. Visual acuity was recorded as the BCVA using the Snellen chart with the use of pinholes or the patients' spectacles. Impaired vision was defined as BCVA between 6/15 and better than 6/60 whereas poor vision was defined as BCVA poorer than 6/60 according to the SUN classification. (Jabs et al., 2005) When comparing pre and postoperative BCVA, the logarithm of the reciprocal of the decimal VA was used to approximate the logMAR. Eyes without form vision were classified into one of the low-vision categories of logMAR conversion: counting fingers = 2.0 and hand motions = 2.3 (Lange et al., 2009) Light perception and no light perception were excluded as they were considered not a formed perception and could not be quantified. (Schulze-Bonsel et al., 2006)

Surgical success was defined as eyes with postoperative IOP ≤21 mmHg and recorded at 1, 2, 3, 4 and 5 years postoperatively, with glaucoma medications (qualified success) or without glaucoma medications (unqualified success). (Edmunds et al., 2001)(Chawla et al., 2012) Postoperative hypotony was defined as IOP < 5 mmHg or <10mmHg in the presence of hypotonous maculopathy.(Chawla et al., 2012)

An eye with a CDR of more than 0.7 or reported as having glaucomatous changes such as focal notching, rim pallor or excavation of the rim is considered to have glaucomatous disc changes.(Foster et al., 2002)

Progression of glaucomatous VF loss was assessed using the Progressor software (version 3.3; Medisoft Inc, London, United Kingdom). The software calculates point-wise linear regression (PLR) analysis and provides local slopes of progression (in

dB/year) for each of the 59 locations in the VF as well as globally, and its level of significance (p values). A Gaussian filter was applied to reduce measurement variability without additional testing or exclusion of tests with too much background noise to allow inclusion of all available VF tests irrespective of reliability criteria. (Fitzke et al., 1995) A test point was considered progressing if the slope of sensitivity over time exceeded 1 dB/year (with $p<0.01$). For edge points, a stricter slope criterion of >2 dB loss/year (also with $p<0.01$) was used. (Viswanathan et al., 1997)

5.4 Data analysis

In addition to the data analysis described in Chapter 2, the following analysis was also used in this study.

Paired t-test was used to compare means between the FE and SE. Survival analysis and the Kaplan Meir graph were plotted to assess the yearly probability of surgical success in the first 5 years of postoperative period. A linear mixed model analysis was used to assess the yearly rate of visual loss and the CDR of the optic disc in the first 5 years of postoperative period. Cox's regression analysis was performed to determine the risk factors for surgical failure and multivariate logistic regression analysis was used to determine the risk factors for bleb failure in trabeculectomy. Results are described as mean and standard deviation unless stated otherwise.

5.5 Results

A total of 43 patients who had bilateral uveitis underwent bilateral glaucoma surgery. Thirteen patients were excluded because of missing data (n=9), inadequate follow-up period (n=3) and co-existence of retinitis pigmentosa (n=1). Therefore, 60 eyes of 30 patients were included for analysis.

The male to female ratio was 1:1.3. The mean age was 39 years (range 7 to 66 years) with 7 children and 23 adults. The FE was the right in 16 patients and left in 14 patients. Fourteen patients (46.7%) had anterior uveitis, 8 patients (26.7%) had intermediate uveitis and a further 8 patients (26.7%) had posterior or panuveitis. The mean follow-up period was 12.0 ±9.4 years (range 3-42 years). The subtypes of uveitis were sarcoidosis (n=2), juvenile idiopathic arthritis (JIA)-related uveitis (n=3), Vogt Koyanagi Harada disease (n=2), tuberculosis (n=1), HLA B27 related uveitis (n=3), birdshot choroidoretinopathy (n=1) and idiopathic (n=18).

Glaucoma surgery was performed on the first eye at a median duration of 6.5 years (range 1-36 years) after the diagnosis of uveitis. The mean interval between surgery of the FE and SE was 30.3 months (range: 0.25 to 180 months). Nine SEs (30%) had surgery within 6 months after the FE surgery and 21 SEs (70%) had it after 6 months. Forty-one eyes (68.3%) had trabeculectomy and 19 eyes (31.7%) had GDI (3 Molteno and 16 Baerveldt devices) with or without antimetabolite augmentation.

5.5.1 Preoperative treatment and the indications for surgery

The mean number of preoperative drops was 3.1 drops. Twenty-seven eyes (45%) had 4 drops preoperatively, 21 eyes (35%) had 3 drops, 9 eyes (15%) had 2 drops and 3 eyes (5%) had 1 drop. All patients received oral acetazolamide before surgery of the FE which was stopped immediately after the FE surgery.

We compared the highest preoperative IOP in the FE and SE to determine whether cessation of the oral CAI had led to accelerated IOP in the SE. The preoperative period for the SE included the time from FE surgery until the SE surgery. We found no statistically significant difference in the mean highest preoperative IOP between the FE

and SE, with a mean highest IOP of 43.1 ± 7.7 mmHg (range 28-56 mmHg) and 40.4 ± 8.3 mmHg (range 26-65 mmHg) in the FE and SE respectively, p=0.21.

The indication for glaucoma surgery was dependency on oral acetazolamide in 9 eyes (15%), advanced glaucomatous disc cupping at borderline IOP control (IOP 19-21 mmHg) in 11 eyes (18.3%), and insufficient IOP control on MTMT with or without glaucomatous cupping in the remaining 40 eyes (66.7%). However, the IOP in most eyes reduced to high teens during preoperative assessment on the day of surgery with MTMT. There was no difference in the distribution of FE and SEs according to IOP and CDR at the time when decision for surgery was made (Table 34).

Table 34: Distribution of first and second eyes according to IOP and CDR preoperatively

Preoperative IOP (mmHg)	First Eye n (%)	Second Eye n (%)	p
19-21	3(10)	3(10)	
22-30	11(36.7)	16 (53.3)	
31-40	8 (26.7)	6 (20)	
41-50	4 (13.3)	3 (10)	
51-60	4 (13.3)	2 (6.7)	0.73[§]
Preoperative CDR			
<0.7	11 (36.7)	17 (56.7)	
≥0.7	19(63.3)	13(43.3)	0.1[¥]

[§]Fisher's Exact test, [¥] Chi square test. IOP=Intraocular pressure, CDR=cup to disc ratio.

The Kaplan Meier graph in Figure 34 illustrates the cumulative percentage of IOP elevation occurring in the second eye after oral acetazolamide was stopped following the first surgery.

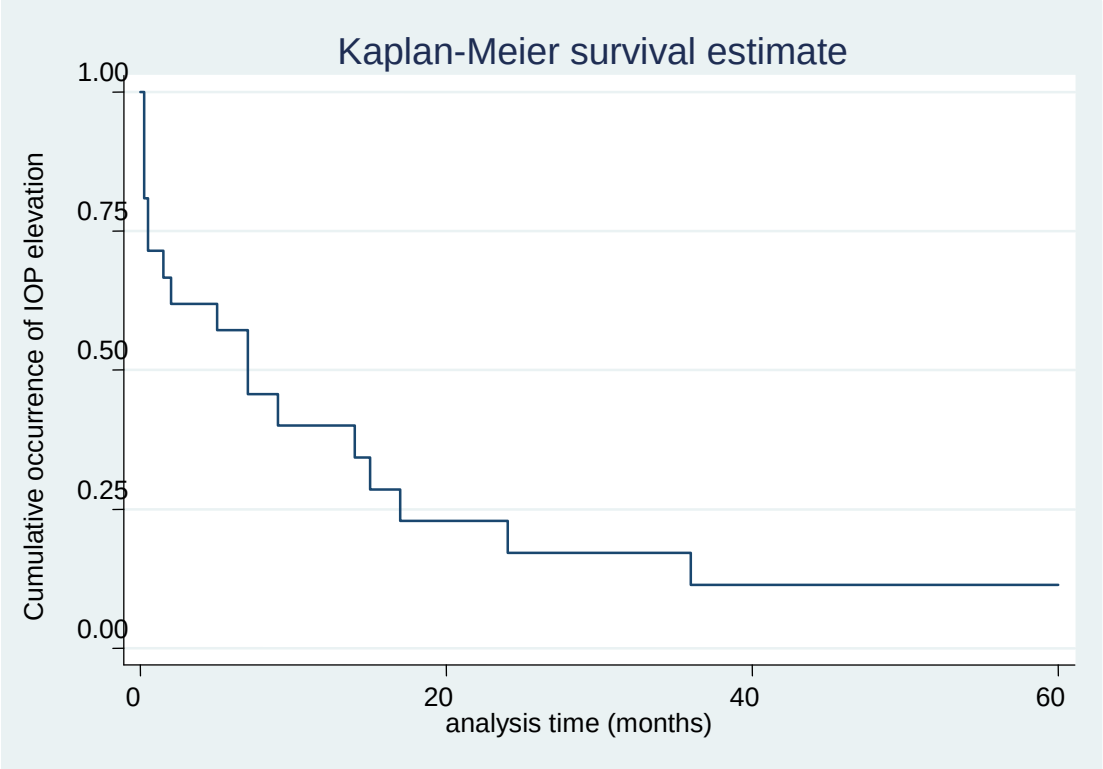

Figure 34: Kaplan Meier graph illustrating the occurrence of IOP elevation in the second eye after oral acetazolamide was stopped following surgery in the first eye.

42.8% of SEs had IOP elevation within the first year after surgery in the FE, 18.4% had it in the second year and 12.2% had it in the third, fourth and fifth year respectively.

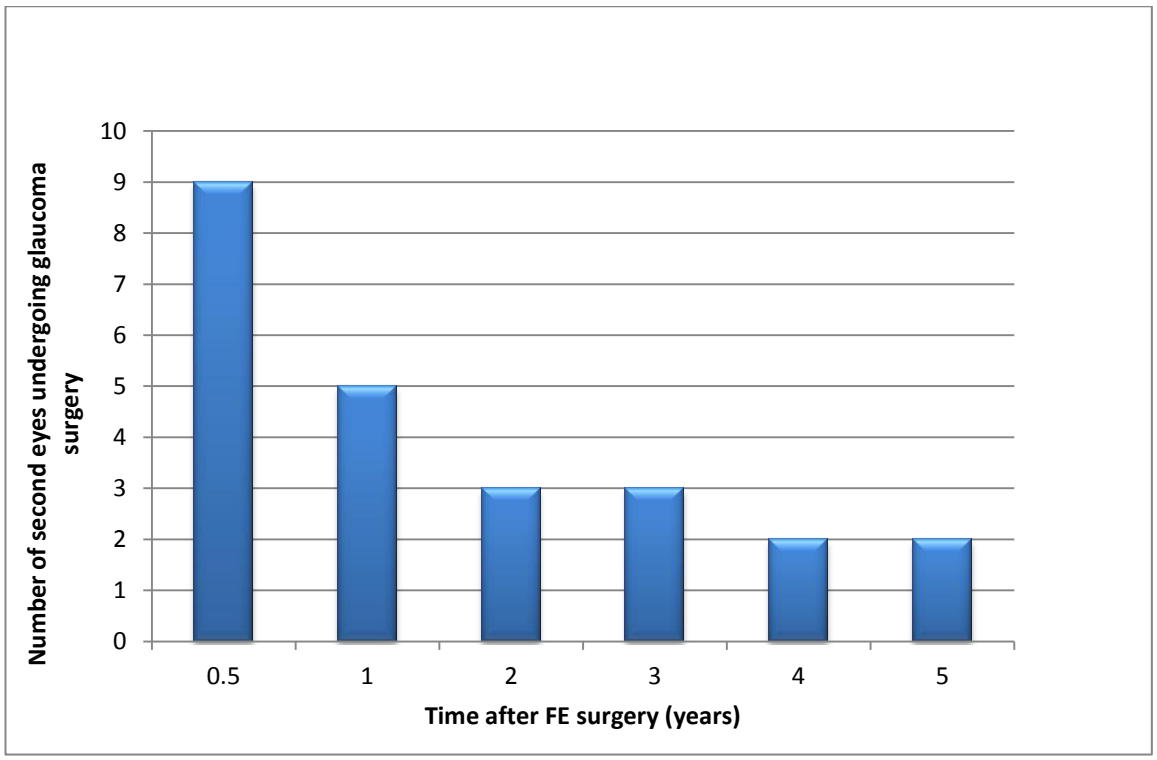

Figure 35: The distribution of second eyes according to the time of surgery after the first eye surgery.

4 SEs (13%) had surgery within 1 month from the FE surgery, 2 eyes (6.7%) had it after 2 months, 3 eyes (10%) after 3-6 months, 5 eyes (16.7%) after 6-12 months, 4 eyes (13.3%) after 2 years and 2 SEs (6.7%) had surgery after 3, 4 and 5 years respectively (Figure 35).

The time between the two surgeries was variable, with about 30% of the SEs having surgery within 6 months after the first surgery (Figure 35). However, it was not so much that the SE IOP goes higher but that with acetazolamide withdrawal following the first surgery, the IOP in the SE goes back to what it was for the time period before the SE surgery. As seen in Table 34, the distribution of IOP in the FE and SE was similar. In SEs which had surgery 6 months after the FE surgery, there was delayed IOP elevation or initial IOP elevation could be controlled with medication.

5.5.2 Postoperative outcome

5.5.2.1 Visual Acuity

While there was no eye with light perception vision preoperatively, 2 FEs had final VA of light perception. The underlying causes were advanced GON alone and a dense cataract in each eye. These eyes were not included in the calculation of logMAR BCVA. The eye that had PL vision due to advance GON had logmar VA of 0.8 (6/36) preoperatively and a postoperative follow-up period of 5 years.

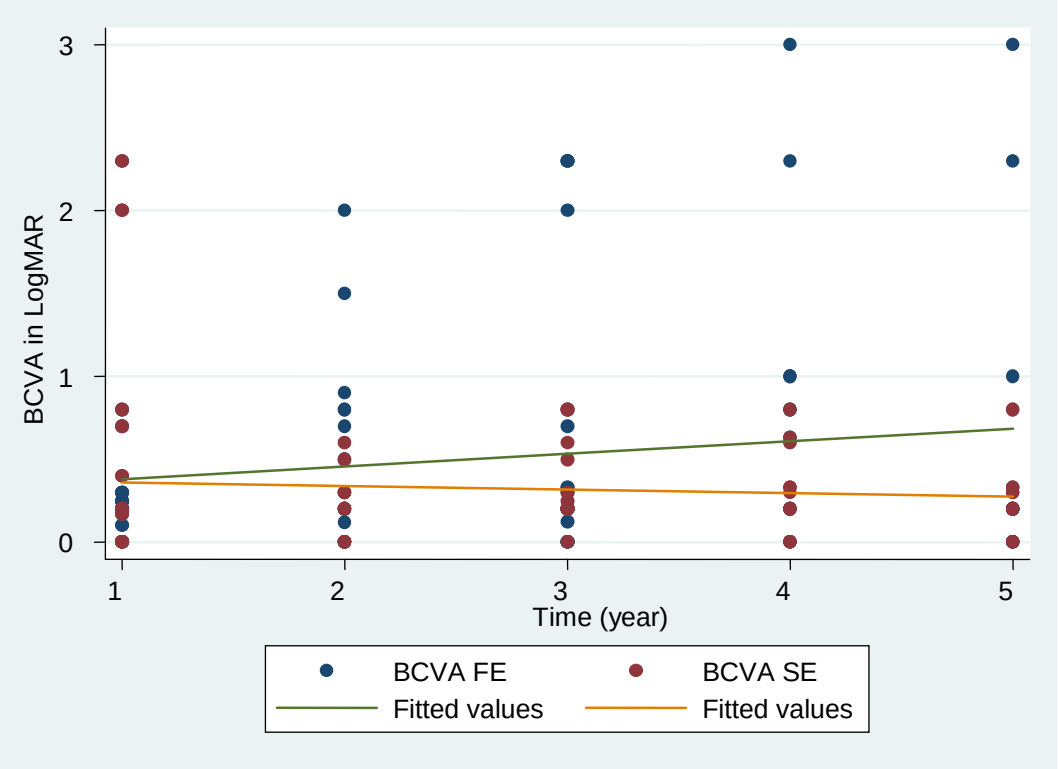

Figure 36: Distribution of the Logmar BCVA across the first 5 years following glaucoma surgery.

BCVA = Best corrected visual acuity, FE = First eye, SE= Second eye.

Figure 36 demonstrates the distribution of the logMAR BCVA within the first 5 years following glaucoma surgery. The regression line suggests that the LogMAR BCVA seemed to be improving in the FE and worsening in the SE. To estimate the rate of average logMAR BCVA change over the first 5 postoperative years, a linear mixed

model of average logMAR BCVA was fitted with the postoperative years as the independant variable and the FE and SE nested within patients. The estimated mean rate of progression was 0.02 logMAR per year and this was found to be not statistically significant (Coefficient estimate 0.02, p=0.38, 95% CI -0.026 – 0.07). Estimation of individual groups of eyes revealed the estimated mean rate of progression in the FE was 0.05 logMAR per year (coefficient estimate 0.052, p=0.143, 95% confidence interval -0.018 – 0.122) and the estimated mean rate of progression in the SE was -0.02 logMAR per year (coefficient estimate -0.02, p=0.473, 95% confidence interval -0.076 – 0.035)

In general, there was neither a significant difference in the median logMAR BCVA preoperatively and at the final visit (0.3 vs 0.2 respectively, p=0.4) nor was there any significant difference in the distribution of FE and SEs with impaired and poor vision preoperatively. However, at the final visit, there was significantly more FE with poor vision and more SE with impaired vision, p=0.02 (Table 35).

Table 35: Comparison of study outcomes between the first and second eye before surgery and at the final visit.

Study outcome	Before surgery			At final visit		
	FE, n=30	SE, n=30	p	FE, n=30	SE, n=30	p
BCVA in logMAR, median	0.3	0.2	0.43$^{\Omega}$	0.2	0.3	0.47$^{\Omega}$
BCVA, no. of eyes (%)						
≥ 6/15	8 (26.7)	6 (20.0)		4 (13.3)	13(43.3)	
≥ 6/60	1 (3.3)	4 (13.3)	0.47§	5 (16.7)	1 (3.3)	0.02§
CDR ≥0.7, no. of eyes (%)	19 (65.5)	13(44.83)	0.12‡	19 (65.52)	16 (55.2)	0.42‡
Highest IOP, mean ± SD (mmHg)	43.1 ± 7.7	40± 8.7	0.15	12.3±4	14.5±7	0.2

$^{\Omega}$ Mann Whitney test, § Fisher's Exact Test, ‡Chi square Test, BCVA: Best Corrected Visual Acuity, FE= first eye, SE= second eye, CDR=Cup to Disc Ratio, IOP=intraocular pressure.

Of the eyes with final BCVA poorer than 6/60 (n=6), only one eye was exclusively due to advanced GON. The rest was due to hypotonous maculopathy following glaucoma surgery and related to low IOP, choroidal neovascular membrane at the macula, combination of aphakia, band keratopathy and advanced GON and a dense cataract (n=1 respectively).

5.5.2.2 Optic disc appearance

Two eyes were excluded in the analysis of optic disc appearance because the optic disc was obscured by a dense cataract and band keratopathy (1 eye each) at the final visit. Among eyes where the optic disc was visible (n=58), 32 eyes (55.2%) had CDR>0.7 preoperatively. This number increased by 3 eyes (9.4% increment) at the last visit and this increase occurred in the SE (3/13 eyes, 23.1% increment). However, the number of FE and SE with CDR≥0.7 at the final visit was not statistically different because of the small number of eyes.

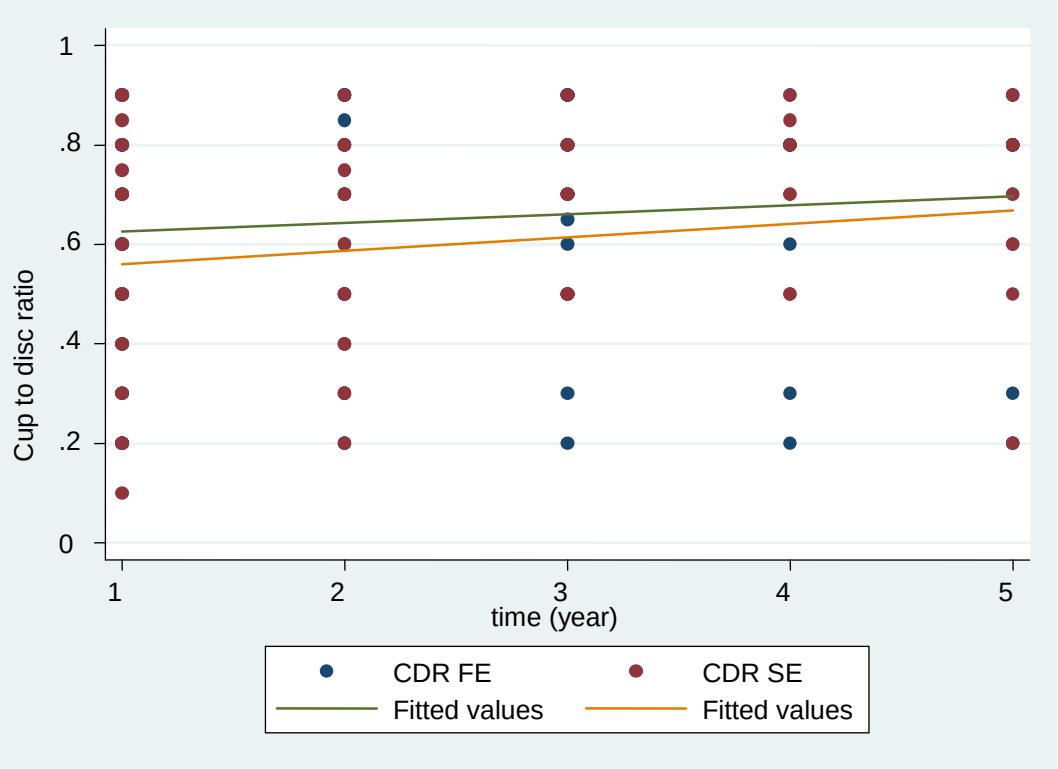

Figure 37: Distribution of the state of the cup to disc ratio in the FE and SE within the first 5 years after surgery. CDR = cup to disc ratio, FE = first eye, SE= second eye.

Figure 37 shows that the state of the CDR in the FE and SE is widely distributed but the regression line is somewhat parallel between the two. A linear mixed model analysis revealed no significant CDR progression between the FE and SE within the first 5 years postoperatively (mean CDR 0.6, coefficient estimate 0.006, p=0.443, 95% CI -0.01-0.02).

To cater for the variability in reporting CDR between observers in the clinic, progression of the CDR was considered present when the ratio was reported as increasing by 0.2 or more. With this definition, 5 eyes progressed within a period of 5 years postoperatively which was 2 FEs and 3 SEs. Although it appeared from the Kaplan-Meier graph in Figure 38 that the rate of CDR progression is higher in the SE, a log rank test revealed no significant difference in the overall CDR progression between

the FE and SE, p=0.34. The survival rates of CDR progression in the FE and SE at 1, 2 and 5 years were 100% and 96.1%, 95.8% and 91.6%, 89% and 68.7% respectively (Figure 38).

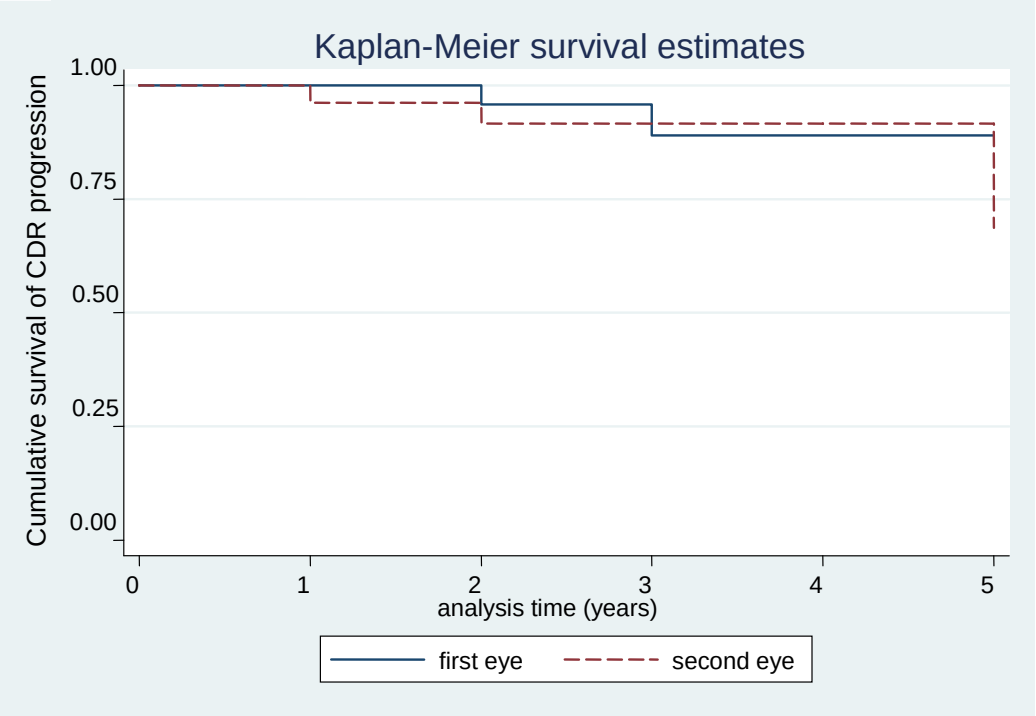

Figure 38: Kaplan Meier graph showing the difference in cumulative survival risk of CDR progression between the first eye (FE) and second eye (SE).

5.5.2.3 Intraocular Pressure and IOP lowering treatment

The mean IOP reduced from 33.2 mmHg at the time when decision for surgery was made (while on MTMT) to 14.0 mmHg at one year postoperatively, resulting in a mean decline of 19.5 mmHg after one year (57.8% reduction, p<0.001). This reduction was more in the FE (from a mean of 35.2 ±12.2 mmHg to 12.6 ±4.5 mmHg, 64.2% reduction), than the SE (from a mean of 31.4 ±9.2 mmHg to 15.25 ±7.8 mmHg, 51.4% reduction) at 1 year postoperatively. However, the IOP in the FE and SE at 1 year

postoperatively (p=0.23) and at the final visit (12.7 ±5.4mmHg vs 14.1±7.0 mmHg in the FE and SE respectively, p=0.4) was not statistically significant.

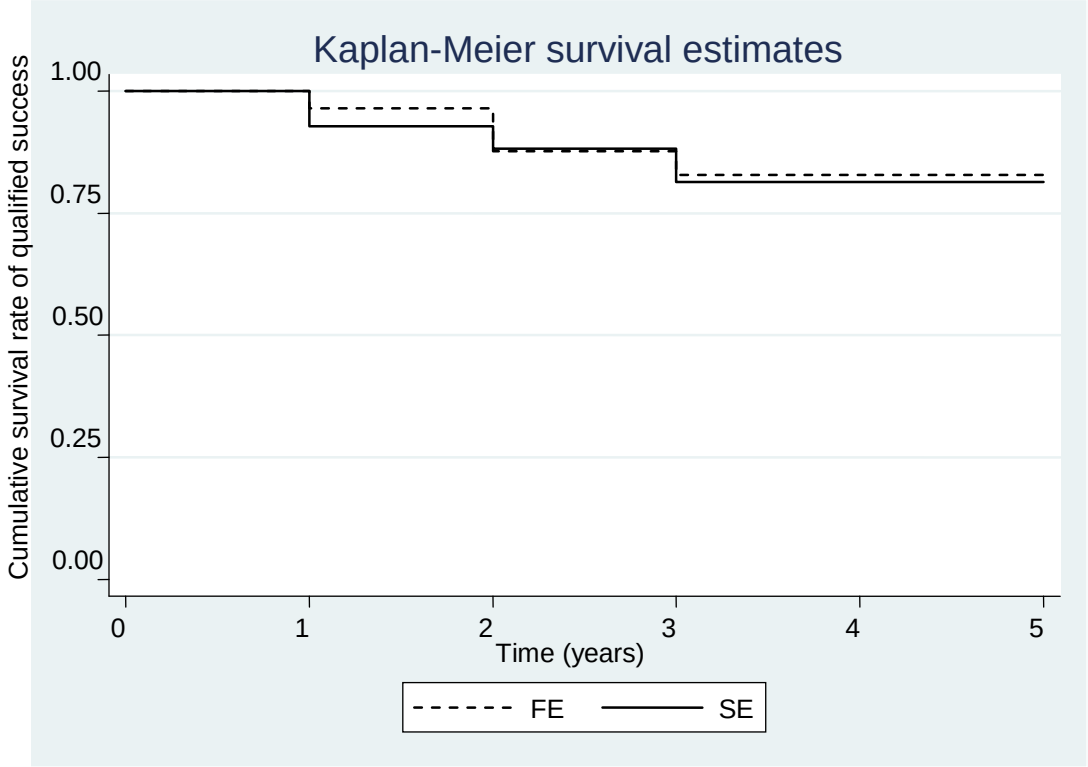

Figure 39: Kaplan-Meier graph comparing the cumulative survival rate of qualified success between the first eye (FE) and second eye (SE).

The overall qualified success at 1 year postoperatively was 92.5% and unqualified success (without drops) was 73%.There was no significant difference in the survival rates of qualified success between the FE and SE, p=0.86. The survival rates of the FE and SE at 1, 2 and 5 years were 96.4% and 93%, 87.6% and 88.2%, 83% and 81% respectively (Figure 39). There was also no significant difference in the survival rate between SEs that had surgery within 6 months or after 6 months post FE surgery (Figure 40).

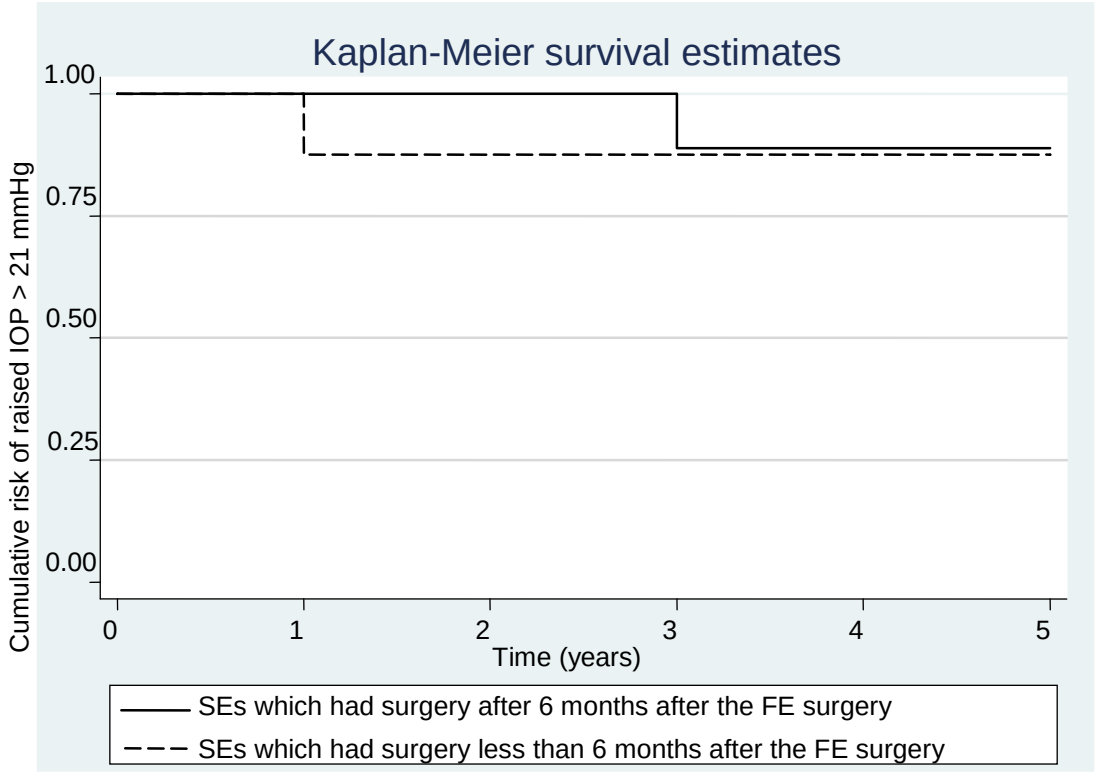

Figure 40: Kaplan-Meier graph comparing the cumulative risk of IOP > 21 mmHg between the second eyes (SE) that had surgery within 6 months or more than 6 months after surgery on the first eye (FE).

Among the eyes that had surgery within the first few months after the first surgery, bilateral surgery was pre-planned to be done within a short period from each other because uncontrolled IOP was anticipated as the IOP in both eyes were equally high at the time of the FE surgery. In patients that had delayed surgery in the SE, IOP increased one at a time in each eye, with uncontrolled IOP initially in the FE warranting glaucoma surgery. After many years, IOP in the SE starts to increase, perhaps because enough trabecular meshwork damage has occurred or the patient has received steroids high enough to cause uncontrolled IOP. Therefore, the SE had its surgery later on. In the FEs that developed complication, SE surgery was also delayed.

Cox regression analysis was performed to evaluate the risk factors for surgical failure (IOP >21 mmHg) within the first 5 postoperative years. Factors included were the patients' age at the time of surgery, number of preoperative drops and the state of the

lens at the time of surgery (whether phakic or pseudophakic/aphakic). The type of glaucoma surgery (whether trabeculectomy or GDI) was not a significant factor (Hazard ratio, HR 1.3, p=0.7) and therefore was not included. After adjusting for the other factors, the risk of failure reduced by 37.7% with every 10 years increase in age (adjusted HR=0.623, p=0.04, 95% Confidence Interval 0.39-0.99). The number of preoperative glaucoma drops and the state of the lens at the time of surgery was not found to be a significant factor for surgical failure in this model.

At the final visit, 34 eyes (53.1%) had IOP ≤ 12 mmHg and 4 eyes (6.25%) had IOP ≥ 21 mmHg. A total of 28 eyes (43.7%) were on hypotensive agents, 6 eyes were on one, 7 eyes on two, 10 eyes on three and 5 eyes on four agents. Twelve out of 41 trabeculectomy eyes (29.3%) had to undergo a secondary procedure, either a revision of trabeculectomy or implantation of a GDI with or without 5-Fluorouracil and betnesol injection. Hypotony occurred in 12 eyes (18.7%) in which 1 eye had intravitreous haemorrhage and 1 eye had to undergo reformation of anterior chamber with viscoelastic substance.

A multivariate logistic regression analysis revealed trabeculectomy in aphakic or pseudophakic eyes were 4 times more likely to undergo a secondary procedure compared to phakic eyes after adjusting for age (OR 4.5, p=0.04, 95% confidence interval 1.1-19.6). The number of preoperative glaucoma drops was not found to be a significant risk factor and was therefore not included in this model.

5.5.2.4 Visual Field Analysis

Of the 30 patients, 23 had sufficient VF tests for analysis, with a mean of 6.5 tests per patient (range: 3 to 15 tests).

Overall, there was no significant difference between the mean number of progressed points preoperatively (0.17 points, range 0-3) and at the final visit (0.63 points, range 0-11), p=0.28. The SE showed progression in 5 patients (21.7%), the FE progressed in 1 patient (4.3%) and no progression occurred in either eye in 17 patients (74%) at the final visit. In the SEs that progressed, the median number of progressed points was 5 locations (range 1 to 11 points) with a mean local slope reduction of -1.74 ± 0.45 dB/year (range -2.39 to -1.26). There was no significant difference in the mean reduction of the global slope between the FE and SE postoperatively (-0.75 ±0.6 dB/year and -0.9 ±0.4 dB/year respectively, p=0.83).

A multivariate linear regression was performed to determine the risk factors for local and global slope progression. The factors examined were the occurrence of hypotony and the highest IOP reading after surgery. We found no association between the local and global slope progression with the risk factors, possibly because of the small number of eyes that progressed (Table 36 and Table 37).

Table 36: multivariate linear regression examining the risk factors for global slope progression

Variable	Regression coefficient	Standard error	p	95% confidence interval
Maximum IOP	0.02	0.04	0.65	-0.07 – 0.11
Hypotony	-0.43	0.82	0.61	-2.1 – 1.3
Duration of follow-up (years)	0.05	0.04	0.18	-0.02 – 0.13

Table 37: multivariate linear regression examining the risk factors for local slope progression

Variable	Regression coefficient	Standard error	p	95% confidence interval
Maximum IOP	0.04	0.05	0.6	-0.62 – 0.7
Hypotony	-0.67	1.4	0.7	-18.1 – 16.8

However, hypotony was significantly associated with the number of progressed points in the Humphrey VF. After adjusting for the maximum IOP and duration of follow-up, hypotony causes an increase in the number of progressed points by 0.7 points (Table 38).

Table 38: multivariate linear regression examining the risk factors for the number of progressed points.

Variable	Regression coefficient	Standard error	p	95% confidence interval
Maximum IOP	-0.004	0.02	0.8	-0.04 – 0.03
Hypotony	0.68	0.33	0.046	0.01 – 1.34
Duration of follow-up	-0.007	0.015	0.648	-0.39 – 0.02

5.6 Discussion

This study was performed to answer the question of whether cessation of oral acetazolamide following glaucoma surgery of the FE may have led to prolonged and severe IOP elevation in the SE and therefore more glaucoma progression in the SE compared to the FE. It involved relatively young uveitic patients (mean age 39 years) which might have developed elevated IOP as a complication of chronic uveitis or corticosteroid treatment. There was a slight female preponderance and nearly half of the patients had anterior uveitis and a quarter of the patients had intermediate and

posterior/panuveitis respectively. There was a wide range of follow-up which may influence some of the progressions seen in these patients.

In 70% of the second eyes, raised IOP requiring glaucoma surgery occurred 6 months after the first surgery suggesting that IOP elevation may not occur early in the SE upon cessation of oral acetazolamide. Furthermore, it did not result in a higher preoperative maximum IOP in the SE compared to the FE as the highest preoperative IOP and the range of elevated IOP were not statistically different between the two groups of eyes. Although about 60% of FEs had CDR > 0.7 preoperatively, as opposed to approximately 40% of SEs, the distribution of the eyes according to the IOP level or the state of the CDR were not statistically different at the time of their respective surgeries.

While there was no difference in the distribution of the FE and SE preoperatively with regards to the proportion of eyes with impaired or poor vision, the proportion of FE with poor vision and SE with impaired vision was significantly more compared to their fellow eye at the final visit. It appeared that there was a dynamic shift in visual acuity in individual eyes representing the ever changing effect of uveitis on the visual acuity. The causes may include occurrence and removal of cataract and the occurrence and resolution of CMO or vitritis. As a result, there was no significant net change in the rate of visual acuity progression within the first 5 years postoperatively as estimated by linear mixed model. Additionally, we found the reason for poor vision in the final visual acuity was a combination of the effect from glaucoma and uveitis. Our final mean BCVA (0.37) scored slightly better than the final BCVA of another study comparing the long term outcome of trabeculectomy between uveitic glaucoma and POAG (final BCVA 0.45 and 0.46 respectively). (Iwao et al., 2012) However, 2 eyes with light

perception have been excluded from the logMAR calculation in our study, since it was not considered a form vision, which might contribute to the better final BCVA.

A few findings may suggest that there was more progression in the SE than the FE. For example, the number of eyes with CDR >0.7 increased by 23.1% in the SE (Table 35) and progression of CDR occurred earlier as shown by the Kaplan Meier graph (Figure 38). However, because of the small number of affected eyes, statistical analysis did not reach significance. Likewise, linear mixed model analysis did not show a significant change in the rate of CDR progression in the first 5 postoperative years.

Unlike primary glaucomas, surgery is performed in uveitis for IOP control, even if the optic disc was not glaucomatous. (Kok and Barton, 2002) This is often the case as the IOP can continue to rise despite MTMT because of the persistent application of steroids to maintain uveitis inactivity. In some cases, there was long term dependency on systemic CAI. Nevertheless, this also indicates that progressive glaucomatous damage is in fact occurring both anatomically (increase in eyes with CDR>0.7) and functionally (increase in number of progressed points on VF test) after surgery, more in the SE than the FE.

Our mean preoperative IOP while on MTMT (33.2 mmHg) was comparable to the 33.7 mmHg mean preoperative IOP in a study on long-term outcome of trabeculectomy in 101 uveitic eyes (Iwao et al., 2012), although our patients had more preoperative drops (3.1 drops) than their study (2.86 drops) and more patients were prescribed oral acetazolamide (75%) compared to their study (66.3%). This could denote that medical treatment may only reduce the elevated IOP (either due to uveitis or steroid treatment) up to a certain level in patients that need glaucoma surgery. Among reasons for this is probably, this group of patients may fall into the “high responder”

group of steroid responders as reported by Armaly.(Armaly, 1965) Nearly 67% of eyes in our study had insufficient IOP control (IOP >21 mmHg) prior to surgery whilst on MTMT, comparable to the 60% reported success of non-surgical treatment in children with uveitis. (Heinz et al., 2009)

In general, glaucoma surgery in our study resulted in a mean IOP reduction by 57.8%, slightly lower than that reported in other studies involving uveitic eyes (59%) (Chawla et al., 2012) but higher in those of non-uveitic eyes (40%). (Folgar et al., 2010) This difference is because of the difference in the definition of preoperative IOP used. The first study used the highest IOP reading whereas the second study took the average of all IOP readings preoperatively. We chose to use the preoperative IOP while on MTMT to determine IOP reduction from surgery alone and not from a combination of medical therapy and surgery. Although the reduction was slightly more in the FE (64.2%) than SE (51.4%), the mean IOP at 1 year postoperatively and at the final visit was not statistically different. The mean number of preop drops was 3.1 drops with about 40% of eyes had 4 drops. All patients received oral acetazolamide prior to the first surgery which was stopped immediately after the first surgery. The difference in the period between the first surgery and second surgery did not have any effect on the surgical success in the SE with the SE showing comparable survival rates of qualified success with the FE within the first 3 years postoperatively (Figure 39).

Although there was no difference in the survival rates of qualified success between the FE and SE, the rates steadily decreased in both eyes within the first 5 years. As a result, glaucoma progression can be seen as a steady decrease in the survival rates of CDR progression, more in the second eye than the first, although this does not translate

into significant VF progression both in the local and global slope of pointwise linear regression as determined by the Progressor software.

Although IOP is not the only factor for glaucoma progression, it is the most important and the only modifiable factor. IOP reduction is the only proven intervention to slow or stop glaucoma progression. The Early Manifest Glaucoma Trial is one of the largest randomized controlled trials to show that effective IOP reduction with non-surgical intervention has resulted in a significant decrease in the number of eyes that progressed.(Heijl et al., 2002) Greater IOP reduction can often be achieved with surgery when medical therapy is insufficient. IOP reduction achieved with surgical intervention may not be enough to cease VF progression as IOP fluctuation has also been identified as a risk factor for VF progression especially in advanced glaucoma and low mean IOP. (Bhandari et al., 1997)(Hong et al., 2007)(Caprioli and Coleman, 2008) In our study, about 20% of eyes had postoperative hypotony. A multivariate linear regression was unable to demonstrate an association between the global and local slope progression of the VF with either the occurrence of hypotony or the maximum IOP reading after surgery, probably because of the small number of eyes that progressed. However, hypotony was the only significant risk factor found to be associated with increase in the number of progressed points.

The final IOP was <12 mmHg in 53.1% of eyes and >21 mmHg in 6% of eyes. About 44% of the eyes had to be on drops for sufficient IOP control. Qualified success at 1 year postoperatively was 92.5% and unqualified success (without drops) was 73%. This is comparable to a study by Chawla et al who reported 90.3% and 71% of qualified and unqualified success respectively at 1 year post trabeculectomy on adult uveitic patients.(Chawla et al., 2012) Although there was no difference in the survival rates of

qualified success between the FE and SE, the rates steadily decreased in both eyes within the first 5 years. As a result, glaucoma progression can be seen as a steady decrease in the survival rates of CDR progression, more in the second eye than the first, although this does not translate into significant VF progression both in the local and global slope of the point wise linear regression as determined by the Progressor software.

While the use of multiple hypotensive agents preoperatively and the state of the lens (aphakia/pseudophakia) were found to be responsible for a higher failure rate in non-uveitic glaucoma surgery,(Broadway and Chang, 2001) we found no association between them and the odds of surgical success in uveitis. It could be that success of glaucoma surgery in uveitis is influenced by many other factors different to those in non-uveitic glaucomas. On the other hand, we found younger patients were more likely to develop surgical failure, again possibly because younger people are inherently more likely to be high responders to steroid, (Lam et al., 2005) which would still be needed after glaucoma surgery for uveitis control, or because of their propensity to scar up more easily compared to the elderly. However, because surgical success only takes into account the IOP at a given time, other bleb saving procedures were not demonstrated as surgical failures. When assessing for risk factors for a secondary procedure, we found that aphakic or pseudophakic eyes were 4 times more likely to require a secondary procedure.

The drawbacks of analysis of VF progression in our cohort of patients were that the number and interval of VF between patients were unequal which may fail to demonstrate the true VF progression. Analysis in our study is best done with the Progressor software which allows inclusion of all available visual fields by using the

Gaussian filter and also assessed VF progression by looking at the trend rather than the event of progression. Even so, we found no significant difference in the mean number of progressed points preoperatively and at the final visit. Additionally, analysis with the software showed no progressed points in about three quarter of patients. In eyes that did progress, the global rate of progression was more in the SE than the FE postoperatively albeit an insignificant difference. The SE progressed in 5 patients as opposed to 1 patient with FE progression. The mean number of progressed points in our study (0.63 points) was far more from the one reported by Fulgar et al. (Folgar et al., 2010) (0.07 progressed points)in a study involving 28 patients with a mixture of POAG, angle closure glaucoma and pseduexfoliation glaucoma. Again, this higher figure of progressed VF points in our cohort of patients could be attributed to other pathologies related to uveitis, such as retinal and macular scars, apart from severe GON. Even if we have achieved comparable IOP reduction with previous studies, our patients still eventually loses vision.

Although the SE showed more progressed points than the FE, there was no significant difference in the mean reduction of the global slope between the FE and SE. We could not isolate the risk factors for local or global progression due to the small number of affected points.

Consistent with recommendation by previous reports, trabeculectomy was the primary surgical procedure in nearly 70% of eyes in our study. Trabeculectomy is the surgical procedure of choice in phakic uveitic patients with no previous intraocular surgery and no added risk of failure such as anterior segment neovascularization. (Kok and Barton, 2002) GDI is recommended in aphakic and pseudophakic patients, especially those with JIA-related uveitis, previous trabeculectomy failures or other risk factors for

trabeculectomy failure. (Kok and Barton, 2002) (Ceballos et al., 2002b) Some studies however have reported comparable success rate of trabeculectomy with mitomycin C in uveitic glaucoma and POAG. (Kaburaki et al., 2009) In our cohort of eyes, more trabeculectomies were performed than GDI. However, almost 30% of trabeculectomized eyes required a secondary procedure, either revision of trabeculectomy or GDI implantation after a failed trabeculectomy. Trabeculectomy in aphakic and pseudophakic eyes were 4.5 times more likely to need these procedures compared to phakic eyes in our study. Postoperative hypotony occurred in 16% of our patients, slightly lower than the figure quoted by previous studies on uveitic eyes (19.4%).(Chawla et al., 2012) We found younger age to be a significant risk factor for surgical failure, in agreement with previous studies (Broadway and Chang, 2001) .

Traditionally, trabeculectomy with an antifibrotic agent has been the initial procedure in patients with glaucoma who have failed medical and/or laser therapy, and GDI only comes into play when trabeculectomy fails. (Chen et al., 1997)(Joshi et al., 2005) Therefore, the success rate of GDI would be expected to be limited because of the refractory nature of the patients' eyes following one or more failed filtering surgeries. However, there has been increasing evidence in recent years that GDI may be the initial procedure of choice over trabeculectomy because of the dreaded complications of trabeculectomy such as bleb-related infections, bleb leaks and bleb dysthesia. (Nguyen, 2009)

The tube versus trabeculectomy (TVT) study assessed the safety and efficacy of a 350 mm^2 Baerveldt glaucoma implant (Advanced Medical Optics, Irvine, California, USA) over trabeculectomy with MMC in a multicenter randomized clinical trial. (Gedde et al., 2005) (Gedde et al., 2007) The trabeculectomy group had lower IOPs than the tube

group during the first 3 months postoperatively possibly because the non-valved Baerveldt implants does not start functioning until 1-3 months because of temporary restriction to allow the fibrous capsule formation to encapsulate the plate for resistance. However, at 1 year, the cumulative probability of failure was 3.9% in the tube as opposed to 13.5% in the trabeculectomy group. Furthermore the mean IOP achieved in the GDI group was 12.4mmHg, disputing the notion that low IOP levels could not be achieved by GDI. At 5 years of follow-up, tube surgery had a higher success rate compared to trabeculectomy with MMC (cumulative probability of failure 29.8% and 46.9% respectively) whereas trabeculectomy with MMC had higher rates of surgical failure and reoperation for glaucoma compared to tube surgery. The findings in the mentioned studies may pave the way for the use of tube shunts beyond refractory glaucomas.

With regards to whether oral acetazolamide should be stopped after trabeculectomy but not after tube surgery, the TVT study did not outline it as such but rather the use of intraoperative and postoperative medications was at the surgeons' discretion. (Gedde et al., 2005) The Ahmed Baerveldt Comparison study later suggested that because the Baerveldt tube is not valved and therefore aqueous outflow is not restricted, occlusion and stenting of the tube was recommended. (Barton et al., 2011) Occlusion of the tube in Molteno implants with the use of a vicryl tie technique has also been described. (Molteno et al., 1986) Inference could be made that oral acetazolamide then should also be stopped after GDI implantation to prevent hypotony, unless deemed otherwise by the surgeon. Our study agrees with this method of practice in which oral acetazolamide was stopped in trabeculectomy and tube surgery alike.

There is very little available reports in the literature on the outcome of mini tubes or shunts like the Ex-PRESS Mini Glaucoma Device for uveitic glaucoma, but anecdotal reports have found the mini shunts to be a good alternative to trabeculectomy or GDI.(Morales-Fernandez et al., 2012) (Rouse and Sarkisian, Jr., 2012) Others report a high incidence of complications arising from the use of these devices in advanced glaucoma cases.(Wamsley et al., 2004) The lack of at least a case series reporting its use in uveitic glaucoma may not establish its true efficacy and safety in uveitis.

The limitations of this study are mainly because of its retrospective design and small sample size. Estimation of the CDR is highly variable between different observers in the clinic and optic disc stereo-photograph, which is the gold standard for estimating progression, was not available in all patients. VFs were also performed at irregular intervals making standardization of VF progression difficult. However, the findings of this study are still relevant to illustrate the clinical outcome in patients with bilateral uveitis and raised IOP. This group of patients with recalcitrant IOP elevation does show glaucomatous progression in certain aspects even though sufficient IOP control was attained. The SE scored lower in a few aspects namely structurally (more SEs with CDR>0.7 at the final visit) and to a lesser extent, functionally (more progressed points and higher progression rate in those points). But because of its small sample size and wide range of follow-up duration, statistical significance was not achieved. A well designed long term prospective and multicenter study with sequential optic disc photographs might be able to demonstrate optic disc progression better and incease the sample size enough for a statistical significance to be reached. The findings in this study may help emphasize the importance of performing optic disc stereophotographs

as frequent as possible in this group of patients. It may also suggest that in some eyes, earlier glaucoma surgery may probably improve the prognosis of the second eye.

5.7 Summary

In conclusion, the SE scored lower than the FE as there was more SEs with impaired vision, more progressed points on Humphrey VF and more eyes with CDR≥0.7 at the final visit. However, there was no difference in the final logMAR BCVA, the final IOP and the final global field progression. Even when we attained sufficient IOP reduction and final IOP was comparable to other studies, some eyes still lost vision from glaucoma and the effects of uveitis.

6 Chapter 6: Conclusion and future directions

IOP elevation in uveitis is a very important complication in uveitis as it may lead to glaucoma and permanent visual loss. Early detection for glaucomatous changes in patients with uveitis and raised IOP is important especially in those who are at risk of glaucoma and visual loss.

6.1 Evaluation of the RNFL thickness in adult uveitic patients.

The first chapter addresses the possibility of utilising the OCT to detect glaucoma in uveitis. This issue was explored because detecting glaucoma in uveitis by means of optic disc assessment and VF changes is influenced by a number of conditions specific in uveitis, such as optic disc swelling affecting the evaluation of glaucomatous changes in the optic disc, CMO causing reduction in VF sensitivity and retinal scars from uveitis which can produce VF defect not attributable to glaucoma.

We used the Spectralis OCT which has been shown by many previous studies to be able to detect early signs of glaucoma, and has an excellent reliability and reproducibility by way of certain in-built features of the instrument such as the Tru-Track feature.

We have found that the RNFL is truly thicker in active uveitis and attaining quiescence has allowed RNFL measurement to refer to the in-bulit normative database for reference. The normal, non-uveitic contralateral eyes of patients with unilateral uveitis had a comparable mean global RNFL thickness to the normal population as reported by previous studies. We compared our normotensive uveitic with the control eyes and found significant thickening of RNFL in the uveitic eyes. The quiescent normotensive

uveitic eyes also had thicker RNFL although at a lesser degree. To minimise this thickening effect of uveitis, we excluded the actively inflamed eyes in the ensuing analysis.

We subsequently assessed the Uv-G eyes which acted as positive controls and determined what sort of RNFL changes we could find, so that we could look for those findings in the Uv-H group. We found that the RNFL in the Uv-G eyes was significantly thinner compared to the Uv-N eyes and this thinning was seen in all except the temporal quadrant. As opposed to studies on POAG which found the superior quadrant to be unaffected by glaucoma, we found the temporal quadrant instead to be unaffected in our study. This was of no surprise to us because the macula can be thickened in uveitis, the severe form being CMO, and the ensuing thickening of temporal quadrant which has a direct continuation with the macula via the papillo-macular bundle with the macula follows. The fact that previous studies have shown that even in anterior uveitis, the macula was found to be thicker compared to non-uveitic eyes, suggest that even in the absence of frank CMO, the macula can be subclinically thickened, and this could translate into thickening of the temporal quadrant of the periapillary RNFL as well. We therefore found the temporal quadrant escaped the thinning effect in our Uv-G eyes.

When examining the Uv-H eyes, we found significant RNFL thinning only in the inferior quadrant compared to the Uv-N eyes. We could not find any significant thinning in any other quadrants. We therefore proposed that RNFL thinning in the inferior quadrant may suggest early glaucomatous changes prior to any apparent clinical glaucomatous disc cupping or VF changes.

We then correlated the RNFL thickness in different groups of eyes with their clinical features taken from the medical records. Among the Uv-N eyes, age and active uveitis were two significant factors affecting the RNFL thickness. With every 10 years increase in age, RNFL thickness reduced by 3.4 μm. This is in contrast to the rate of RNFL loss found in the Control eyes in our study as well as the rate of RNFL loss reported in previous studies. Active inflammation on the other hand, increases the RNFL by 11.8 μm.

Among the uveitic eyes which had suffered IOP elevation (Uv-H and Uv-G eyes) we found that higher peak IOP and longer duration of follow up were significant factors for RNFL thinning.

We also looked into the risk factors for raised IOP (Uv-N vs Uv-H eyes) and of glaucoma (UvH vs Uv-G eyes). We found that male gender and anterior uveitis were two significant risk factors for raised IOP. A chi square test between gender and uveitis type however revealed that it was in fact the anterior uveitis which is the underlying cause for IOP elevation. This conclusion was made because the proportion of males in anterior uveitis was higher relative to the proportion in intermediate and posterior/panuveitis. A further evaluation of the subtypes of uveitis revealed that the proportions of males were significantly higher in Possner-Scholssman's Syndrome and JIA-related uveitis, both of which are primarily of the anterior uveitis type.

Assessment of the Uv-G eyes failed to isolate male gender as a risk factor for glaucoma. Instead, higher peak IOP and longer duration of follow-up were two significant risk factors for glaucoma. This agrees with the fact that, in secondary glaucoma like in uveitic glaucoma, glaucoma occurs because of prolong exposure to high IOP.

To assess how accurate the discriminating ability of the OCT to differentiate Uv-H and Uv-G eyes was, we calculated the AROC in the Uv-H and Uv-G eyes. We found that the superior and inferior quadrants were among the quadrants with high AROC values. Although the values were smaller, the quadrants agree with the findings in POAG eyes.

There are limitations in how much information can be derived from retrospective data like in this study. The lack of longitudinal data does not allow fundamental questions to be answered like how long after quiescence does it take for the RNFL thickness to return to baseline level, what effect does controlling inflammation with various drugs has on the RNFL, does treatment with IOP lowering drugs has any effect on the RNFL and so on. These questions can be answered in a well designed prospective study that can explore more of this aspect of uveitis.

6.2 IOP elevation in children with uveitis and its effect on the RNFL

The next part of the study looked primarily at the demographics and prevalence of IOP elevation and glaucoma in children with uveitis. Risk factors for IOP elevation and glaucoma was also isolated. RNFL assessments in these children were performed secondarily.

Approximately three quarter of patients had bilateral uveitis. IOP elevation occurred in nearly 40% of our patients, with a yearly prevalence of about 10-13% within the first 4 years after diagnosis. The cumulative probability of IOP elevation in individual eyes also increased with increase in follow-up, reaching a maximum of about 40% at 6 years.

The prevalence of raised IOP was significantly higher in chronic (35% higher) compared to acute uveitis. Anterior and intermediate uveitis formed a sizeable proportion of

acute and chronic uveitis respectively and therefore the onset of raised IOP occurred later in intermediate and earlier in anterior uveitis (Figure 26).

Similar to the adult population we also found male gender and chronic uveitis to be significant risk factors for IOP elevation in children. However, unlike in adults, we could not detect any association between male gender and the type or chronicity of uveitis in children.

Chronic uveitis was not only a strong risk factor for IOP elevation, but also a perfect predictor for glaucoma. Similar to adults, a higher peak IOP was also a strong risk factor for glaucoma and male gender again was no longer a predictor for glaucoma.

Topical hypotensive agents were required in about 80% of eyes with raised IOP at the onset of IOP elevation. Conversion of strong steroid to weaker ones did not necessarily result in controlled IOP with slightly more than 75% of eyes requiring topical hypotensive agents at the next follow-up. Oral CAI was added to topical agents in 44% of patients for additional IOP control, resulting in a further IOP reduction by a mean of 9.4 mmHg. About 75% of Uv-G eyes inevitably needed glaucoma surgery, while none of the Uv-H eyes had glaucoma surgery.

The causes of impaired vision (VA worse than 6/15) at the last visit was contributed for the most part by uveitis, with cataract and CMO as among the common causes of impaired vision. Visual impairment in 35% of Uv-G eyes was also contributed to a certain degree by glaucomatous optic neuropathy.

IOP elevation was steroid induced in about 90% of hypertensive eyes, occurring after a median duration of 6 months subsequent to starting steroids. However, the level of IOP elevation was not necessarily higher in earlier onset raised IOP. Peak IOP on the

other hand, was higher in uveitic-induced compared to steroid-induced IOP elevation. Chronic uveitis was a significant risk factor for steroid response after adjusting for the duration of follow-up.

Among eyes with steroid-induced IOP elevation, approximately 69% were high responders, 28% was intermediate and 3% were low responders. High responders were associated with younger age group, regional steroid injection and lower IOP at presentation. About 40% of high responders underwent glaucoma surgery.

We went on to analyse available RNFL scans in these children. Intermediate uveitis had the highest global RNFL thickness, which was significantly thicker than anterior uveitis. Similar to adults, actively inflamed Uv-N eyes had thicker mean global RNFL than quiescent eyes, which was in turn still thicker than control eyes. Subsequent RNFL analysis therefore excluded actively inflamed eyes.

Unlike in adults, we found significant RNFL thinning only in the inferior quadrant of Uv-G eyes and we could not find significant thinning of Uv-H eyes in any of the quadrants. However, comparison of quiescent eyes between Uv-G and Uv-H eyes revealed significant thinning in the naso-inferior sector of Uv-G eyes.

Active inflammation was associated with increased RNFL thickness notably in the inferior and temporal quadrant, whereas higher peak IOP was associated with reduction in the naso-superior and naso-inferior quadrant after adjusting for age and active uveitis.

Repeated measure analysis using linear mixed model did not detect any significant change in the global RNFL thickness within the span of 3 years in all groups of eyes. Refinement of the analysis however detected significant RNFL reduction over time in

the superior and temporal quadrants of the Uv-G eyes and the naso-superior quadrant of the Uv-H eyes.

A prospective study with sequential OCT scans at common intervals will be able to answer the question of what is the time taken for resolution of any RNFL thickening due to uveitis and what affects the time taken for the RNFL to normalize. Perhaps more severe inflammation will take a longer time and treatment of inflammation with corticosteroids may hasten the resolution of RNFL thickness. Utilising the OCT to monitor glaucoma progression can also be validated with a longitudinal study to demonstrate the causative effect of uveitis and IOP elevation on the optic disc. IOP readings at common intervals will also allow the duration of IOP elevation to be estimated which can in turn, be used to assess the effect of the duration of IOP elevation on the RNFL thickness as IOP readings taken in the variable clinic visits in this retrospective data may not reflect the true severity of IOP elevation. Using normal eyes from normal children as a control group and comparing it with the normal contralateral eyes of children with unilateral uveitis will not only determine whether there is subclinical RNFL thickening in the normal eyes of children with unilateral uveitis, but also a more desirable control group to be compared with. Performing a multicenter study will also boost the number of sample size especially the Uv-G group which is relatively small in this study which may influence the ability to generalise the results or conclusions to the general population.

6.3 Glaucoma progression in eyes after bilateral glaucoma surgery

The last part of the study aimed to answer the question whether delayed glaucoma surgery in the SE of patients with bilateral hypertensive eyes due to uveitis requiring bilateral glaucoma surgery, or stoppage of oral acetazolamide in the FE after glaucoma

surgery which may or may not result in prolonged IOP elevation in the SE, have any detrimental effect on the SE. The surgical success of glaucoma surgery was also determined.

Preoperatively, there was no difference in the distribution of the FE and SE in terms of the level of IOP elevation and the state of the CDR. In all patients, oral acetazolamide was stopped immediately after the FE surgery. This did not lead to a peak IOP in the SE any higher than the FE. The occurrence of IOP elevation in the SE varies with about 43% of SEs had it within the first year after the FE surgery. Consequently about 30% of the SEs had surgery within 6 months after the FE surgery.

Analysis of the logMAR BCVA suggest that it seemed to be worsening in the FE and improving in the SE but the mean rate of progression estimated by linear mixed model did not show any significant change within the first 5 years after their respective surgeries.

There was neither a significant difference in the median preoperative and final logMAR BCVA nor was there any significant difference in the distribution of FE and SEs with impaired and poor vision preoperatively. However, there was significantly more FE with poor vision and more SE with impaired vision at the final visit, with 2 FEs having final vision of light perception due to advanced GON and cataract. Other causes of poor vision were hypotonous maculopathy, choroidal neovascular membrane at the macula and a combination of aphakia, band keratopathy and advanced GON.

There was an increase in the number of eyes with CDR ≥ 0.7 preoperatively and at the final visit and the increase in number occurred in the SEs. However, the number of FEs and SEs with CDR ≥ 0.7 at the final visit was not statistically different. Again, a linear

mixed model did not detect any significant changes in CDR in the FE and SE within the first 5 years after their respective surgeries. Using the definition that the progression of CDR was considered present when the ratio was reported as increasing by 0.2 or more, 3 SEs and 2 FE progressed. The cumulative survival rates of CDR progression were higher in the FE than the SE at 1, 2 and 5 years although a log rank test did not detect any significance.

Glaucoma surgery resulted in approximately 60% reduction of IOP in our study, which occurred more in the FE than the SE at 1 year postoperatively. The overall qualified success was 92.5% and unqualified success was 73% at 1 year postoperatively. There was neither a significant difference in the survival rates between the FE and SE at 1, 2 and 5 years nor was there any significant difference in survival rates between SEs that had surgery within 6 months or after 6 months post FE surgery.

We found the risk factor for surgical failure within the first 5 postoperative years was younger age after adjusting for the number of preoperative hypotensive drops or the state of the lens at the time of surgery (whether phakic or pseudophakic/aphakic). The type of glaucoma surgery (either trabeculectomy or GDI implant) was also not a risk factor for failure. However, trabeculectomy in aphakic/pseudophakic eyes were 4 times more likely to undergo a secondary glaucoma procedure such as needling, a revision of trabeculectomy or secondary GDI implant after a failed trabeculectomy.

Analysis of available VFs using the Progressor software revealed no significant difference in the preoperative and final mean number of progressed points on the Humphrey VF test. More SEs showed point progressions than FEs although the local and global slope of progression was not significantly different between the two groups of eyes. We could not detect risk factors for the local and global slope progressions

possibly because of the small number of eyes that progressed, but hypotony was significantly associated with the number of progressed points after adjusting for maximum IOP and the duration of follow-up.

A prospective study with sequential optic disc stereograph will allow a proper assessment of the optic disc taking into account the CDR in relation to the disc size and other glaucomatous features to determine the presence of glaucomatous disc changes and its alteration over time. It will also ensure Humphrey VF tests to be performed before surgery and at regular intervals after surgery which will improve illustration of the rate and the risk factors for VF progression. This study also emphasized the importance of having optic disc stereographs done as a routine in clinic visits to properly establish GON progression as visual acuity and VF changes may be affected by uveitic changes alongside GON.

In conclusion, we have been able to isolate patient and ocular risk factors for IOP elevation and glaucoma. We also demonstrated what sort of RNFL changes could be seen in hypertensive uveitic eyes and glaucomatous uveitic eyes. This subgroup of patients who are at a higher risk of glaucoma may benefit from regular monitoring of glaucomatous changes by means of peripapillary RNFL measurement to ensure that early and aggressive treatment can be instituted to control both inflammation and elevated IOP.

6.4 Limitations

The assessment of data from retrospective studies is inherently subject to limitations. The lack of data on pachymetry measurements in our cohort of patients limits the validity of this study because although we have excluded patients with frank corneal edema, IOP measurement with the Goldman Applanation Tonometer is influenced by corneal thickness. (Park et al., 2012) Because of the varied intervals in between visits, the exact duration of elevated IOP in serial measurements could not be determined. Additional information such as gonioscopic findings and sequential OCT scans may help in answering vital questions such as the time for the RNFL thickness to return to baseline after an attack of uveitis and the outcome of IOP elevation from chronic uveitic changes to the angle, which are beyond the scope of this retrospective study.

Both eyes of the patients were included in this study. Systemic factors like systemic uveitis and systemic steroid treatment might have similar effect to both eyes as opposed to localized ocular inflammation. Furthermore, taking the contralateral normal eye of a patient with unilateral uveitis may not entirely fulfil the criteria of control eyes. The ideal study would be to take only one eye per patient and to include eyes from normal individuals as the control group, instead of taking the contralateral normal eyes of patients with unilateral uveitis.

As the technology of OCT has progressed, so has the accuracy of RNFL measurements in glaucoma. Ever since this study was concluded, a lot of progress has been achieved especially the new glaucoma module introduced by Heidelberg in 2013. The BMO-based minimum rim width measurement has been found to be more accurate in determining an identifiable anatomical border of the rim and it takes into account the

varying geometry at the point of measurement. (Chauhan et al., 2013) The software module also includes a new Anatomic Positioning System (APS) for the SPECTRALIS that accurately places all OCT-scans relative to the position of the fovea and Bruch's Membrane opening (BMO). The lack of normative database of the spectralis OCT in children also limits the clinical application of the findings in this study and to come to a meaningful conclusion.

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Appendix 1

Poster presented at the Annual Congress, Royal College of Ophthalmology, Liverpool, May 2012.

Identification of a subgroup of uveitic patients at risk of visual loss from glaucoma

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Introduction

Glaucoma is ranked as the third most common complication in uveitis patients after cystoid macular edema and cataract, but while the other two are potentially reversible, glaucoma is an insidious and often overlooked complication of uveitis and associated with irreversible and worse visual outcome [1] .

The prevalence of intraocular pressure (IOP) elevation in uveitic patients requiring treatment has been reported to be between 29.8 to 41.8% after a mean follow-up period of 7.5 years [2]. Elevated IOP is commonly seen in chronic uveitis, increasing age and longer duration of uveitis [2].

Many patients with uveitis have ocular hypertension (OHT) with raised IOP but normal optic discs and visual field. Optical coherence tomography (OCT) gives an in-depth cross-sectional measurement of the retinal nerve fiber (RNFL) thickness around the optic disc, changes of which may precede those detected by conventional visual field testing [3].

We aimed to see whether patients with uveitis and OHT could be subdivided into those that have changes to the nerve fiber layer on OCT and may be at greater risk of developing glaucoma and those that do not. We then looked at disease features associated with nerve fiber layer loss in those where it was present.

Methods

Ethical approval was obtained from the Research Governance Committee of Moorfields Eye Hospital (protocol Vision loss in uveitis I LIGS1021). This cross-sectional study involves measuring the RNFLthickness using the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) with circular scans located 3 mm from the center of the optic disc of eyes with uveitis and history of elevated IOP above 21 mmHg on at least 2 occasions, but clinically normal optic disc and visual fields (termed secondary ocular hypertension (sOHT). The thickness was compared to uveitic eyes with IOP elevation and glaucomatous optic neuropathy (uveitic glaucoma, UG). Data was analysed using GraphPad Prism 5 for Windows and SPSS version 13. Chi square test was used for all categorical data and t test was used to compare means. Mann Whitney U test was used to compare the means of non-parametric data.

Results

Two hundred eyes from 291 patients with uveitis were included. One hundred and nineteen eyes were categorized as sOHT and 81 eyes as UG (by visual fields testing and optic nerve examination).

In both the sOHT and UG group, approximately 80% of eyes were steroid responders and the remaining 20% had hypertensive uveitis as the cause of elevated IOP.

Eyes with UG had a longer duration of follow-up, higher number of IOP spikes and higher maximum IOP compared the sOHT group.

Table 1: IOP profile in sOHT and UG

	sOHT	UG	p value
Mean duration of follow-up (years)	6.793	9.401	0.0015(t-test)
Steroid responders (% eyes)	84.6	87.4	0.521 (chi2)
Hypertensive uveitis (%eyes)	15.4	16.8	
Mean frequency IOP elevation	5.73	7.45	0.0133
Mean Max IOP ever attained during follow up	35.04mmHg	40.01mmHg	<0.0001

Table2: Analysis of eyes with sOHT

g	Abnormal OCT	normal OCT	p value
No of eyes	26 (21.8%)	93 (78.1%)	
Type of uveitis (no of eyes)			
Ant uveitis	11	31	0.357 (Fisher Exact test)
Int uveitis	9	46	
Post uveitis	1	3	
Pan uveitis	5	13	
Mean duration of follow-up	7.93years	6.46 years	0.097 (t-test)
Mean no. of IOP elevation	8.1 times	4.9 times	0.003 (Mann Whitney test)
Mean highest IOP	44.65 mmHg	34.4 mmHg	0.0002 (Mann Whitney test)
Steroid responder (%of eyes)	75%	87.3%	
Hypertensive uveitis (%of eyes)	25%	12.7%	0.06(chi square)

We further analyse the subgroup of eyes with sOHT and abnormal OCT results. Eyes with RNFL thinning had a longer duration of follow-up, more number of IOP elevation, higher maximum IOP and hypertensive uveitis. The type of uveitis is not associated with RNFL thinning. (Table2)

Discussion

In eyes with uveitis and elevated IOP, preperimetric glaucoma changes seen as RNFL thinning on OCT scanning is about 22%. These eyes seems to have similar clinical features as those with established glaucoma, which are longer duration of follow-up, higher maximum IOP ever attained and higher number of IOP elevation. Not only did this study supports the fact that IOP elevation is an important risk factor for secondary glaucoma as in the case of uveitis or steroid use [4], it also showed that higher number of IOP elevation, longer duration of follow-up, hypertensive uveitis and higher maximum IOP rise are also important risk factor for glaucomatous optic neuropathy. The type of uveitis does not seem to be associated with RNFL thinning, possibly as a result of selection bias. Eyes with retinal changes which may produce abnormal visual field defect not attributable to glaucoma like papillitis and multifocal choroiditis has largely been excluded, resulting in a skewed number of eyes with posterior uveitis.

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