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Dear Friends,

The time has come to welcome yet another edition of KJO and it's a pleasure interacting with you once again. The highlights of this issue include studies on meta-analysis of DME, which has special significance with diabetes on the rise; a unique article on genomic project in relation to RP and a comprehensive article on applications of OCT.

As editor of KJO, the question that keeps nagging me is, "What next: how can we make our journal even better?" Upon contemplation and discussion with experts, I come to understand one compelling necessity: that our journal outreach can be further enhanced if we "reach out" to the world by indexing our journal.

Indexing the journal is one step that can drastically change the acceptance and importance of our journal in an age of information. The inflow of articles to our journal will also be from a wider audience that even cuts across geographic boundaries. Indexing a journal is considered a testimony to its quality. There are numerous indexing services available. Index Medicus has been the most comprehensive index of medical scientific journal articles and has been in publication since 1879. However, many other popular indexing services have developed over the years, like MedLine, PubMed, EMBASE, SCOPUS, Electronic Databases, SCIRUS and many more, not to mention regional and national versions of Index Medicus. By indexing, we are assigning a unique identification number for our scientific publication, and making it internationally available for access online, though the respective indexing service. This will enable connecting with cutting-edge ophthalmic research happening around the globe where even our articles can be cited.

In this context, it is important to be aware of a related terminology called "impact factor" of a journal, that can be used to rate an indexed journal. Impact factor signifies the relative importance of a journal within its field and is used to compare different journals within a certain field. In any given year, the impact factor of a journal is the average number of citations received per paper published in that journal during the two preceding years. New journals, which are indexed from their first published issue, will receive an impact factor after two years of indexing. Journals with higher impact factors are deemed to be more important than those with lower ones. The impact factor relates to a specific time period and it should be possible to calculate it for any desired period. Even though there has been criticism in the method of calculation of impact factor, this rating is still accepted to denote the quality of a journal.

The world outside has moved ahead and we may need to put in extra effort to catch up. However, with further passage of time, we will only be lagging behind further if we do not take the right step now. Indexing the journal requires tremendous effort and a large number of stringent criteria are to be satisfied for the journal to be accepted for indexing. I solicit your whole hearted support and co-operation as we embark on this next venture to take us further.

Jai KSOS,

Dr Ashok Nataraj
Editor, KJO

Guest Editorial

Rehabilitation of the Visually Challenged

Dr. S.Hariharan MS (Ortho), DPMR

No one would argue with the premise that the restoration of vision is the best possible kind of rehabilitation for the visually disabled. In this perspective, the surgical area of rehabilitation, in particular has assumed a significant role in the total process. New surgical techniques and developments in Ophthalmology during the recent past years have greatly expanded the horizons of physical restoration.

However, the focus of this article is on youths and adults for whom surgery is impractical as well as those who suffer a major visual loss even with best corrective methods. These two groups include individuals defined as legally blind or visually challenged. These visually challenged need the most extensive social and / or rehabilitation services in order to get integrated in society.

An individual shall be considered to be blind if he has central visual acuity of 20/200 or less in the better eye with the use of correcting lens. In the severely handicapped groups, more than 50% and perhaps in excess of 60% are in the age range of 60-65 years and older. It follows, therefore, that a program of rehabilitation services is as essential for the geriatric blind population as for the young adults and children.

At the other end of the age-range, we have the school-age and pre-school groups of blind and severely visually impaired persons. Of greatest current concern is still another group of severely visually impaired individuals. This is the multiply handicapped group. Suffering from severely disabling conditions in addition to blindness, this group is posing new problems for the rehabilitation workers who deal with the visually challenged. Any rehabilitation program for this group will be woefully inadequate for those enrolling for educational services in the next several decades.

Rehabilitation Needs and Problems

The greatest need of the blind rehabilitant is for an understanding and acceptance of his disability. The ramifications of blindness are severe and varied, and very often, very much under estimated. Blindness in and of itself does not cause deep-seated emotional problems unless the symptoms of emotional upset go unrecognized and untreated.

Family attitudes are very important factors to reckon, the disabled person should be accepted by family. To cite an example – Mr.M had just returned home from a rehabilitation program, where he learned communicative skills, activities of daily living, mobility and other precursors to vocational training. Everyone who had worked with him was enthusiastic about his vocational potential, and the plan was that after a short stay at home, he would go on to an intensive period of vocational training. However, during his stay at home, his wife made it quite apparent that his use of a long cane, white or coloured, was embarrassing to her and a source of pity and gossip among the neighbours. A little propaganda of this kind can quickly undo the self confidence that has been instilled in a client. For Mr.M, it became virtually impossible to take the next big step in his rehabilitation. The family has to take up a big role to attain the maximum goals for the client.

Community should also come forward to accept all their people with blindness. As far as people with visual challenge are concerned, our community has always been ready to accept them as one among them and hence the integration of people with blindness has never been a problem.

Mobility

Perhaps the greatest loss a blind person experiences is that of mobility, of freedom of movement from place to place, the ability to go from one place to another unhampered by not seeing. Two methods of travel training for the blind person that are universally accepted employ the long cane and the guide dog. The guide dog movement was started after World War I in Germany. Only less than 2% of the blind population can make use of a guide dog. For the others, a practical and popular solution to the mobility problem is the use of the long cane. Special training is required for the use of the cane.

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Other "Sight Substitutes"

It is important to recognize that the application of rehabilitation services to the visually challenged population does not mean increasing the sight. It means, rather, the improvement of visual function for the person who has residual vision and the provision of 'sight substitutes' for those who are totally blind or who have only light projection or light perception.

Mobility instruction is a sight substitute technique – by using cane techniques or by a guide – dog.

Another example of sight–substitute is in the area of communications – especially reading, by using Braille, talking books, tape recordings and computers.

For the partially sighted, large type print or special microscopic lenses are provided which permit reading the printed page through enlarging or magnifying the letters.

Needed Personnel

When a person has just lost his sight, special personnel are needed to teach him skills in such activities of daily living such as grooming, table etiquette, social graces and the use of sight substitutes. Special personnel are also required for the use of Braille, talking books etc.

Special assistance is also necessary in training the individual to accept and utilize new approaches to recreation and also for prevocational training.

Ophthalmological Information

The nature of eye disease, need for taking special care during work situations and the need for special equipments – all these should be properly considered by the counselor before deciding on rehabilitation.

Hearing

Hearing is a blind person's major sight substitute. It is critical for communication, for orientation by sound–location, and for determining the extent to which a blind person can become a proficient traveler. Hearing can be considered as a method of 'Facial vision' in the rehabilitation of visually challenged.

Other medical information

Diabetes and its complications, especially loss of sensation in the hands and feet pose a major problem in the rehabilitation of the blind persons. Special care should be exercised in selecting work so that the visually impaired diabetic is not placed in close proximity to moving machinery.

Neurological and orthopedic disabilities that affect balance and gait also pose special attention in the rehabilitation of the visually challenged. Identifications through smell are of great importance to blind persons, over and above supplying environmental orientation in mobility.

Education

There are numerous opportunities now for the educational rehabilitation of blind children. Textbooks are available in Braille. Integration of blind children in normal schools is also a major step in their rehabilitation. Computers have done wonders in their education.

Vocational planning and placement

The key to successful rehabilitation is the extent and quality of vocational training provided. Work opportunities for the blind and visually impaired in all areas of employment have increased many times since last century. And automation itself, as symbolized by the computer, has provided a new and lucrative opportunity for hundreds of blind workers, with ever–expanding horizons. The national and international associations for the visually challenged persons are now the leaders in their rehabilitation.

A fairly substantial part of the international program is concerned with research and demonstration projects designed to assist or to rehabilitate the visually challenged persons. The projects range from the provision of mobile ophthalmological clinics in remote rural areas, to training and placement programs in large industrial cities. We have established in India several rehabilitation training programs for the blind with avenues for successful placement in jobs.

The author is a Medical Rehabilitation specialist (Physiatrist) of more that forty years of experience in Medical Colleges of Kerala. Was also the Principal of Govt. Medical College, Trivandrum and also of a few other private sector Medical Colleges. He was heading the Dept. Of Physical Medicine & Rehabilitation as Professor for many years. He had also functioned as a WHO – short term consultant in community based rehabilitation of people with disabilities.

Major Review

DME Management Update
A Meta Analysis of Trials in DME

Dr. Manoj Soman DNB, FRCS, Dr. Devendra V. Phalak MS, Dr. Unni Nair MS, FRCS

Introduction

Diabetes mellitus is a major cause of avoidable blindness in both the developing and the developed countries. Patients with diabetic retinopathy are 25 times more likely to become blind than non diabetics . Prevalence of diabetic retinopathy in Wisconsin epidemiological study of diabetic retinopathy [1] was 50.1% and it was 54.2 % in the diabetes control and complication trial (DCCT) in Insulin dependent diabetes mellitus[2] (IDDM) and 35-39% in United Kingdom Prospective Diabetes study[3] in Non insulin dependent diabetes mellitus (NIDDM). In India, the prevalence rates of diabetic retinopathy in NIDDM patients have been reported to range from 17.6% to 37%.[4,5,6,7] Diabetes and diabetic retinopathy is more prevalent in Kerala and Kerala is now considered the diabetic capital of India[8]. One population based screening study in south Kerala (unpublished data) found that among the eyes with diabetic retinopathy 86.86% had NPDR, 13.90% had PDR. CSME was seen in 24.34% of NPDR eyes and 31.92% of eyes with PDR. Overall 25.59% of the eyes were diagnosed to have CSME. This observation is similar to other studies done in this subcontinent. Narendran and coworkers in their series had reported that CSME was seen in 29.41% of affected eyes6. Dandona et al had reported 14.3% had clinically significant macular oedema.7 The common causes of visual impairment in diabetic retinopathy include macular edema and complications due to proliferative retinopathy[8]. As majority of diabetics have type 2 disease where macular edema is common, overall macular edema accounts for more vision impairment than proliferative retinopathy[9,10]. Diabetic macular edema is thus the main cause of visual impairment in diabetic patients. Diabetic macular edema is currently diagnosed clinically and evaluated by OCT and angiography. The role of OCT in the diagnosis and management of diabetic macular edema needs no further emphasis in the present scenario. Though the ETDRS used term CSME is still relevant most of the recent OCT based studies have now emphasised on 'centre involved macular edema' which is currently the guide to plan DME management. OCT based cut off values for centre involved diabetic macular edema are variable in different studies and range from 250-300 microns[11]. The DRCR.Net[12] and the RCPS guidelines[13] consider central thickness of > 250 microns as significant for active intervention.

Pathophysiology Overview

DMO is caused mainly by disruption of the blood-retinal barrier[14]. In the pathophysiologic cascade leading to DME, chronic hyperglycemia leads to oxidative damage to endothelial cells as well as to an inflammatory response. The ensuing ischemia results in overexpression of a number of growth factors, including not only VEGF but also insulin-like growth factor-1, angiopoeitin-1 and -2, stromal-derived factor-1, fibroblast growth factor-2, and tumor necrosis factor. Synergistically, these growth factors mediate angiogenesis, protease production, endothelial cell proliferation, migration, and tube formation. Tumor necrosis factor-alpha (TNF-alpha) and VEGF play a role in the early stages of angiogenesis, with TNF-alpha promoting leukocyte adhesion and VEGF promoting leukostasis, resulting in ischemia14. Vascular endothelial growth factor-A (VEGF-A) is a major contributor to the inflammatory process and, in particular,to angiogenesis and permeability. Hypoxia caused by microvascular disease stimulates the release of VEGF-A to aid perfusion. There are six major isoforms of VEGF-A: 121, 145, 165, 183, 189 and 206[15,16]. In addition to causing widespread microvascular injury, there is now evidence that hyperglycaemia results in preceding neuronal dysfunction, which may contribute to visual loss[17].

Overview of Current Treatments

Laser photocoagulation has been the mainstay of treatment for DME until a few years ago. The landmark Diabetic Retinopathy Study[18] and the Early Treatment Diabetic Retinopathy Study (ETDRS) [19,20] demonstrated its clinical effectiveness. However, although laser photocoagulation was clearly effective in preserving vision, it was less successful in restoring it, once lost. In EDTRS, although laser was shown to reduce the risk of moderate visual loss (a loss of three ETDRS lines) by 50%, visual acuity improved in only 3% of patients.[20] However, in some recent trials, laser

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has improved the proportion of patients with more than or equal to 10 letters by 7–31%.[21-24] In addition, laser is not without side effects. Foveal burns, visual field defects, retinal fibrosis and laser scars have been reported.[25] Over the following decade it became apparent that certain patients suffered severe visual loss despite aggressive treatment.[26]

Steroids and anti-VEGF drugs are newer treatments in DMO. Intravitreal corticosteroids have potent anti-inflammatory effects. Triamcinolone (Kenalog) is not licensed for eye use but has been used to treat DMO for over 10 years. Triamcinolone, recently, was licensed for eye use. The development of intravitreal implants has allowed sustained release formulations. Fluocinolone acetonide (Iluvien, Alimera Sciences) and dexamethasone (Ozudex, Allergan) are implants that have been introduced recently. However the group of agents which have revolutionised the way we manage DME presently is Anti VEGF therapy. Various Anti-VEGF agents have shown superior efficacy compared with laser. These include Bevacizumab (AVASTIN) and Ranibizumab (LUCENTIS) which are monoclonal antibodies against VEGF-A, Pegaptanib (MACUGEN) which is a PEGylated aptamer, with a high affinity to the VEGF isoform 165, Aflibercept (Regeneron) is a recent addition to the anti-VEGF class that targets all forms of VEGF-A and placental growth factor. Most of the trials that used these above agents have demonstrated significant visual benefit if treatment was persisted and have been proven to be superior to laser photocoagulation which at best helps to stabilise the vision. These anti-VEGF drugs appear to be a significant advance in the treatment of DMO and are regarded now as the treatment of choice for patients affected by this condition.

Anti-VEGF therapy for Diabetic Macular Edema

Inhibition of VEGF has become a topic of interest in recent years in the area of age-related macular degeneration. The properties of VEGF, and the consequences of its inhibition, also suggest a role for this approach in the management of DME. In the pathophysiologic cascade leading to DME, chronic hyperglycemia leads to oxidative damage to endothelial cells as well as to an inflammatory response[14]. The ensuing ischemia results in overexpression of a number of growth factors, including not only VEGF but also other factors. These growth factors mediate angiogenesis, protease production, endothelial cell proliferation, migration, and tube formation. Blockade of all involved growth factors will likely be necessary to completely suppress the detrimental effects of ischemia, but even isolated blockade of VEGF may have beneficial effects on DME. VEGF increases vascular permeability by relaxing endothelial cell junctions, which increases permeability and leakage[14,15]. Inhibition of VEGF blocks this effect to some extent, as demonstrated in several recent clinical trials and case series involving the anti-VEGF molecules pegaptanib, ranibizumab, and bevacizumab.

Pegaptanib sodium (Macugen®, Eyetech Pharmaceuticals, Melville, NY/Pfizer, New York, NY) is an anti-VEGF aptamer, a small piece of RNA that self-folds into a shape that binds to and blocks the effects of VEGF165, one isoform of the VEGF family of molecules. This drug had been studied earlier in a phase II trial for DME but no follow up studies have been done subsequently and is therefore currently not popular or recommended in DME management. Ranibizumab (Lucentis™, Genentech, San Francisco, CA) is an humanized monoclonal antibody fragment that also binds and blocks the effects of VEGF. Unlike pegaptanib, ranibizumab binds and inhibits all isoforms of VEGF. Ranibizumab was approved by the FDA for the treatment of age-related macular degeneration earlier and is currently approved for DME. Bevacizumab (Avastin®, Genentech, San Francisco, CA) is the full antibody from which ranibizumab is derived. This anti-VEGF molecule is FDA approved for systemic treatment of metastatic colon cancer, but not for any ophthalmic indications. Though various case studies and trials including one DRCR.Net protocol that studied the role of Bevacizumab in DME, its use in DME is currently off-label. Aflibercept (Regeneron/Bayer HealthCare) is a recent addition to the anti-VEGF class that targets all forms of VEGF-A and placental growth factor. VEGF Trap-Eye is a 115-kDA recombinant fusion protein com-prising the key VEGF binding domains of human VEGF receptors 1 and 2 fused to the Fc domain of human immunoglobulin G1.23 VEGF Trap-Eye is a pan isoform VEGF-A inhibitor whose binding affinity to VEGF is substantially greater than that of either beva-cizumab or ranibizumab.

Ranibizumab in DME

Metaanalysis of Ranibizumab in DME revealed nine RCTs[27-37] which have evaluated ranibizumab as a potential new treatment for patients with DMO , seven were sponsored by industry, and two were led by independent investigators).

Monotherapy is better

READ-2 was the first large RCT. It compared ranibizumab (0.5 mg) alone, and ranibizumab in combination with laser and laser alone. At 6 months, BCVA had improved significantly in the ranibizumab alone group compared with laser alone or ranibizumab plus laser. Addition of laser to ranibizumab did not provide additional BCVA gain[28,29]. REVEAL compared ranibizumab (0.5 mg) with ranibizumab plus laser and laser alone. At 12 months, both ranibizumab arms resulted

in a statistically significantly better improvement in BCVA compared to laser alone. The addition of laser did not confer further benefit30. Within the past few years, the results of RESOLVE,31 RESTORE32 and RISE and RIDE33 have been published in peer-reviewed journals. RESTORE randomized similar groups as the READ-2 study (ranibizumab (0.5 mg) alone, laser alone and ranibizumab plus laser); outcomes were evaluated at 12 months. Ranibizumab improved mean BCVA, with laser providing no additional benefit32. Two-year extended follow-up suggested that these results continued. 34 RESOLVE compared two doses of ranibizumab (0.3 and 0.5 mg) with sham injection. The greatest improvement in BCVA at 12 months was in the 0.3 mg group (11.8 letter gain) compared to the 0.5 mg group (8.8 letter gain) or sham injection (1.4 letter loss). In this study, rescue laser was allowed after 3 months of treatment, if BCVA had decreased by 10 letters or more, or if the investigator considered the macula not to be flat as assessed by OCT. Only 4.9% of the ranibizumab group required rescue laser, compared with 34.7% in the sham injection group. 31 READ-2 and RESTORE were suitable for pooling through meta-analysis and, when doing so, it was found that ranibizumab statistically significantly improved mean BCVA compared with laser. In regard to the proportion of patients gaining more than or equal to 15 letters, individual trials showed a statistically significant difference between laser and ranibizumab. Adding laser to ranibizumab did not add any significant benefit. In fact, the mean change in BCVA and the proportion of patients with more than 15 letter gain favoured, ranibizumab alone compared with ranibizumab plus laser, although not statistically significantly so. This was probably a chance effect. RISE and RIDE were identical in design. The study arms are similar to those in the RESOLVE study, 0.3 or 0.5 mg ranibizumab compared with sham. In the RISE study, the proportion of patients with 15 or more letter gain was greatest in the 0.3 mg group at 24 months, whereas in the RIDE study this was greatest in the 0.5 mg group. READ-3 has been published and compared monthly injections of intravitreal ranibizumab high dose (2.0 mg) and low dose (0.5 mg). 35 At 6 months, there was no statistically significant difference in BCVA between groups

Is Combination therapy better?

In the DRCRN trial, Elman and colleagues compared ranibizumab (0.5 mg) plus prompt (within 3–10 days post ranibizumab) or deferred (≥24 weeks) laser with sham injection plus prompt laser, or triamcinolone (4 mg, Trivaris) plus prompt laser. At 1 year, both ranibizumab groups reported greater gains in mean BCVA change than triamcinolone or laser alone. 36 Interestingly, at 2 years (n=628), the proportion of patients with 10 or more letter gain was not statistically significantly different between ranibizumab plus prompt laser and laser alone groups, but was statistically significant in the ranibizumab plus deferred laser compared with laser alone comparison. 37 The reason for this is not clear. RESTORE, READ-2 and DRCRN (12 month data used) were suitable for pooling through meta-analysis to compare ranibizumab plus laser and laser alone. Ranibizumab plus laser resulted in a statistically significantly greater change in mean BCVA, proportion of patients with more than 15 letter gain and CMT reduction versus laser alone. With regard to adverse events, conjunctival haemorrhages were higher in the ranibizumab arms compared with laser (RESTORE) or no treatment (RESOLVE). In the RESOLVE, RISE and RIDE studies, a considerably higher incidence of intraocular pressure (IOP) increase was reported in the ranibizumab arm compared to control. This increase in IOP was not demonstrated in the RESTORE study. There were no consistent differences in systemic adverse events between ranibizumab and laser or placebo. [31-34]

Summary of major clinical trials involving Ranibizumab in DME

RESOLVE was a Twelve-month, multicentre, sham controlled double-masked study on the safety and efficacy of ranibizumab in DME with centre involvement and included 151 eyes. Patients were randomly assigned 1:1:1 to RBZ (0.3 or 0.5 mg) or sham. The treatment schedule comprised three monthly injections, after which treatment could be stopped/reinitiated with an opportunity for rescue laser photocoagulation. The ranibizumab arm that received 0.3 mg showed the best response. In this study, rescue laser was allowed after 3 months of treatment, if BCVA had decreased by 10 letters or more, or if the investigator considered the macula not to be flat as assessed by OCT. Only 4.9% of the ranibizumab group required rescue laser, compared with 34.7% in the sham injection group.

RESOLVE STUDY Groups	Mean gain in letters (ETDRS)	Reduction in Central retinal thickness	Mean no'of injections
Ranibizumab 0.3 mg	+ 11.8	-200.7 microns	10.2
Ranibizumab 0.5 mg	+ 8.8	-187.6 microns	10.2
Sham injection	- 1.4	-48.4 microns	8.9

READ-2 was a prospective, randomized, interventional,

multicentre clinical trial involving ranibizumab for centre involved macular edema and involved 126 participants. Subjects were randomized 1:1:1 to receive 0.5 mg RBZ at baseline and months 1, 3 and 5 (group1), focal or grid laser photocoagulation at base-line and month 3 if needed (group 2) or a combination of 0.5 mg RBZ and focal or grid laser at baseline and month 3 (group 3). At 6 months, BCVA had improved significantly in the ranibizumab alone group compared with laser alone or ranibizumab plus laser. Addition of laser to ranibizumab did not provide additional BCVA gain.

READ 2 STUDY groups	Mean gain in letters (ETDRS)	Reduction in Central retinal thickness
Ranibizumab 0.5 mg	+ 7.4	-106.3 microns
Laser	-0.43	-82.8 microns
Ranibizumab + laser	+3.8	-117.2 microns

RESTORE was an randomized, double-masked, multi-centre, laser-controlled phase III study to demonstrate the superiority of ranibizumab 0.5 mg monotherapy or combined with laser over laser alone in centre involving DME and included 345 patients. Patients were randomized to RBZ + sham laser (SL), RBZ+L or sham injections +L. RBZ/sham was given for 3 months then pro re nata (PRN) and laser/SL was given at baseline then PRN (patients had scheduled monthly visits). After the first year when the superiority of ranibizumab was proven, the study was continued for 2 years with patients getting RBZ on PRN basis and the laser group became eligible for RBZ.

RESTORE STUDY Groups	Mean gain in letters (ETDRS)	Reduction in Central retinal thickness	Mean no'of injections
Ranibizumab +sham laser	+ 6.1	-118.7 microns	7.0
Ranibizumab + laser	+ 5.9	-128.3 microns	6.8
Sham injection+ laser	+0.8	-61.3 microns	7.3

RISE/RIDE were two parallel, methodologically identical, phase III, multicentre, double-masked, sham injection controlled, randomized studies involving Ranibizumab injection in subjects with clinically significant macular oedema with centre involvement . There were 377 patients in RISE and 382 patients in RIDE. Patients received monthly intravitreal RBZ (0.5 or 0.3 mg) or sham injections. In the RISE study, the proportion of patients with 15 or more letter gain was greatest in the 0.3 mg group at 24 months, whereas in the RIDE study this was greatest in the 0.5 mg group.

RISE STUDY Groups	Mean gain in letters (ETDRS)	Reduction in Central retinal thickness
Ranibizumab 0.3	+ 14.2	-261.2 microns
Ranibizumab 0.5	+ 11	-269.1 microns
Sham injection	+4.3	-200.1 microns

RIDE STUDY Groups	Mean gain in letters (ETDRS)	Reduction in Central retinal thickness
Ranibizumab 0.3	+ 10.6	-261.8 microns
Ranibizumab 0.5	+ 11.4	-266.7 microns
Sham injection	+4.7	-213.7 microns

DRCR.Net Protocol I was an randomized, multicentre clinical trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for centre involved DME and involved 854 participants. Patients were randomized to one of the following four groups: Group A: Sham injection+ focal laser, Group B: 0.5 mg injection of intravitreal RBZ + prompt laser, Group C: 0.5 mg injection of intravitreal RBZ + deferred focal laser, Group D: 4 mg injection of intravitreal Triamcinolone + prompt laser. At 1 year, both ranibizumab groups reported greater gains in mean BCVA change than triamcinolone or laser alone. Interestingly, at 2 years (n=628), the proportion of patients with 10 or more letter gain was not statistically significantly different between ranibizumab plus prompt laser and laser alone groups, but was statistically significant in the ranibizumab plus deferred laser compared with laser alone comparison.

DRCR NET STUDY-1yr Groups	Mean gain in letters (ETDRS)	Reduction in Central retinal thickness	Mean no'of injections
Sham injection+ laser	+ 3	-133 microns	-
Ranibizumab + prompt laser	+ 9	-144 microns	11
Ranibizumab + deferred laser	+9	-170 microns	13
IVTA + prompt laser	+4	-95 microns	4

READ-3 tried to compare two different dosage of RBZ in DME treatment. It was Phase 2, 2-arm randomized controlled trial involving 152 patients and involved 2 groups; Group 1 (RBZ 2.0) monthly injec-tions, group 2 (RBZ 0.5): monthly injections. After month 6, eyes evaluated and additional RBZ injections given on an as needed basis if DME still present on OCT. At 6 months, there was no statistically significant difference in BCVA between groups.

READ 3 STUDY Groups	Mean gain in letters (ETDRS)	Reduction in Central retinal thickness
Ranibizumab 2.0	+ 7.46	-163.86 microns
Ranibizumab 0.5	+ 8.69	-169.27 microns

Bevacizumab in DME

Eight RCTs investigating the use of bevacizumab in DMO were identified[27,38-48]. One RCT, the BOLT study, randomised patients to laser therapy or 1.25 mg intravitreal bevacizumab. At 24 months, the mean changes in BCVA and the proportion of patients who gained 10 ETDRS letters or more was statistically significantly higher in the bevacizumab arm than in the laser arm.[39,40,41] Faghihi et al[42] compared 1.25 mg bevacizumab (average 2.23 injections per patient) with 1.25 mg bevacizumab plus a single laser treatment (average 2.[49] injections per patient). After 6 months, the authors found both treatments to be effective at improving BCVA, but neither treatment was found to result in a greater benefit. Lam et al[43] compared two doses of bevacizumab (1.25 and 2.5 mg) in patients with diffuse DMO. Patients with focal DMO associated with localised retinal thickening were excluded. At 6 months, following 3 initial monthly injections (no treatment in the remaining 3 months), both groups showed a statistically significantly increased mean BCVA compared with baseline vision, but there was no difference between doses. Four trials have investigated the combination of bevacizumab and triamcinolone. Ahmadieh et al[44] compared combined bevacizumab (three 1.25 mg injections at 6 week intervals) plus triamcinolone (2 mg baseline injection only) with bevacizumab alone (three 1.25 mg at 6 week intervals) and sham injection in patients who had DMO unresponsive (definition not reported) to previous laser (last session more than 3 months previously). The combination arm and bevacizumab alone arm improved mean BCVA more than the sham injection. For BCVA, the combination of bevacizumab plus triamcinolone was non-statistically significantly better than bevacizumab alone. Soheilian et al[45,46] compared combined bevacizumab (1.25 mg) plus triamcinolone (2 mg) with bevacizumab alone and laser alone in patients who were laser naïve. At 36 weeks, bevacizumab alone improved BCVA more than either combination therapy or laser, although the difference was not statistically significant. Extended follow-up at 24 months showed that there was no statistically significant difference between groups for BCVA; however, the direction of effect favours the bevacizumab and combination arms more than the laser.[46] Lim et al[47] also evaluated the combination of bevacizumab plus triamcinolone when compared with bevacizumab alone or triamacinolone alone. At 12 months, the authors found no statistically significant difference between groups for BCVA or CMT. The Efficacy Study of Triamcinolone and Bevacizumab Intravitreal for Treatment of Diabetic Macular Oedema (ATEMD) study, compared combined therapy with bevacizumab (1.25 mg) and triamcinolone (4 mg) with each of these alone.[48] At 6 months, they found no statistically significant difference between groups. No bevacizumab trials were suitable for meta-analysis because treatment arms were not comparable among included studies. There was a low frequency of adverse events reported in the included trials. A higher incidence of mild anterior chamber reaction was reported in bevacizumab groups compared with controls. The incidence of IOP increase was comparable between bevacizumab and laser. Soheilian et al[45,46] were the only authors to report the incidence of lens opacity. No patients in the bevacizumab alone group were found to have lens opacities but in four patients (8%) in the bevacizumab plus triamcinolone group, this finding was observed over the 36-week follow-up period.

Summary of major clinical trials involving Bevacizumab in DME

BOLT STUDY Groups	Mean gain in letters (ETDRS)	Reduction in Central retinal thickness	No of sessions
Bevacizumab 1.25	+ 8.6	-146 microns	13
Laser	-0.5	-118 microns	4

One study comparing bevacizumab with ranibizumab has been reported.[49] This study (n=63), which directly compared monthly injections of ranibizumab (0.5 mg) with bevacizumab (1.5 mg) found that at 48 weeks, there was no statistically significant difference between bevacizumab and ranibizumab.

Pegaptanib in DME

Two studies have evaluated pegaptanib in DMO and both compared it with sham injection. Cunningham et al50 compare three doses of pegaptanib (0.3, 1 and 3 mg) and sham injection in laser-naïve patients (n=172). At 6 months, patients in the 0.3 and 1 mg groups performed statistically

significantly better than those in either the 3 mg or sham groups. Six injections (median) were administered in the 0.3 and 1 mg groups, whereas only five (median) injections were administered in the 3 mg group. The second trial (n=260), reported by Sultan and colleagues[51], compared pegaptanib (0.3 mg) and sham injection. At 2 years, the pegaptanib group showed a statistically significantly greater improvement in mean BCVA compared with sham. However, there was no statistically significant difference in the proportion of patients with an improvement of 10 letters or more. Patients were allowed rescue laser at the assessors' discretion (25.2% of patients in the pegaptanib group and 45% of patients in the sham group received rescue treatment). Although neither trial individually demonstrated a statistically significant difference favouring pegaptanib over sham, when pooled together in meta-analysis, a statistically significant difference was found in favour of pegaptanib (OR 1.94, 95% CI 1.01 to 3.71). Adverse events for pegaptanib if analysed, there was a higher incidence of eye pain compared to control (31% vs 17%).[50] Cataract formation was similar between the pegaptanib and control groups. There was a higher incidence of IOP increase in the pegaptanib arm compared to control (17.4% vs 6.3%).[51]

Other anti-VEGF agents in DME

Aflibercept has been evaluated in the Da Vinci study[52,53]. Four regimens of aflibercept (0.5 mg 4 weekly, 2 mg 4 weekly, 2 mg monthly for 3 months, then every 8 weeks, and 2 mg monthly for 3 months followed by treatment as required) were compared with laser. At 6 months, all aflibercept arms had a statistically better BCVA and CMT change than the laser arm. The regimen that resulted in the greatest BCVA gain and CMT reduction was 2 mg every 4 weeks; however, statistical significance between aflibercept arms was not reported[52]. One year extended follow-up showed that all aflibercept arms were found to have a statistically significantly better BCVA compared to laser[53]. Adverse events analysis revealed a higher incidence of IOP increase and eye pain in the aflibercept group compared with laser. Other adverse events were too infrequent to draw meaningful conclusions. The incidence of cataracts was not reported.

Summary of major clinical trials involving Aflibercept in DME

The Da Vinci study is a randomized, double-masked, multi-centre, phase 2 clinical trial of VEGF Trap- aflibercept molecule and involved 221 participants. Participants were assigned randomly to one of five treatment regimens: VEGF Trap-Eye 0.5 mg every 4 weeks (0.5q4); 2 mg every 4 weeks (2q4); 2 mg every 8 weeks after three initial monthly doses (2q8); or 2 mg dosing as needed after three initial monthly doses (2PRN), or macular laser photo-coagulation (L). The regimen that resulted in the greatest BCVA gain and CMT reduction was 2 mg every 4 weeks; however, statistical significance between aflibercept arms was not reported. One year extended follow-up showed that all aflibercept arms were found to have a statistically significantly better BCVA compared to laser.

DA VINCI STUDY Groups	Mean gain in letters (ETDRS)	Reduction in Central retinal thickness	No of injections
VEGF Trap 0.5 mg every 4 weeks	+ 11.0	-165.4 microns	11.7
VEGF Trap 2 mg every 4 weeks	+13.1	-227.4 microns	10.8
VEGF Trap 2 mg every 8 weeks after 3, mthly injections	+9.7	-187.8 microns	7.2
VEGF Trap 2 mg PRN after 3, mthly injections	+12	-180.3 microns	7.4
Laser	-1.3	-58.4 microns	-

Adverse events in Anti VEGF therapy

No large observational studies were identified that compared adverse events following anti-VEGF drugs in DME. Using an internet-based survey, Fung et al[54] found the incidence of adverse events in bevacizumab to be low. One small outbreak of sterile endophthalmitis was reported with a single batch of bevacizumab in Canada, emphasising the need for sterility when preparing aliquots.[55] Curtis et al[56] carried out a very large retrospective cohort study in 146 942 patients aged 65 who were treated with pegaptanib, bevacizumab and ranibizumab. The authors reported that one of their comparisons showed an increase in overall mortality and stroke risk with bevacizumab compared to ranibizumab, with HRs of 0.86 (95% CI 0.75 to 0.98) and 0.78 (0.64 to 0.96), respectively. However, owing to the very large cost differences between bevacizumab and ranibizumab, the authors noted that selection bias might be operating, with poorer people (with poorer health) more likely to be treated with bevacizumab. They therefore carried out another analysis using only ophthalmological clinics which used only one drug, to avoid selection bias. This analysis showed no significant difference: overall mortality HR for ranibizumab 1.10 (95% CI 0.85 to 1.141); MI 0.87 (0.53 to 1.14); stroke 0.87 (0.61 to 1.24). No large observational studies were identified that compared adverse events following anti-

VEGF drugs in DME eventhough data on anti VEGF adverse effects have been analysed by some authors. 57,58 Gower et al[59] analysed 77 886 anti-VEGF injections from Medicare data (46% ranibizumab and 54% bevacizumab). The authors found an increased risk of overall mortality and cerebrovascular events in the bevacizumab group (HR 1.11 99% CI 1.01 to 1.23 and 1.57, 1.04 to 2.37, respectively). There was no statistically significantly increased risk in the ranibizumab group. The authors acknowledge that a limitation of the study is a failure to adjust for important confounding factors (such as smoking, hypertension and hyperlipidaemia). Considering the cost difference, it is likely that patients treated with bevacizumab would have been in a lower socioeconomic class and therefore at high risk of mortality and vascular disease.

STEROIDS IN DME

Steroids have both anti-inflammatory and anti-angiogenic properties and because of these properties, they are increasingly becoming a popular therapeutic option in retinal practice. Although these glucocorticoids mediate their effects through modulation of inflammatory cytokines and their anti-VEGF effect to achieve a clinical outcome, they also affect both common and unique gene expression pathways involving oxidative stress and neuroprotection, which are also important pathways affecting retinal disease. This is mediated through complex interactions with the glucocorticoid receptor in the cytoplasm, which is then transported to the nucleus where gene expression pathways are activated or repressed. Nongenomic effects of steroids involving steroid activated signaling also occurs that can have profound clinical effects.[60,61] Intravitreal steroids are now being used in the treatment of various retinal conditions including diabetic and vasculo-occlusive macular edema, exudative macular degeneration, pseudophakic cystoid macular edema, and posterior uveitis. Although there are well known serious potential complications with intravitreal steroids, including glaucoma and cataracts, recent studies have shown that intravitreal steroids may be used as a safe alternative to the standard practice of laser therapy for the treatment of macular edema secondary to diabetes or vein occlusions. Although there are several steroid formulations that may be used, this article focuses on the use of intravitreal dexamethasone, Fluocinolone and triamcinolone acetonide.

Triamcinolone

Ten trials evaluating triamcinolone were identified.[27,62-70] Three doses were assessed in the included studies (1, 4 and 8 mg) and triamcinolone has been combined with laser or bevacizumab. Ip and colleagues were the only authors to evaluate triamcinolone 1 mg.[62,63,64] They found a statistically significant improvement in mean BCVA at 2 years in the laser group compared with the triamcinolone group and no significant difference between 1mg compared with 4 mg. Ip and colleagues (n=840) found that laser therapy resulted in a greater improvement in mean BCVA at 2 years compared to 4 mg triamcinolone.[62,63,64] Gillies et al66 compared 4 mg of triamcinolone (Kenacort) with sham injection. Mean BCVA improved statistically significantly with triamcinolone at 24 months compared with sham injection (3.1 letter gain compared with 2.9 letter loss, p=0.01). Lam et al[67] compared triamcinolone 4 mg alone with 4 mg of triamcinolone plus laser or laser alone. At 6 months, the authors found no difference in BCVA between any of the groups. Elman et al[21] compared 4 mg of triamcinolone plus laser with ranibizumab plus prompt (within 3–10 days) or deferred (more than 24 week) laser and laser alone. At 2 years, they found a statistically significant difference in mean BCVA between ranibizumab plus prompt/ deferred laser compared with laser alone (7 letter gain/ 9 letter gain compared with 3 letter gain), but no difference with triamcinolone plus laser compared with laser alone (2 letter gain compared with 3 letter gain). ATEMD study48 compared 4 mg triamcinolone alone with 4 plus 1.25 mg bevacizumab. At 6 months, they found no statistically significant difference between groups. The Elman and Lam studies were suitable for meta-analysis, which showed non-statistically significant improvements in mean BCVA and the proportions of patients with more or equal than 15 letter gain in the triamcinolone plus laser group compared with laser alone. Triamcinolone was associated with consistently higher incidences of IOP increase and cataracts.[62,63,64] Gilles and colleagues66 reported a cataract rate of over 50% by 3 years in patients treated with triamcinolone. The role of posterior subtenons triamcinolone has been studied by various authors and the DRCR net study clearly showed the inferiority of posterior subtenons steroids over laser.[68,69,70]

DRCR.Net PST study; This study involved 109 participants who were randomly assigned to receive either focal photocoagulation (N = 38), 20 mg anterior subtenon's injection of triamcinolone (N = 23), 20 mg anterior subtenon's injection followed by focal photocoagulation after 4 weeks (N = 25), 40 mg posterior subtenon's injection of triamcinolone (N = 21), or 40 mg posterior subtenon's injection followed by focal photocoagulation after 4 weeks (N = 22). Follow-up visits were performed at 4, 8, 17, and 34 weeks. Changes in retinal thickening and in visual acuity were not significantly different among the five groups at 34 weeks (P=0.46 and P=0.94, respectively). There was a suggestion of a greater proportion of eyes having a central subfield thickness < 250

microns at 17 weeks when the peribulbar triamcinolone was combined with focal photocoagulation. Elevated intraocular pressure and ptosis were adverse effects attributable to the injections. This study concluded that in cases of DME with good visual acuity, peribulbar triamcinolone, with or without focal photocoagulation, is unlikely to be of substantial benefit. Based on these results, a phase 3 trial to evaluate the benefit of these treatments for mild DME is not warranted.

DRCR.Net IVTA study: This study evaluated the efficacy and safety ofIVTA (4 and 1 mg) against laser in DME. It was a prospective multicentre study involving 840 participants. For the 2-year primary outcome, the mean change in the visual acuity letter score from baseline was +1 ± 17 in the laser group, −2 ± 18 in the 1 mg triamcinolone group and −3 ± 22 in the 4 mg triamcinolone group. This study concluded that Macular laser procedures have much better visual acuity outcomes in long term when compared with intravitreal triamcinolone monotherapy.

Fluocinolone

Two trials assessed fluocinolone implant for DMO[71,72]. The FAME study compared two doses of fluocinolone (0.2 and 0.5 μg/day) with sham injection in patients with at least one prior laser treatment.[71] Approximately 25% of patients in each group had more than one prior laser treatment. At 24 months, both doses of fluocinolone showed a statistically significant improvement in mean BCVA compared to sham. There was a modest difference between fluocinolone groups. Rescue laser was given after the first 6 weeks for persistent oedema and was allowed every 3 months. A range of 35–37% of patients in the fluocinolone group and 59% in the sham injection group required rescue laser. Extended follow-up at 36 months showed that both the fluocinolone arms continued to result in a statistically significant benefit compared with sham.[73]

Pearson et al[72] (n=196) compared fluocinolone (0.59 mg) with standard of care, either laser or no treatment. At 3 years, there was no statistically significant difference in the proportion of patients with 15 letter gain or more (31% fluocinolone compared with 20% standard of care) between groups and the proportion of patients losing 15 letters or more in the fluocinolone group (17% compared with 14%). Increased incidence of cataracts may have contributed to this difference. Pearson and colleagues[72] reported a higher incidence of cataracts at 3 years in the fluocinolone group compared with standard of care (55.9% compared with 21.7%). In the extended report of the FAME study, there was a considerably higher incidence of cataract surgery in phakic eyes in the 0.2 and 0.5 μg/day fluocinolone groups (80% and 87.2% compared with 27.3%) and increased IOP at any point (37% and 46% compared with 12%). Following the demonstration in the FAME trial that a lower dose was about as good as higher ones, the higher doses are unlikely to be used.

The FAME study was done to assess long-term efficacy and safety of 25 g intravitreal Fluocinolone inserts ILLUVIEN releasing 0.2 μg/day (low dose) or 0.5 μg/day (high dose) FA (release for 3 yrs) compared to sham injections in the ratio of 2;2;1 in patients with DME. This was a three-arm placebo-controlled randomized controlled trial involving 956 participants. Significantly improved visual acuity in patients with DME in group A and B over 2 years and significantly fewer incisional glaucoma procedures were needed in the low-dose insert group. Almost 90% of the phakic patients required cataract surgery.

FAME STUDY Groups	Mean gain in letters (ETDRS)	Reduction in Central retinal thickness
FA 0.2 micrg/day	+ 4.4	-167.8 microns
FA 0.5 micrg/day	+5.4	-177.1 microns
Sham injection	+1.7	-111.3 microns

Retisert: Retisert is a sterile, non-biodegradable 0.59 mg fluocinolone intravitreal implant implanted surgically through a pars plana scleral opening. It releases 0.5 μg/day for 1000 days. The Retisert trial evaluated the 3-year efficacy and safety results of FA intravitreal implants in eyes with persistent or recurrent DME. It was a Prospective, evaluator-masked, controlled, multicentre clinical trial involving 196 participants and patients were randomized 2:1 to receive 0.59-mg FA implant or standard of care (SOC additional laser or observation).Three years after implantation, the difference in the rates of three-line VA improvements was no longer significant between two groups.

Dexamethasone

Two included trials assessed the use of dexamethasone to treat DMO[74,75] Haller compared two doses of dexamethasone, administered as an intravitreal implant (350 and 700 μm) through a 20-gauge transscleral incision, with no treatment. At 90 days only, the 700 μm group showed a statistically significantly higher proportion of patients with 10 or more letter gain. The 350 μm group showed a non-statistically significant improvement compared with laser alone (21% compared with 12%). At 180 days, there was no statistically significant difference between either the dexamethasone group or no treatment group. The treatment effect appeared to peak at 3 months.[74] The second trial, by Callanan and

colleagues[75] (n=253), compared dexamethasone plus laser with laser alone. Although a greater improvement in mean BCVA was seen at 1–9 months in the dexamethasone plus laser group compared with laser alone, there was no statistically significant difference at 12 months. A mean of 1.6 implants were used over the 12 month period. In the 350 and 700 μm groups compared with no treatment, there was a higher incidence of anterior chamber cells (29.1/26.4% compared with 1.8%), anterior chamber flare (27.3/20.8% compared with 8.8%), vitreous haemorrhage (20/22.6% compared with 5.3%) and increased IOP (14.5/9.4% compared with 0%). However, there was no statistically significant difference in cataract formation between groups at 12 months.[74] Callanan et al[75] reported an increase in IOP in the dexamethasone plus laser group compared with laser alone (20% compared with 1.6%).

Surgical considerations in DME

Indications for vitrectomy for macular edema include DME associated with taut posterior hyaloids, thickened posterior hyaloids, epiretinal membrane and vitreomacular traction. Also eyes with resistant DME unresponsive to laser and intravitreal pharmacotherapy have benefitted from vitreoretinal surgery. 76-87 The success of surgical procedure- vitrectomy with and without ILM peeling has been reported by various authors. Most of these data are retrospective studies with relatively small numbers (range, 7–65) and no case controls. Despite this, the rates of improvement of VA and resolution of ME have been remarkable when one considers that most cases were refractory to previous focal photocoagulation treatment. The main drawback of the procedure has been the rate of complications. Besides cataract formation, the most frequently encountered complications among 336 cumulative cases were vitreous hemorrhage in 21, ERM formation in 23, and retinal tears in 21. [76-87] It should be noted that there has been no case of endophthalmitis reported to date. Even with these, the cumulative results showed an improved VA in 56% (range, 38–92%), while ME resolved clinically in 83% (range, 55– 100%) over mean follow-up periods ranging from 6 to 16 months. Certain findings were associated with good or with poor surgical outcomes. Good preoperative prognostic factors included the presence of macular perfusion, VA of 20/100 or better, lack of previous macular photocoagulation and a short interval time (< 1 month) between times of diagnosis of diffuse ME to vitrectomy. The finding of vitreomacular adhesions and macular serous detachment by OCT, although not mentioned, would logically be a good surgical prognostic factor too. Poor prognostic factors included the presence of macular ischemia , VA equal to or worse than 20/200, previous macular photocoagulation, and the presence of large or subfoveal hard exudates.[76-87]

Why does vitrectomy and hyaloid removal with or without ILM peeling relieve ME?

The release of vitreomacular traction is one obvious mechanism. This has been well-demonstrated by OCT and reported by various authors. OCT studies have also demonstrated the resolution of associated subclinical shallow macular traction detachments and serous macular detachments. Vitrectomy appears to increase oxygenation of the macula. Kadonoso and colleagues81 demonstrated increased perifoveal capillary blood flow after vitrectomy in their series. Others have reported that vitrectomy with lens removal allows aqueous to provide increased levels of oxygen to the inner retina and that movement of oxygen transcorneally to the vitreous has been demonstrated to be more effective in vitrectomized eyes.[83] In addition to higher oxygen levels, aqueous has procoagulant properties and also contains high levels of ascorbic acid that acts as an antioxidant and a suppressor of neovascularization. Removal of the posterior hyaloid also removes toxic substances, such as histamine, free radical scavengers, and VEGF, which may be harbored in the preretinal space.79 Peeling of the ILM would appear to enhance the beneficial effects of vitrectomy. The technical difficulty associated with its surgical removal is ameliorated with staining that specifically targets the ILM.[87]

With respect to cataract surgery in patients with DME, pre-existing macular oedema should be treated preoperatively, where possible. If this is not possible, intravitreal anti-VEGF or steroid injection may be given at the conclusion of the cataract operation. DME may progress more rapidly following cataract surgery, hence it is advisable to monitor the eyes with pre-existing retinopathy and DME more closely in the postoperative period.[88]

Interpretation of the results

The anti-VEGF drugs appear to be clinically effective in treating DMO in studies up to 2 years.Ranibizumab has the most robust evidence base and has shown superiority compared to laser and sham injection in all trials and meta-analyses. Adding laser to ranibizumab conferred no benefit in most of the studies. However the DRCR.Net did find benefit in especially deferred laser group. Thus it seems that primarily DME should be treated with anti VEGF agents at monthly or frequent intervals atleast for 6 months before addition of laser as observed by DRCR.Net study which has recently completed 5 years of follow up. Bevacizumab has also been shown to be superior to laser in limited

studies. The addition of triamcinolone to bevacizumab did not provide further benefits. Which is better; Ranibizumab or Bevacizumab is still debatable as only a few studies are available that has compared these drugs in DME. The fact that Ranibizumab has robust evidence to support its superiority on DME management cannot be implied on Bevacizumab which though a similar molecule has many differences. Pegaptanib has only been compared to sham injection and therefore meaningful recommendations cannot be drawn from the available studies. How Pegaptanib favours in comparison to laser or ranibizumab/bevacizumab is not known. Further published data are required before drawing conclusions on aflibercept. However, although the anti-VEGF drugs are a significant advance, they fail to improve BCVA by 10 or more letters in half or more patients, and so they do not provide a complete answer to DME. Inclusion criteria for various studies are also different and therefore no blanket criteria for case selection can be adopted. Baseline vision, Central foveal thickness, prior treatment, background retinopathy, glycemic control, systemic co morbidities etc may be confounding factors. Also eyes with vitreomacular traction, epiretinal membranes, taut hyaloids or ILM etc may be better candidates for surgical intervention.

Steroid treatments have inconsistent results and are undoubtedly associated with increased IOP and cataract. The effects of dexamethasone implants appear to peak at 3 months. At 6 months, there was no significant difference compared with laser. This might imply that earlier retreatment is needed if the beneficial effect is to be maintained, but increasing the number of treatments would very likely increase the associated complications, especially with the relatively large needle size. The addition of laser did not appear to add further benefit.

There was no significant difference in cataract formation at 6 months with dexamethasone compared to observation, but it is likely that a higher incidence of cataracts would be seen with longer follow-up. Significantly more patients suffered increased IOP in the dexamethasone group compared with observation. Fluocinolone has been shown to be effective compared with sham injection. However, when compared to standard of care (laser or observation at clinician's discretion), there was no significant difference in the proportion of patients with a 15 letter or more gain. Both studies reported higher incidence of cataract formation in the fluocinolone group, with over 80% at 3 years at the higher dose. Results for Triamcinolone are inconsistent. The DRCR net[64] found that laser was more effective, while others have found no statistically significant difference. Triamcinolone combined with laser, however, seemed to have similar efficacy as ranibizumab combined with laser

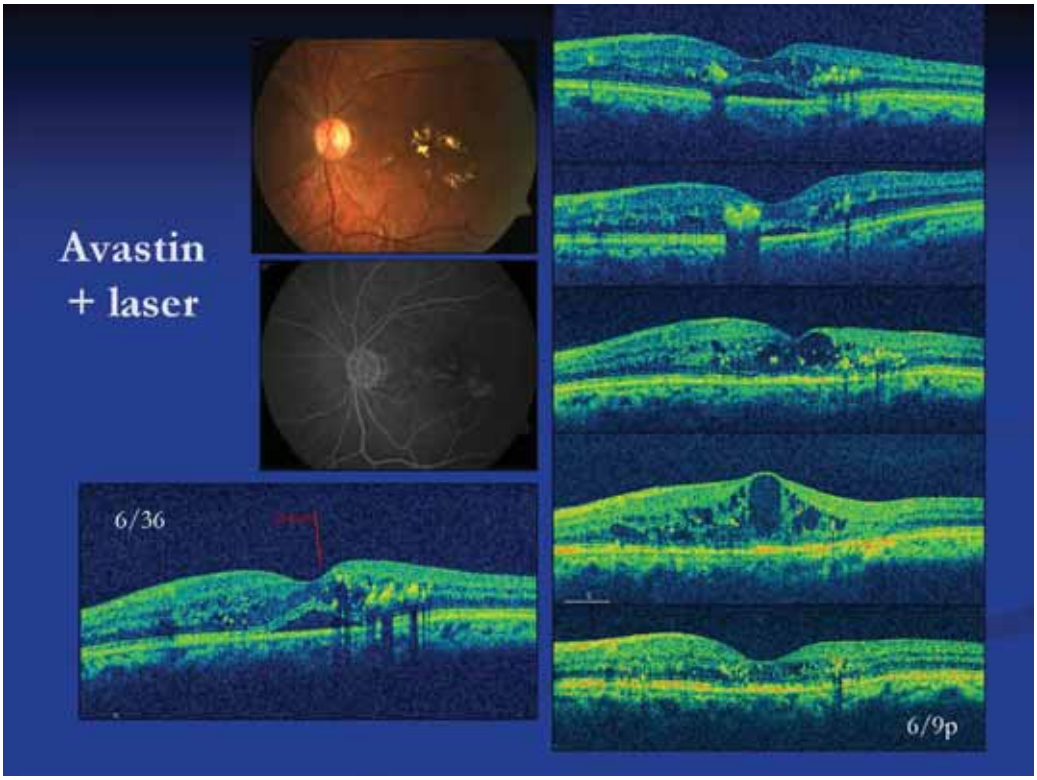


Fig 1; Patient with centre involved macular edema followed up for 1 year requiring multiple intravitreal avastin injections to maintain CFT less than 250 microns and demonstrating visual improvement.

in pseudophakic eyes.. Triamcinolone has consistently been associated with increased incidence of cataract and raised IOP. Steroids and laser therapy may affect CMT in a different manner from anti-VEGF drugs. For example, when ranibizumab alone is compared with ranibizumab plus laser, it appears to be more effective in terms of mean change in BCVA and proportion of patients with more than 15 letter gain. However, ranibizumab plus laser is more effective at reducing CMT. Furthermore, when triamcinolone plus laser is compared with ranibizumab plus laser, the latter appears to be more effective in terms of change in BCVA and proportion of patients with more than 15 letter gain, but triamcinolone plus laser is more effective at reducing CMT. However, eventhough Anti VEGF seems superior to steroids in DME management, it should be noted that about half of the patients do not get good results with anti-VEGFs. Only 50% of patients had gains in VA of 10 or more letters. So the anti-VEGFs are 'game-changers', but their impact should not be overestimated. In those who do not respond to anti-VEGFs or laser, there remains a place for steroids, despite their high adverse effect rates. The European licence for fluocinolone recognises this, by stating that it should be used when other therapies have not had sufficient effect. Considering other aspects, Bevacizumab is not licensed for intraocular use when compared to Ranibizumab which is FDA approved and the legal issues of advocating this in practice have to be considered. However it costs considerably less than other forms of therapy and currently remains the most common agent used. The Royal College of Ophthalmologists' Clinical Guidelines for DME management summarises the management in a nutshell[13].

CFT > 250 microns BCVA < 6/9	CFT > 250 microns BCVA > 6/9	Noncentral DME
Ranibizumab (level A) Ranibizumab plus laser (level A) Bevacizumab (level B) Laser photocoagulation (level A) Fluocinolone inserts (level B) Dexamethasone inserts (level B)	Observation (level A) Ranibizumab (level B) Laser photocoagulation (level A)	Observation if VA > 6/9 (level A) Laser photocoagulation if VA <6/9 (level A)

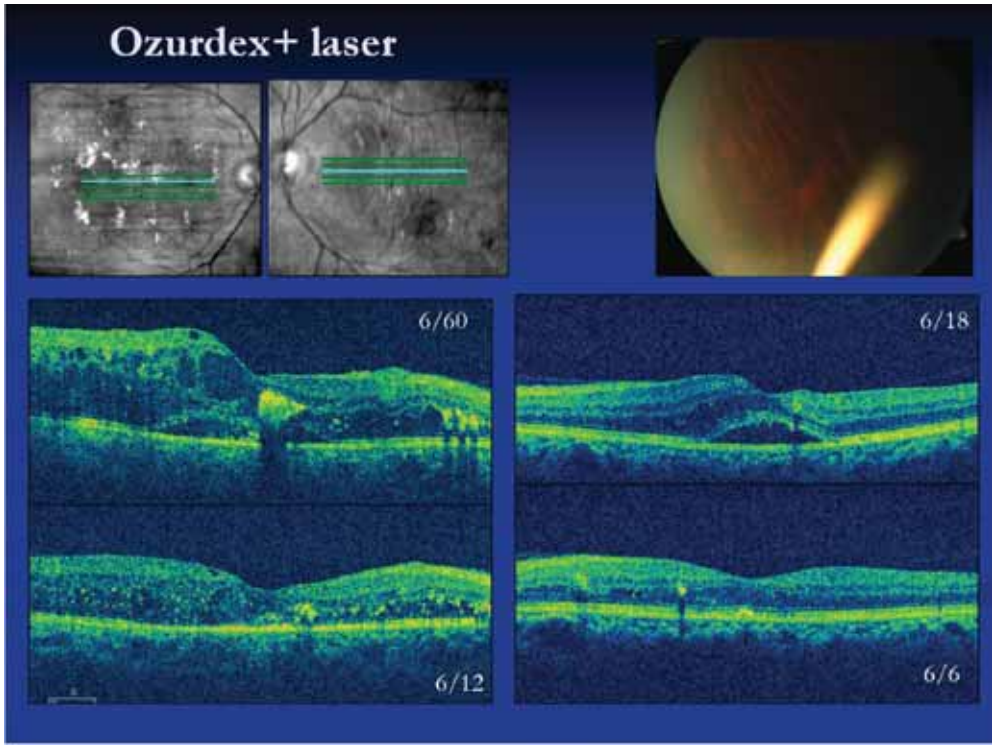


Fig 2; Patient with centre involved macular edema in both eyes who received intravitreal Ozurdex followed up for 12 months. This patient required 2 injections in the right eye and a single injection in the left eye to maintain CFT less than 250 microns and demonstrating visual improvement. The intravitreal Ozurdex implant insitu can be seen in the picture.

Level A: where strength of evidence was universally agreed and is based on multiple RCT; Level B: where the probability of benefit to the patient outweighed the risks and is based on single/few RCT's and non randomised trials, case series and case reports.

Some additional considerations for choosing the right intravitreal agent

Avoid Anti Vegf therapy	Old patients with an ischemic heart disease or stroke in the recent past (within 4 months), uncontrolled hypertension, advanced renal disease
Avoid intravitreal steroids	Steroid responders, eyes with glaucoma, renal disease

Conclusion

With respect to anti VEGF therapy, currently there is more evidence for the effectiveness of ranibizumab and bevacizumab than for pegaptanib and VEGF-trap eye. Anti-VEGF drugs especially Ranibizumab appear to be a significant advance in the treatment of DME and are regarded now as the treatment of choice for patients affected by DME. Studies assessing the effectiveness of steroids have reported mixed results. The high rates of cataract and increased IOP are a drawback. Triamcinolone combined with laser may be a good option for pseudophakic patients and may be more cost-effective than treatment with ranibizumab. However, the need for fewer administrations, potentially one every 3 years with fluocinolone, is advantageous. Currently, the role of laser in the treatment of DME is debatable given the established superiority of anti VEGF over laser in most situations. However in non centre involved DME, the ETDRS guidelines of laser photocoagulation still holds undisputed. The role of additional laser after anti VEGF therapy after 6 months has also been established. Surgical indications are definite and reserved for those eyes with vitreomacular interface abnormalities and medically resistant macular edema.

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Major Review

Optical Coherence Tomography - Evolution and Clinical Applications

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Introduction

Optical coherence tomography (OCT) is a noninvasive imaging modality that has revolutionized the practice of clinical ophthalmology over the past decade. OCT provides high-resolution cross-sectional images of the retina, optic nerve head and retinal nerve fibre layer (RNFL)unobtainable by any other current modality, andenablesqualitative and quantitativeevaluation.As opposed to other retinal imaging modalities that provide én face images, it provides for sectional information, and in that sense is analogous to an in vivo "optical biopsy" (Figure 1). It is safe, fast, reproducible, does not require greatly skilled technicians, and has minimal, if any, interobserver issues.Several advances in recent times have contributed to vast improvements in resolution and speed of OCT devices, and expanded their applications manifold.In 2010, in the US alone, an estimated 16 million OCT procedures were done, amounting to $ 780 million in reimbursement.[1]

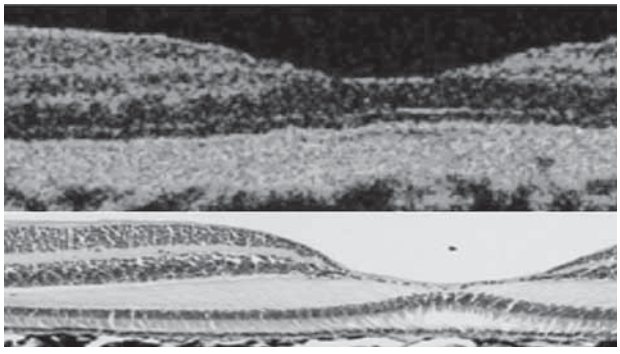


Fig 1. Macular OCT with representative histology

Evolution

OCT technology was originally employed in the telecommunications industry to localize faults in fiberoptic networks (termed 'ranging').[2] A disruption in a fibreoptic cable would reflect back light and low-coherence interferometry would extract time of flight information toenable distance mapping. The first ophthalmic use of this technology was in precision axial length measurements.[3,4] Low coherence interferometry is the backbone of currently used optical biometric devices like IOLMaster(Carl ZeissMeditec, Germany), LensStar (Haag Streit AG, Switzerland) and ALScan (Nidek, Japan). Three other developments in the optics-photonics industry contributed significantly to the development of the OCT. The availability of superluminescent diodes(Figure 2) gave a huge boost to OCT development as they represented an excellent low cost and low maintenance light source option. The human eye reflects back less than 1/10000th of light incident on the retina. To overcome the safety issue apparent with increasing retinal illumination to obtain better scan signals, optical heterodyne detection was employed. This is a technique to improve detection and interpretation of faint signals.The incorporation of high speed line camera technology to enable fast successive repetitive A-scans over a line was essential toscan tissue in a linear pattern and hence obtain 2 dimensional images. James Fujimoto and his group at the Massachusetts Institute of Technology demonstrated the cross-sectional imaging ability of this technology[5] by combining data of several 1-D scans (A-scans)to form a 2-D image (B-scan). They were also the first to employ color codes for brightness representation, thereby generating the false colored images we are now so familiar with.

The first commercial OCT system (OCT 1) was introduced by Carl Zeiss in 1996. With minor improvements, a second generation OCT device was introduced in 2000. These devices were slow (100 A-scans/second) and provided limited resolution, resulting inrestricted acceptance by the ophthalmology community. However, the third generation OCT device introduced in 2002 (Stratus, Carl Zeiss Meditec) changed the scenario. It offered better speed (400 A-scans/

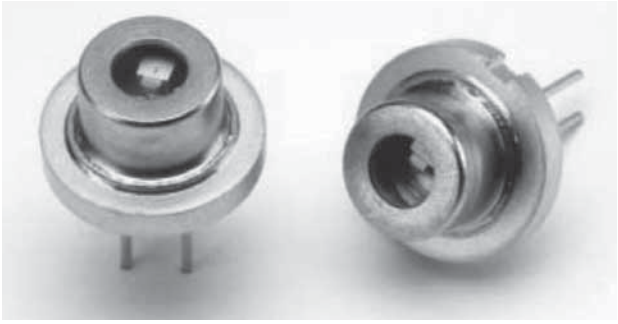


Fig 2.Superluminescent Semiconductor Diodes

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second) and resolution than earlier machines. It gained widespread adoption into ophthalmology and quickly became the standard for clinical trials in retinal diseases. Another major advance in the OCT field (application of Fourier techniques) led to the introduction in 2006, of a much faster device (27,000 A-scans/second) with better resolution (RTVue, OptoVue, USA). This was the first spectral domain OCT (SD-OCT), and was very quickly followed by similar devices from several manufacturers (Cirrus, Carl Zeiss Meditec; Spectralis, Heidelberg Engineering; 3D-OCT, Topcon). The major difference between earlier OCT systems and this generation was the replacement of a moving reference mirror with a fixed one. The movement of the reference mirror placed serious restrictions on the speed of scanning. Commercially available OCT systems today provide imaging with 5μ axial resolution and 10-15μ transverse resolution.Currently, swept-source OCTs (SS-OCT) are being developed and offer even higher scan speeds (>2,50,000 A-scans/second) and resolution than current commercial devices. Coupling adaptive optics with OCT has led to the development of devices with a resolution upto 1μ that can image at the cellular levelin vivo.

Basics of OCT

Ocular tissue is made up of layers of differing refractive indices. The interface between these layers represents a discontinuity at which incident light is backscattered. OCT illuminates sample tissue using light from a broadband source and collects backscattered light from the same. In this aspect, it is the optical analogue of ultrasound imaging. Optical signals reflected from backscattering sites carry time-of-flight and intensity information. Optical ranging (from time-of-flight information) tells us from where the signal came from. Intensity of the backscattered signal points to reflectivity of the interface/ tissue. Low coherence interferometry is used to extract these data from reflected signals.

An OCT system (Figure3,4) consists of a broadband light source (Fig 4A)connected to a fibreoptic Michelson's interferometer. Generated light travels to a beam splitter (Fig 4B), which splits the incident light to two beams. One of these beams illuminates the sample tissue (Fig 4C) and the other travels to the reference mirror (Fig 4D). Reflected beams from both return to the beam splitter and the resulting interference pattern is detected by a photo-detector or spectroscope (Fig 4E). A tissue scanning mechanism moves the scan axis across the sample in a linear fashion. A computer (Fig 4F) assimilates data from thousands of point scans and processes it to generate linear (two-dimensional) (Fig 4G) and three-dimensional images.

Images generated by the imaging engine are originally in grayscale. A false color coded representation is presented in the final image to aid with interpretation of reflective intensity. In this color coding, warm colors (red, yellow) represent hyper-reflective tissue and cold colors (blue) represent hypo-reflective tissue. Non-reflective areas (e.g. vitreous, intraretinal fluid) appear as black. Retinal layers are visible as alternating hyper-reflective (plexiform layers) and hypo-reflective (nuclear layers) bands.

Clinical applications

1. Interpretation

OCT scanning results in cross-sectional images of the retina unlike angiography or fundus photography. Hence, familiarity with cross-sectional or 'histological' anatomy of the retina greatly facilitates interpretation of OCT images.

Normal Anatomy

Optically transparent vitreous is invisible and appears as the black (non-reflective) region in the upper part of an OCT image. In cases with some degree of posterior vitreous detachment, the posterior vitreous cortex may be visible as a discrete moderately reflective line (green). The retinal nerve fiber layer (RNFL) appears next, as a hyper-reflective (red) band at the vitreoretinal interface. The RNFL overlies alternating hypo-and hyper-reflective bands of retinal tissue. The hyper-reflective (green) bands represent axonal (mostly horizontal) layers like the plexiform and nerve fiber layers. The hypo-reflective (dark) bands represent nuclear layers and photoreceptor outer segments. A relatively broad (70-80μ) highly reflective layer visible as a thick red line underlying these alternating green and dark bands corresponds to the retinal pigment epithelium (RPE) and choriocapillaris complex. This marks the outer boundary of the retina and is used as a landmark for calculation of retinal thickness. Immediately above this RPE-choriocapillaris complex, and separated from it by a hypo-reflective band signifying photoreceptor outer segments, is a thin hyper-reflective red line that represents the inner segment- outer segment (IS-OS) junction. Above this layer, a moderately reflective line may be seen frequently and signifies the location of the external limiting membrane (ELM). Together, the ELM, IS-OS junction, photoreceptors and RPE constitute the outer retinal layers and are of great prognostic importance in a range of retinal diseases. At the fovea, only the outer nuclear layer overlies the photoreceptors.

The choroid underlying the RPE-choriocapillaris complex is visible as voids interspersed with mildly hyper-reflective tissue. The voids represent the medium and large choroidal vessels. In routine OCT, the choroidal signal fades away

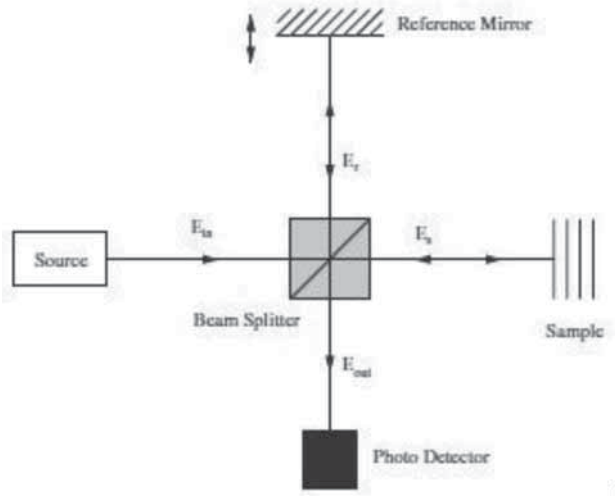


Fig 3. Basic OCT principle- Interferometry

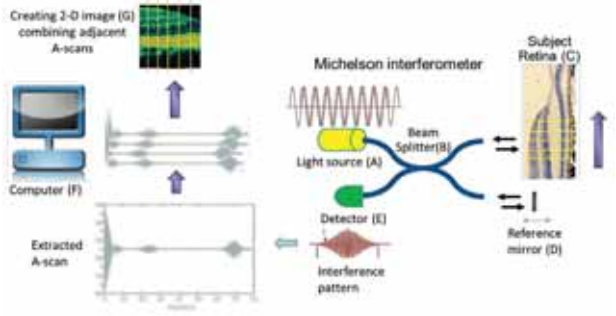


Fig 4. Working OCT Design

rapidly without a distinct posterior boundary. Where enhanced depth imaging (EDI) is employed, the choroidal outer boundary (inner sclera) may be visualized, enabling quantification of choroidal thickness.

Pathoanatomy

Retinal pathology can create a range of structural alterations in the normal architecture that can be recognized on OCT images by their configuration, location and reflective properties. Awareness of the optical properties of tissue likely to be present in the area of scanning is essential. Transudate or fluid accumulation reduces reflectivity of tissue and, when localized, results in an optical void. Blood, hard exudates, pigment and fibrous tissue are hyper-reflective and when sufficiently thick, may not allow scan beams to pass through, resulting in shadowing out of underlying structures. RPE atrophy may result in less backscattering at this layer with enhanced signal from the underlying choroid. Fluid accumulation is a result of a variety of pathologies from central serous chorioretinopathy (CSCR) to diabetic macular edema. Areas with fluid accumulation exhibit increased retinal thickness. When intraretinal, this fluid leads to optical rarefaction or cyst formation (Fig 5A, B). When a

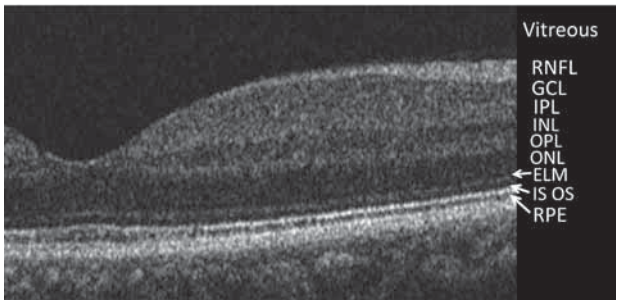


Figure 5. Normal cross sectional retinal anatomy on SD-OCT

distinct optical void is present between the neurosensory retina and the RPE, it representssubretinal fluid (SRF) or neurosensory detachment (Fig 5C). When an optical void is present underlying the RPE band, it signifies pigment epithelial detachment (PED) (Fig 5D).

Less-than-normal retinal thickness measurementsare a result of atrophy or abiotrophy. The loss in retinal thickness may be more pronounced in the inner retina (as in vascular occlusions) or outer retina (long standing CSCR or retinal dystrophies).There can be discontinuity in the retinal tissue at the fovea, which may be partial (signifying lamellar macular hole) or complete down to the RPE (full thickness macular hole). 'Extra' tissue may be present overlying the retina (fibrovascular proliferation, epiretinal membranes) or underlying it (choroidal neovascular membranes). Image contours can also present evidence of dynamic forces (pull, as in vitreomacular traction; push, as in choroidal tumors) acting on the retina.

2 Retina

2.1 Vitreoretinal interface disorders

Posterior vitreous detachment (PVD), when limited or macular in nature can be visualized on the OCT image as a thin green line of posterior vitreous cortex.With complete PVD, the posterior vitreous cortex moves too anteriorly to be imaged in one frame with the retina. Vitreoschisis can be identifies as double or multiple linear shadows of moderate reflectivity. Vitreomacular traction (Fig 6) is caused by continued pathologic adherence of the vitreous at the macula in the setting of a perifoveal vitreous detachment or vitreoschisis leading to traction, macular distortion and cystoid macular edema (CME).[6-8] OCT demonstrates a V-shaped posterior hyaloid,attached at the fovea and detached temporal and nasal to it. The vitreous may be adherent at the optic disc and along the arcades in these cases. There may be associated epiretinal membranes (ERM), CME, intraretinal splitting or a tractional foveal detachment. Surgery is usually successful in releasing the traction and reversing the anatomical derangement, with improvement in vision in most cases.

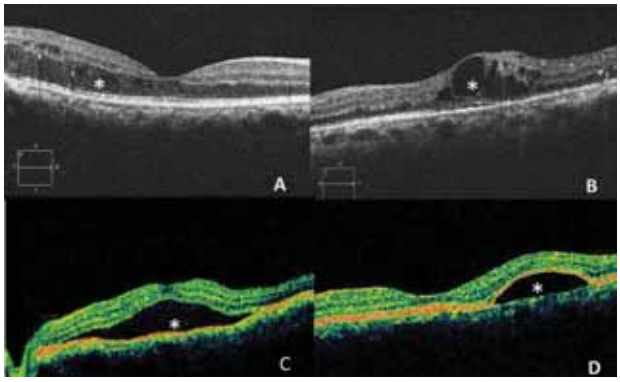


Figure 6. Appearance of fluid on OCT images, A: optical rarefaction (*); B: cyst formation (CME) (*); C: subretinal fluid (SRF) or neurosensory detachment (*); D: Pigment epithelial detachment (PED) (*)

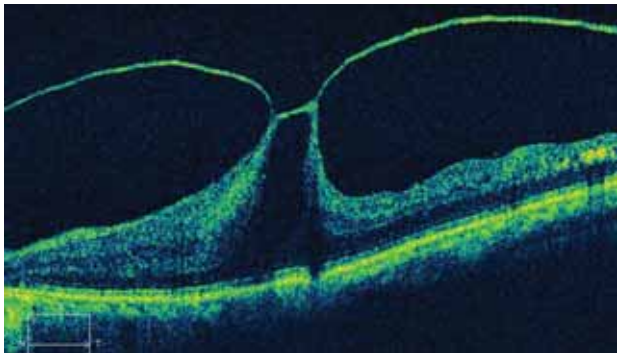


Figure 7. Vitreomacular traction

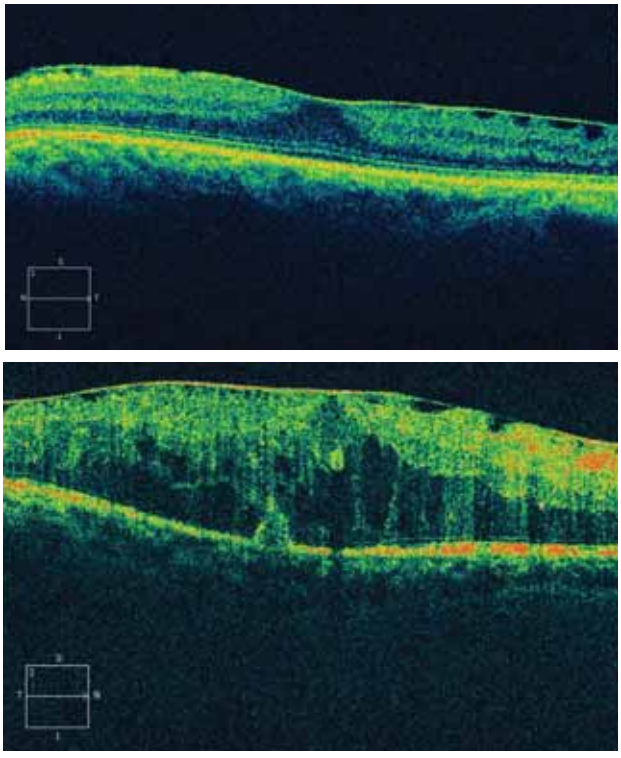


Figure 8. Epiretinal membranes (Left, with minimal retinal thickening; Right, Macular edema)

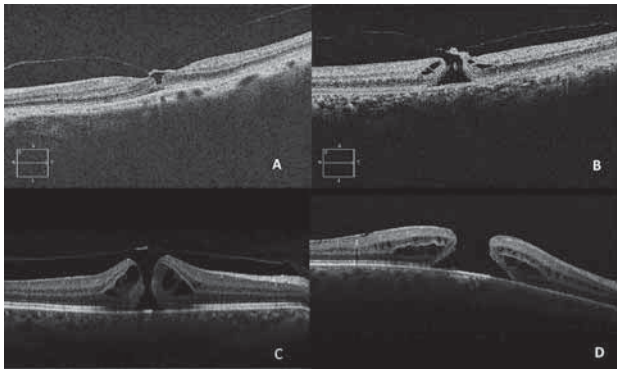


Figure 9. Idiopathic Macular Hole. A: Stage 1- Foveal pseudocyst; B: Stage 2- Full thickness macular hole (FTMH) with foveal vitreous attachment; C: Stage FTMH with operculum and limited PVD (note papillary vitreous attachment); D: Stage 4- FTMH with complete PVD

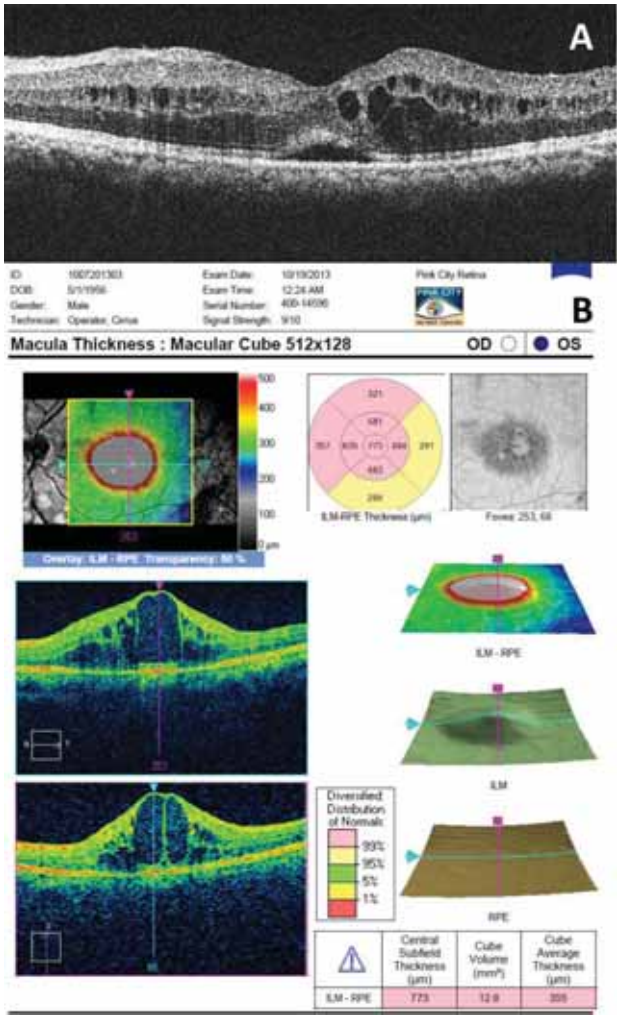


Figure 11. Without high resolution crosssectional imaging, it is challenging to characterize fluid accumulation in the retina, quantify it or segregate its components. A: The macular edema has mixed morphology with a combination of spongiform and cystoid edema and neurosensory detachment; B: Retinal Thickness Parameters

Epiretinal membranes, either idiopathic or secondary to intraocular inflammation, retinal vascular disease, or postoperative, occur in 2.2% to 18.5%of the population.[9-13] An ERMis visible on the OCT image as a taut hyper-reflective line contiguous with or anterior to the inner retinal surface.[14] The ERM may be globally adherent or have varying degrees of separation from the inner retina (Fig 7). ERMs may result in loss of the foveal contour,irregularity and corrugation of the inner retinal layers, and macular thickening.All these changes are clearly characterized on the sectional image provided by the OCT. The status of the outer retinal structures (photoreceptor layer, IS-OS junction, ELM) may have prognostic significance in cases where ERM surgery is indicated.[15-18]

OCT has contributed vastly to the understanding and management of idiopathic full thicknessmacular holes. The traction theory of formation of macular holes and their stages, proposed by Gass,[19,20] has been reinforced and supplemented by OCT imaging (Fig 8).[21-23] It has been demonstrated on OCT that macular hole formation proceeds through successive stages, the first event beingperifoveal PVD with persistent vitreofoveal adhesion causing traction on the fovea. This is followed by foveal cyst formation (occasionally with foveal detachment), which may progress to full-thickness retinal defect or a lamellar defect or to spontaneous resolution with complete vitreofoveal separation.[24-25] OCT is indispensable in the preoperative assessment of full-thickness macular holes for accurate staging, measurement of hole dimensions and derivation of several indicesand assessment of retinal architecture.[26-29] These serve as useful predictive factors for macular hole surgery. Postoperative assessment of macular hole closure can be characterized on OCT imaging (Fig 9).[30] SD-OCT has also enabled correlation of outer retinal morphological features with visual outcome in eyes with surgically closed idiopathic macular hole.[31-33]

Lamellar macular holes (LMH) are partial thickness defects in the inner retina probably caused by a combination of oblique traction of vitreous and tangential tractional force of overlying ERM. On OCT images, LMH is seen as a partial-thickness defect of the inner retina, with an irregular foveal contour and reduced foveal thickness, intact outer retinal layers at the base of the hole, and a splitting of the inner from the outer retinal layers surrounding this defect (Fig 10A).[34] A large number of these are associated with ERMs. Lamellar holes, when symptomatic, are amenable to surgical correction.[35] Macular pseudoholes are a distinct entity with a clinical appearance of a sharply defined reddish area at the fovea mimicking a macular hole. On OCT imaging, pseudoholes display a steep fovea contour, surrounding ERM and a normal or slightly increased central and paracentral retinal thickness. There is no retinal defect and no disturbance of outer retinal structures (Fig 10B). OCT is an invaluable tool in distinguishing these clinically similar macular pathologies.

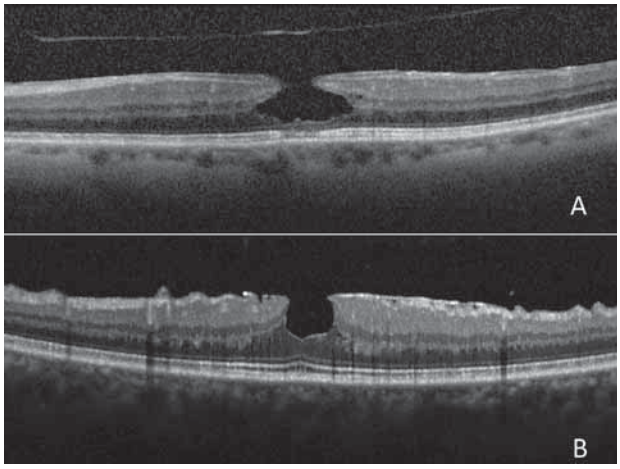


Figure 10. A: Lamellar Macular Hole; B: Pseudohole

2.2 Intraretinal disorders

Macular edema is an integral manifestation of several retinal pathologies. Vascular retinopathies (diabetic retinopathy, vein occlusions), inflammatory conditions (post-operative, posterior or intermediate uveitis), pharmacologic agents and hereditary retinal degenerations can result in retinal thickening at the fovea that is clinically visible. However, the best characterization of macular thickening is possible only on OCT imaging (Fig 11), and this is now the standard of care in the management of these patients.Sectional images reveal internal morphology of the retinal edema, from diffuse thickening to cystoid and schitic pattern, which have been found to correlate with retinal sensitivity loss.[36] Quantification of retinal thickness and volume can be performed and has become the gold standard in all clinical trials on macular edema. Temporal trends and treatment effects can be evaluated on serial scans. Changes on OCT may indicate initiation or cessation of treatment for macular edema. The OCT is particularly invaluable in the diagnosis and management of cases with non-clinically significant macular edema and mild macular thickening.

Retinal dystrophies and degenerations have distinct features on the OCT depending upon the stage of the disease. Retinitis pigmentosa and some dystrophies presents with retinal thinning.[37] In most of these conditions, the outer retinal layers are mainly affected, especially the outer nuclear layer, photoreceptor layer and IS OS junction.[38-40] Choroidal thinning, apparent on enhanced depth OCT imaging, is a feature of some of these dystrophies.[41,42] Vitelliform

dystrophies present with increased retinal thickness initially with intact outer retinal layers.[43,44]

Drug toxicitiesmay be detected at an early stage using SD-OCT. Hydroxychloroquine toxicity reveals parafoveal loss of the inner segment-outer segment and cone outer segment tip lines at early stages of toxicity leading to a dipping of the overlying ELM and retinal layers in this region.[45,46] The changes are most marked about 1 mm from the fovea.[47] OCT changes may progress to parafoveal thinning of the outer nuclear layer and eventually to retinal pigment epithelium damage. OCT assessment of parafovealretinal thickness[48] and architectureis an important investigation along with 10-2 visual fields in patients on long term antimalarials.

OCT imaging is very useful in the detection of myopic foveoschisis, a condition otherwise extremely difficult to diagnose clinically or with conventional imaging. OCT imaging has also been applied to image retinal lesions away from the macula.[49] It may be employed in detecting subclinical lesions and assist in decision making in clinical dilemmas.

2.3 Subretinal pathologies

OCT is invaluable in the management of AMD patients. OCT assessment can detectsubtledisease activity before clinical examination can. On OCT images, a choroidal neovascular membrane is visible as a focal or broad area of thickened RPE- choriocapillaris complex with local fluid accumulation, either intraretinal or subretinal. Broad areas of hyperreflectivity overlying the RPE band may give an impression of reduplication of the RPE (Fig 12). Hemorrhages appear as hyper-reflective areas with shadowing beneath the same. PEDs appear as dome shaped elevation of RPE choriocapillaris band. When serous in nature, the underlying choroid signal is visible below the PED. Hemorrhagic PEDs present with shadowing out of the underlying structures. Disruption of outer retinal structures and choroid alterationscan be betterappreciated and documented with OCT imaging.[50,51] VMT is often noted in cases of wet AMD. [52,53] The ability todetect the presence of even the smallest traces of subretinal and intraretinal fluid on cross sectional imageshas made OCT a vital tool in decision making. Treatment regimens based on OCT have proven to be very effective in preserving vision in patients with wet AMD.[54,55] It has been demonstrated that manual qualitativeassessment of OCT images may represent thepreferred method to assess leakage in AMD without relying on the machine[56] or absolute central macular thickness values to base decision making upon. Automatic retinal layer identification and segmentation (on which retinal thickness measurements depend) is often erroneous in AMD cases (Fig 12). Drusen can be appreciated on OCT as irregular undulations or bumps of the RPE complex. Focal hyper-reflectivity over the drusen may be correlated to RPE atrophy. Areas with geographic atrophy display loss of the RPE hyper-reflective band with increased choroidal reflectivity, and disruption of the IS OS junction and ELM. The Bruch's membrane, normally indistinguishable on OCT from RPE in pigmented eyes, may be seen prominently.[57]

Central serous chorioretinopathy (CSCR) is seen on OCT as a dome shaped elevation of neurosensory retina. In acute CSCR, the retinal architecture is well preserved. In long standing CSCR, overlying retina shows cystoid spaces and thinning on OCT. PEDs and fibrin may be seen underlying the retinal elevation. OCT is useful in monitoring patients' progress while waiting for spontaneous resolution, if observation has been opted. It is also valuable in detecting subtle fluid in chronic cases (Fig 13).

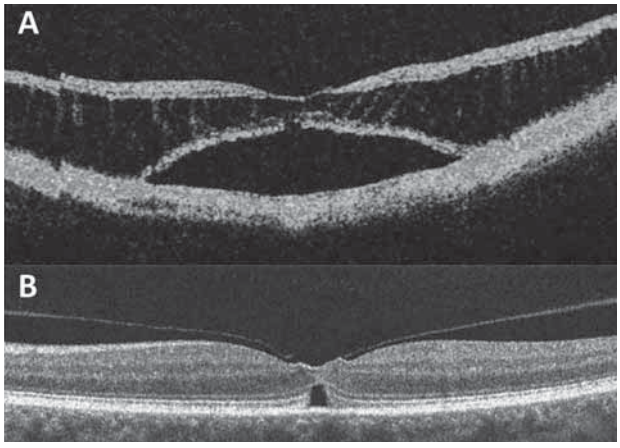


Figure 12. Visual loss with normal foveal contour. A: Myopic foveoschisis; B: Macular microhole

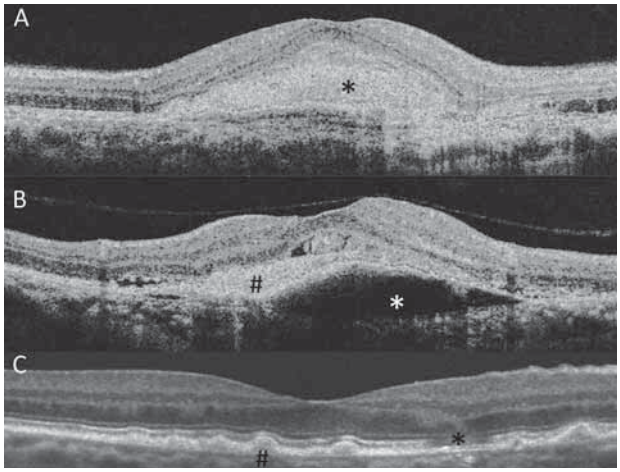


Figure 13. OCT in AMD. A: Choroidal neovascular membrane. Note 'reduplication' of RPE (*); B: Hemorrhagic PED (*) with subretinal CNVM (#); C: Dry AMD with Drusen (#) and Geographic atrophy (*)

3 Glaucoma

Identification of structural optic nerve damage iscrucial in the diagnosis of glaucoma and monitoringits clinical course.[58] OCT provides objective, reproducible,automated, quantitative measurements of the optic nerve head andRNFL thickness. Software on the OCT recognizes landmarks to map out the optic nerve head (ONH) and the RNFL. Measurements, such as rim and cup area and vertical andhorizontal cup-disc ratio are then presented along with quantitative measurements of RNFL thickness in every clock hour. The OCT system also provides statistical comparison of test values to the population normative database, and depicts these in a color coded format for easy recognition of abnormalities.OCT can detect RNFL abnormalities that often exist in eyes with early glaucoma with normal standard automated perimetry.[59,60] RNFL thickness is better than ONH parameters in the detection of preperimetric glaucoma, and rim area is similar to average RNFL thickness in the diagnosis of advanced glaucoma.[61,62] OCT compares favorably to confocal scanning laser ophthalmoscope and scanning laser polarimetryin discriminating between normal eyes and glaucomatous eyes.[63,64] Longitudinal follow-up of glaucoma progression is possible using software available on OCT systems.[65,66] However, there is insufficient long-term evidence as to the validity or superiority of using any particular software as OCT systems have evolved rapidly in the last few years, resulting in inadequate follow-up of patients on the same system. Currently, the standard of care in glaucoma management is clinical assessment coupled with one or more of the ONHstructural imaging modalities.[67] Additionally, it is not recommended to use OCT for general population glaucoma screening.[68]

Recently, interest has been generated in macular imaging for glaucoma detection. The limitation imposed on retinal layer segmentation by earlier generation OCT due to their low resolution has been offset by the newer SD-OCTs. Ganglion cell layer- inner plexiform layer (GCIPL) and ganglion cell complex (GCC=GCIPL+ macular RNFL) measurements have been actively investigated in the diagnosis of glaucoma. The diagnostic capability of GCIPL has been found comparable with RNFL, and minimum GCIPL has been reported to be the most sensitive for the diagnosis of glaucoma.[69-72] Regional GCIPL measures have performed as well as regional RNFL measurements for detection of early glaucoma, though average RNFL thickness performed better than average GCIPL measures.[73] Though ganglion cell measurements offer good diagnostic capability in detection of early glaucoma, they miss abnormal findings in glaucomatous eyes when RNFL defects the angular distance between fovea and RNFL defect is great (e.g. wedge defect near the arcades).[74] Currently, peripapillary RNFL measurements represent the most reliable of the structural parameters measured on OCT across the glaucoma spectrum.[75]

4 Anterior segment

SD OCT devices available today are capable of anterior segment imaging, though to a limited extent. Some devices need additional lenses for anterior scanning, whereas others have inbuilt adjustments for the same. Sectional images of the cornea are useful for corneal thickness assessment and for visualizing stromal pathology, e.g. after laser in situ keratomilieusis at the flap interface. Standard OCT has also been used to assess the anterior chamber angle, but has little value as it requires extrapolation. This is because the scanning beam of routine OCTs (830 nm) cannot penetrate tissue beyond the scleral spur. Visante OCT (Carl Zeiss Meditec, Dublin, CA) uses longer wavelength scanning beams and is superior for the assessment of the anterior segment. Phakic lenses can also be monitored using the OCT.

Future directions

The field of medical OCT is progressing rapidly, with the introduction of several innovative and powerful technologies. A recent application of existing OCT technology has been the integration of the OCT system to the operating microscope. This enables intraoperative OCT assessment of the macula during delicate macular surgery. A portable handheld OCT is also available for imaging the retina in supine patients. It is of particular use in pediatric population for imaging under anesthesia. OCTs with Doppler flow measurement ability are now available for clinical use.Poised to enter the clinical ophthalmology field are faster machines that use swept-source lasers for scanning (enabling very high scanning speeds and better resolution) and OCTs that employ longer wavelength light sources for better penetration and choroidal visualization. Multimodality integration is being attempted at several research centers to enable even more efficient utilization of OCT systems. Adaptive optics OCTs with cellular level resolution are already being utilized for experimental work. Better computational techniques and improved software for better segmentation continues to be developed.

Conclusions

Optical coherence tomography is a valuable clinical tool for the diagnosis and management of retinal diseases and glaucoma. Its use has enable better understanding, diagnosis, decision making and management in a wide variety of conditions.Ophthalmic practice continues to be

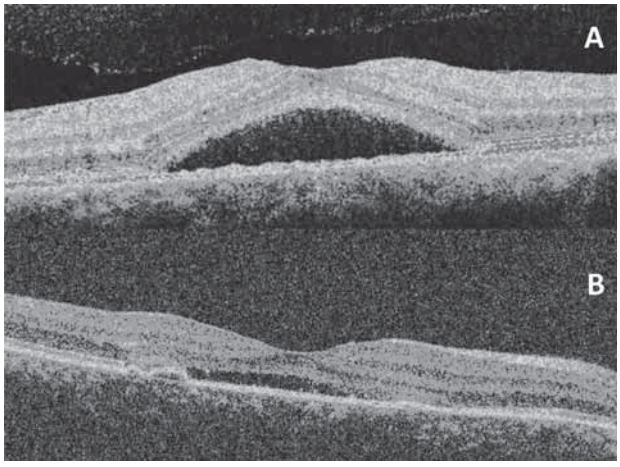


Figure 14. Central Serous Retinopathy. A: Acute, with intact retina overlying the SRF pocket; B: Chronic CSR with thinned retina and subtle, clinically unapparent subretinal fluid

enriched and refined by the wealth of knowledge coming out of OCT imaging, and several management paradigms in ophthalmology are now based upon information provided by OCT. The indications and applications of OCT continue to expand as experience grows and better technology becomes available. Major technologicaladvances in OCT are certain to impactresearch and clinical practice in ophthalmology in the future.

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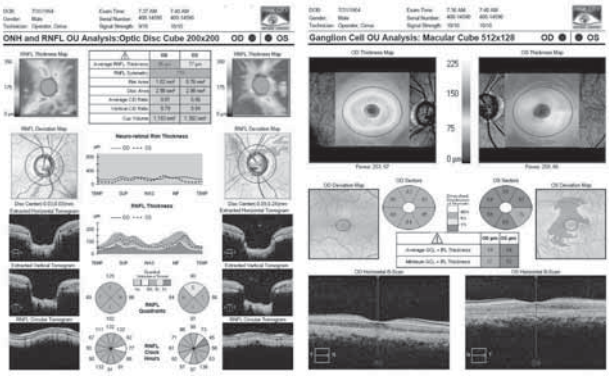


Figure 15. OCT in Glaucoma. Left, ONH parameters and RNFL map with analysis; Right, Macular GCL + IPL map

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Major Review

The Genome Project: The Search for the Retinitis Pigmentosa Genes

Dr. M.J.Denton Ph.D

Although it was established as early as 1855 that some forms of RP are inherited and although by the 1980s the three main mendelian classes were well established and a great deal was already known about the function of photoreceptor cell and the biochemistry of phototransduction and the visual cycle as well as the histopathological changes associated with the progression of RP, yet neither the chromosomal location nor the identity of one single gene responsible for RP or any other inherited retinal dystrophy was known. A major reason for this lack of knowledge was that until the beginning of the genome project there was no way of identifying disease genes or mapping them to particular chromosomal regions.

However during the 1970s two major developments occurred. Firstly it became apparent that scattered through the human genome there were many polymorphic sites ie., places where the DNA molecule varied within the population providing a limitless number of so called 'marker loci' which raised the possibility of locating disease genes by the method of linkage analysis. Secondly a series of dramatic technological advances occurred including the development of positional cloning methods, the use of recombinant DNA and restriction enzymes, and collectively these new techniques provided the technical means to exploit the possibility of using linkage to locate disease genes.

Polymorphisms: Many different types of polymorphisms have been discovered which have proved useful in gene mapping. Restriction fragment length polymorphisms (RFLPs) were one of the first types of polymorphisms used early in the genome project for gene mapping. Other types of polymorphisms used in gene mapping are microsatellites, which are short stretches of DNA made up of a varying number of short repeated sequences VNTRs (variable number tandem repeats) and single nucleotide polymorphisms (SNPs).

An single individual can only have 2 polymorphic variants (two polymorphic alleles) at any one chromosomal location— that is one variant at one site in one chromosome and a second at the corresponding site in the other homologous chromosome. However in the population at large there may be many more than 2 variants at any one genetic locus (chromosomal location) and in the case of VNTRs there may be 10 or more variants in the population.

Linkage: When two marker loci are close together on a chromosome they are said to be 'linked' and tend to segregate together during meiosis. This is because the chance of recombination decreases the less the physical distance between two loci. The greater the distance along the DNA molecule between two polymorphic sites the greater the chance that linkage will be broken by recombination during meiosis.

An important term is centimorgan. When two markers are one centimorgan apart it means there is a one in 100 chance that a recombination will occur in that interval during meiosis. When two markers are 10 centimorgans apart there is a one in ten chance of a recombination occurring in the interval that separates them. In terms of physical distance one centimorgan equals 1 million bases in the DNA. As there are 3000 million bases in the human genome this means that the human genome is 3000 centimorgans long.

Extensive linkage analysis studies over the past two decades have provided genetic researchers with accurate linkage maps showing the position of a vast number of marker loci on all human chromosomes and the distance in centimorgans between adjacent markers along all of the chromosomes. Thus any particular disease gene is bound to be linked to one or several of these marker loci and thus because the position of the marker loci is established, it is easy, by finding tight linkage between a marker locus and a disease gene, to map the disease gene and locate it in a particular chromosomal region. The fact that there are highly polymorphic variants scattered throughout the genome on all chromosomes and the fact that in the case

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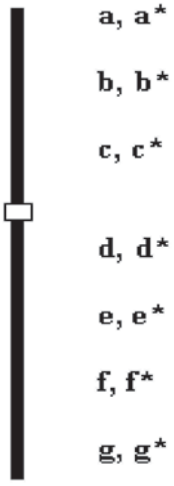
of every disease gene (or any gene for that matter) there are several tightly linked marker loci ie., loci that that are physically close to the disease gene and are unlikely to be dissociated on meiosis ie., likely to remain linked and inherited in tandem through several generations provides the basic means of gene mapping and is one of the key techniques which has led to the mapping over the past two decades of thousands of disease genes.

Genome scans and candidate genes: There are two major approaches to gene mapping. One approach used when there is no prior knowledge of the function or structure of the disease gene as to what its function might be in the organ or cell of interest (the retina or photoreceptor) is to search systematically for a marker locus linked to a disease gene in a large pedigree in which the disease is segregating an approach which normally involves a so called genome wide search. Such a search might start on the short arm of the chromosome 1 and test markers stretched along the length of the chromosome. If no marker is found on chromosome 1, chromosmome 2 is scanned and so forth until eventually a marker is detected which co segregates, ie., is tightly linked to the disease gene (Gelehrter et al, 1998; Primrose and Twyman, 2003). [1][2]

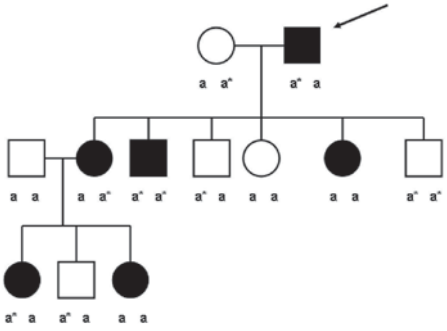
The essence of the technique is to find a marker which cosegregates with the disease—and this means where every individual in the family who has the disease also the marker. As the gene might be (a priori) anywhere in the genome then ALL regions of the genome must be systematically examined. Generally families chosen for linkage based searches for disease genes contain several affected individuals and are often multigenerational. A large multigenerational family contains many more occasions when recombination (during meioses) might occur between a marker locus and the disease gene.

The second approach—the candidate approach—is to screen genes known to be expressed in the tissue of interest and which may on a priori grounds functional grounds be potential causes of disease (such as rhodposin in the case of the retina and RP or hemoglobin in the case of hemolytic anaemia). In applying the candidate approach polymorphic markers closely linked to candidate genes are chosen and tested for linkage in the family with the disease. Again relatively large families with several affected are the families of choice as the more affected in a pedigree the easier it is to establish linkage between a disease gene and a polymorphic marker locus. After linkage to a marker locus in a particular region of the genome has been established the adjacent candidate gene (or genes) are directly sequenced in an affected individuals in an attempt to find a mutation which might disrupt the function of the gene and account for the disease phenotype. When a possible mutation is detected all the affected are then screened for that mutation. Succinct accounts of gene mapping in the field of retinal genetics are given by Bessant et al, 2003 and Brown et al, 2006) [3][4]

BOX 2 LINKAGE

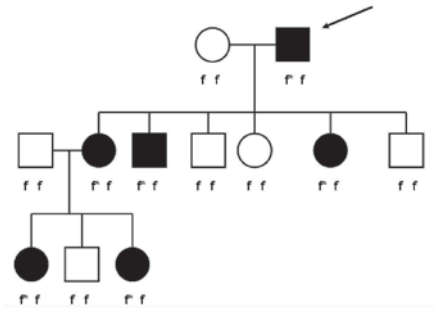


In the chromosome diagram above seven variable sites are shown along a chromosome. At each site there are two alternative DNA variants ie., a/a*, b/b* etc., in the population (these might be base pair differences or any other sort of detectable difference including for example VNTRs or SNPs. The more physically close two sites the less the chance of their being a crossover event between them which would break linkage.



In the pedigree diagram above which shows a pedigree with an autosomal dominant disease the affected indicated by the arrow is heterozygous at site a/a* but the segregation pattern of his two alleles in his descendents show the disease gene cannot be linked to either a or a*. Some affected have inherited a while other have inherited a*.

However as shown in the pedigree diagram below at site f/f* the segregation pattern suggest that f* may be linked to the disease gene. All affected descendents have inherited f*.



This suggests that the disease gene may be close to site f/f*. Only when a marker cosegregates with the disease in several individuals in a pedigree can linkage be established. Note: the chance of an unlinked marker cosegregating with a disease gene in any single meiosis is 50%. Generally a marker must cosegregate with the disease gene through at least 10 or more meiotic events to establish linkage. Put simply this means that the linkage between the marker and the disease locus has not been broken by recombination during 10 meiotic events. The likelihood that this would happen by chance is less than 1 in 1000. Linkage is considered established where the probability that the marker is linked to the disease gene is equal to or more than 1000 to 1. The LOG of 1000 is 3 and the conventional way of expressing linkage is to call this a LOD score of 3. A LOD score of 3 is taken to assume that linkage established.

The beginning of the genome project: The first dramatic step towards identifying the genes responsible for RP (and all inherited diseases of the retina) was taken in late 1984 when Bhattacharya et al, (1984) announced the location of a gene for X linked RP (RP2) on the short arm of the X chromosome in Xp1 (table 1). Later my own group located a second X-linked gene (Denton et al, 1988)[5] in Xp2 (RPGR, table 1). This second location was confirmed by subsequent studies (Wirth et al, 1988; Ott et al, 1990) [6][7] Subsequent studies revealed RPGR to be the most common X linked gene causing RP (Bader et al, 2003)[8]. The fact that there were two RP genes so close together on the X was a major discovery as it meant that at least in the case of X linked RP the disease was genetically heterogeneous and this suggested that if a small region of chromosome X contained two RP genes there may be many RP genes scattered throughout the genome and that the disease might be massively heterogeneous. All subsequent work has shown that this is indeed the case. All forms of RP, arRP, adRP and XLRP have all turned out to be massively heterogeneous .

Following this early landmark work on XLRP the next major advance came in 1989 when Peter Humphries' group in Trinity College Dublin localized the first adRP gene to a region on the long arm of chromosome 3 by linkage analysis of a large Irish pedigree (McWilliam et al, 1989; Farrar et al., 1990)[9][10]. Subsequent mutational screening of the rhodopsin gene (RHO) in US adRP families, carried out in Thadeus Dryja's lab in Boston (Rhodopsin was an obvious candidate known to be located in the region on chromosome 3 implicated by Humphries linkage studies) identified several mutations segregating with the disease (Dryja, et al, 1990; 1991)[11]. Rhodopsin was the first gene 'RP' gene to be identified.

The second RP gene identified (RDS) was a gene on the short arm of chromosme 6 encoding the protein peripherin a major component of the ROS disc membranes (Farrar et al, 1991)[12]. Mutations in RDS cause adRP.

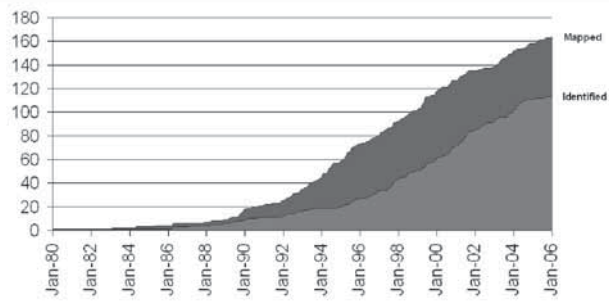
Meanwhile other researchers were initiating studies aimed at identifying arRP loci. One of the first recessive RP genes to be located (CRB1) on the long arm of chromosme 1 in the region of 1q31-32 (van Soest et al, 1994)[13] resulted from linkage studies of a large inbred Dutch pedigree. Shortly afterwards my own research group in Pakistan identified a second pedigree in which the RP gene was linked to the same chromosomal region (Leutelt et al, 1994) [14]. Screening of one of the candidate genes in the 1q31-32 location, a human homologue of the Drosophila crumbs gene, which specifies a protein expressed in the insect eye, identified mutations associated with RP (den Hollander et al, 1999)[15].

Mapping disease genes where there is genetic heterogeneity necessitates the study of individual families which contain sufficient affected individuals to provide independent evidence of linkage. Because there are so many RP genes linkage information cannot be combined from two or more families as a particular marker may be linked to the RP gene in one family but unlinked to the RP gene in the second family. Most of the adRP and XLRP loci identified in the late 1980 and 1990s were the result of linkage analysis studies of individual large pedigrees with multiple affected. Large XLRP and adRP pedigrees with multiple affected are quite easy to find in western countries but in the case of recessive RP large pedigrees with multiple affected are quite rare and restricted, as in the case of the large Dutch pedigree mentioned above (van Soest et al, 1994)[13] to rural regions in which a significant amount of inbreeding has occurred.

However in certain non western regions of the world, in south Asia and other parts of the world where consanguineous marriages are common and where sibships are quite large, large families suitable for applying linkage methods to gene mapping are common. Researchers studying south Asian pedigrees including researchers at the Sankara Nethralaya in Chennai made significant contributions to knowledge of the genetics of recessive RP (Maw et al, 1995; Maw et al, 1997; Gu et al, 1997)[16][17][18] during the 1990s. The first two RP genes expressed in the RPE; RPE65 and CRABP, two genes involved in the re cycling of 11 - cis retinal were identified studying families from southern India. (Maw et al, 1997; Gu et al , 1997)[17][18].

Since the first location of an RP gene (RP2) in 1984 the pace of discovery has accelerated radically and as of now (February 2007) about 200 genes are known to cause retinal dystrophy and of these 41 cause the RP phenotype. [See the web site maintained by Daiger and coworkers (http://www.sph.uth.tmc.edu/Retnet/home.htm] Some idea of the dramatic advances in genetic knowledge of retial disease including RP is illustrated in the graph shown below.

THE INCREASE IN IDENTIFIED AND MAPPED RETINAL DISEASE GENES [1980 -2006]



Showing increase in number of retinal disease genes since the beginning of the genome project. From web site "Retnet"http://www.sph.uth.tmc.edu/RetNet,copyright Univ. of Texas Health Science Center at Houston, supervised by Daiger SP, Sullivan, LS and Browne SJ of the Laboratory of Molecular Diagnosis of Inherited Eye Diseases at the University of Texas-Houston Heath Science Center. [Permission granted by Professor SP Daiger]

In the review below and in the tables information has been taken from several sources. The most important source is the RP web site <http://www.sph.uth.tmc.edu/Retnet/home.htm>. Other souces consulted include: Phelan and Bok (2000)[19], Rivolta et al (2002)[20], Bessant et al (2003)[3], Kalloniatis and Fletcher (2004)[21], Kennan et al (2005)[22], Brown et al (2006)[4] and Daiger et al, (2007)[23]. Another source is Pagon and Daiger (2005) 'Retinitis Pigmentosa Overview' posted at the web site <http://geneclinics.org/profiles/rp-overview/details.html>.

THE CURRENT RP GENE INVENTORY (February 2007)

Because of the number of RP genes and the great diversity of their actions a number of ways of classifying them for the purpose of review and discussion are possible. They might be classified by mendelian type (X linked, adRP arRP) or they might be classified in terms of their functional roles in the cell. The way chosen here is to group them in terms of their functional or structural roles. For each RP gene cited the gene symbol, the chromosomal location, the protein and the diseases it causes (including non RP retinal dystrophies) are listed.

Table 1

Gene symbol	Location	Protein	Diseases
PHOTOTRANSDUCTION CASCADE			
RHO	3q22.1	Rhodopsin [light detecting transmembrane G protein]	adRP, arRP, autosomal dominant CSNB
PDE6A	5q33.1	Phosphodiesterase 6A cGMP-specific, rod , alpha subunit	arRP
PDE6B	4p16.3	Phosphodiesterase 6B cGMP-specific, rod, beta subunit	arRP, autosomal dominant CSNB
CNGA1	4p12	cGMP gated cation channel alpha subunit	arRP
CNGB1	16q13	cGMP gated cation channel beta subunit	arRP
GUCA1B	6p21.1	Guanylate cyclase activating protein 1B	adRP, autosomal dominant MD

VISUAL CYCLE AND RHODOPSIN REGENERATION			
SAG	2q37.1	Arrestin (S-antigen)	arRP, Oguchi disease (autosomal recessive CSND)
LRAT	4q32.1	Lecithin retinol acyltransferase	arRP, autosomal recessive LCA
RLBP1	15q26.1	Retinaldehyde binding protein	arRP, recessive Bothnia dystrophy
RPE65	1p31.2	Retinal pigment – specific 65 kD protein	arRP, autosomal recessive LCA
RGR	10q23.1	RPE-retinal G protein coupled receptor [Rhodopsin homologue in RPE and Muller cells binds all – trans retinal]	arRP, autosomal recessive choroidal sclerosis
TRANSCRIPTION FACTORS			
NR2E3	15q23	Nuclear receptor sub family 2, sub group E, number 3	arRP, autosomal recessive enhanced S-cone syndrome
NRL	14q11.2	Neural retinal lucine zipper [required for rod photoreceptor development]	arRP, adRP
CRX	19q13.32	Homeobox transcription factor	adRP, autosomal recessive LCA, autosomal dominant LCA, autosomal recessive CORD
CYTOSKELETON			
RP2	Xp11.23	Novel protein homogous to cofactor C [involved in tubulin folding]	XLRP
FSCN2	17q25.3	Retinal fascin homologue 2 [involved in crosslinking and bundling actin in the connecting cilia]	adRP, MD
BASEMENT MEMBRANE			
USH2A	1q41	Usherin [basement membrane protein with laminin EGF and Fibronectin type III domains; component of basement membranes of many tissues including retina]	arRP, autosomal recessive Ushers syndrome
DISC STRUCTURE			
ROM1	11q12.3	Retinal outer segment protein 1	adRP, digenic RP with RDS
RDS	6p21.2	Peripherin 2 [outer rod protein]	adRP, digenic RP with ROM1 dominant MD; dominant adult vitelliform MD
RP1	8q12.1	Retinitis pigmentosa RP1 protein [outer disc and axoneme structure, localizes to connecting cilia]	adRP, arRP
DISC PHAGOCYTOSIS			
MERTK	2q13	C-mer protoncogene receptor tyrosine kinase [needed for phagocytosis of outer photoreceptor segments by the RPE]	arRP
CO2 HYDRATION			
CA4	17q23 2	Carbonic anhydrase 4 [membrane anchored protein found in retinal choriocapillaris]	adRP
SPLICING / PRE mRNA PROCESSING			
PRPF3	1q21 2	Human homologue of yeast pre-mRNA splicing factor 3 [highly conserved ubiquitously expressed]	adRP
PRPF8	17p13.3	Human homologue of yeast pre mRNA splicing factor 8 [highly conserved ubiquitously expressed]	adRP

PRPF31	19q13.42	Human homologue of yeast pre mRNA splicing factor 31 [highly conserved ubiquitously expressed]	adRP
RP9	7p14.3	RP9 protein or PIM1-kinase associated protein 1[protein has a role in pre-mRNA splicing and interacts with a U2 complex splice factor]	adRP
INTRACELLULAR TRANSPORT AND TRAFFICKING			
TULP1	6p21.31	Tubby like protein 1 [possibly involved in transport of rhodopsin from inner to outer segment]	arRP, autosomal recessive Ushers syndrome
ABCA4	1p22.1	ATP-binding cassette transporter protein [located in the rims of the rod outer segments]	arRP, autosomal recessive MD (Stargardt disease/fundus flavimaculatus), autosomal recessive CORD
RPGR	Xp11.4	Retinitis pigmentosa GTPase regulator [intracts with PDE6D and RPGRIP1 and is found in the waist of the photoreceptor associated with the cilia;may be involved in opsin transport]	XLRP, X-linked COD, X-linked CSNB, X-linked atrophic MD
GTP SYNTHESIS AND METABOLISM			
IMPDH1	7q32.1	Inosine monophosphate dehydrogenase type 1 [involved in guanidine nucleotide synthesis]	adRP, autosomal dominant LCA
NEURONAL DEVELOPMENT			
SEMA4A	1q22	Semaphorin 4A [involved in neuronal development and or immune response]	adRP, autosomal dominant CORD
CERKL	2q31.3	Ceramide kinase – like protein [involved in neuronal cell survival and apoptosis expressed in retinal ganglion cells and other tissues]	arRP
EXTRACELLULAR / CELL CELL INTERACTIONS			
CRB1	1q31.3	Crumbs homologue 1 [possibly involved in cell – cell interactions and cell polarity]	arRP, autosomal recessive LCA
FUNCTION UNKNOWN			
PRCD	17q25.1	Progressive rod-cone degneration protein [widely expressed in retina and many tissues- function unknown]	arRP

Abbreviations: adRP, autosomal recessive RP; arRP, autosomal recessive RP; XLRP, X-linked recessive RP; CSNB, congental stationary night blindness; LCA, Leber congenital amaurosis; MD, macular degeneration; CORD, cone rod dystrophy; COD, cone dystrophy.

TOTAL: 33 identified genes. In addition to the identified RP genes, several locations containing as yet unidentified genes have been mapped. These include to date: adRP: RP31, 9p22-p13; RP33, 2cen-q12.1. arRP: RP22,16p12.3-p12.1; RP25, 6cen-q15; RP28, 2p16-p11; RP29, 4q32-q34; RP32, 1p31-p13.3. XLRP: RP6, Xp11.23; RP23, Xp22; RP24, Xq28-q27; RP34, Xq28qter.

The information for this table was taken from: RP web site (http://www.sph.uth.tmc.edu/Retnet/home.htm ,supervised by Daiger SP, Sullivan, LS and Browne SJ of the Laboratory of Molecular Diagnosis of Inherited Eye Diseases at the University of Texas-Houston Heath Science Center, last updated 27th Feburary 2007; Bessant et al (2003) [3]and Daiger et al (2007)[23].

TABLE 2
GENES CAUSING CONGENITAL STATIONARY NIGHT BLINDNESS
[EXCLUDING THOSE LISTED IN TABLE 1 WHICH ALSO CAUSE RP]

Gene symbol	Location	Protein	Diseases
CABP4	11q13	Calcium binding protein 4	Autosomal recessive CSNB
GRM6	5q353	Glutamate receptor 6 [distinctive, abnormal rod ERG response to 15 Hz flicker; expression is restricted to cone ON bipolar cells; protein is a receptor for neurotransmitter glutamate released from rods and cones	Autosomal recessive CSNB
CACNA1F	Xp1123	L-type voltage-gated calcium channel alpha-1 subunit	X-linked CSNB; Åland island eye-like disease
NYX	Xp114	Nyctalopin; member of the small leucine-rich proteoglycan (SLRP) protein family expressed in several tissues but more abundant in retina and kidney; [NYX mutations are found in a majority of X-linked complete-CSNB patients]	X-linked CSNB

Abbreviations: CSNB, congentital stationary night blindness

TOTAL: genes identified 11.

The information for this table was taken from: RP web site (http://www.sph.uth.tmc.edu/Retnet/home.htm ,supervised by Daiger SP, Sullivan, LS and Browne SJ of the Laboratory of Molecular Diagnosis of Inherited Eye Diseases at the University of Texas-Houston Heath Science Center, last updated 27th Feburary 2007; Bessant et al (2003) [3]and Daiger et al (2007)[23].

TABLE 3
GENES WHICH CAUSE LCA
[EXCLUDING THOSE LISTED IN TABLE 1 WHICH ALSO CAUSE RP]

Gene symbol	Location	Protein	Diseases
AIPL1	17p13.2	Arylhyrocarbon-interacting receptor protein-like1	Autosomal dominant LCA, Autosomal dominant CORD
CEP290	12q21.32	Centrosomal 290-kd protein	Autosomal recessive LCA, Recessive Senior –Loken syndrome, recessive Joubert syndrome
GUCY2D	17p13.1	Retina specific guanylate cyclase 2D	Autosomal recessive LCA, autosomal dominant CORD
RPGRIP1	14q11.2	RPGTPase regulator interacting protein 1	Autosomal recessive LCA

Abbreviations: LCA, Leber congenital amaurosis; CORD, cone rod dystrophy.

TOTAL: 13 genes identified. In addition to the identified LCA genes, several locations containing as yet unidentified genes have been mapped: LCA3. 14q24; LCA5. 6q11q16; LCA9. 14q24.1

The information for this table was taken from: RP web site (http://www.sph.uth.tmc.edu/Retnet/home.htm ,supervised by Daiger SP, Sullivan, LS and Browne SJ of the Laboratory of Molecular Diagnosis of Inherited Eye Diseases at the University of Texas-Houston Heath Science Center, last updated 27th Feburary 2007; Bessant et al (2003) [3]and Daiger et al (2007)[23].

TABLE 4
GENES WHICH CAUSE MACULAR DEGENERATION

Gene Symbol	Location	Protein	Diseases
ARMD1	1q31.1	Hemicentin 1 (fibulin 6)	Probable cause of AMD in one family
CFH	1q31.3	Complement factor H [CFH increases the life-time risk of AMD 2-to-7 fold confirming an important role for complement in AMD]	AMD
C1QTNF5	11q23.3	C1q and tumor necrosis-related protein 5 collagen; protein is a small collagen secreted by RPE; a possible constituent of Bruch's membrane	Autosomal dominant MD, late onset; Autosomal dominant AMD with lens zonules
ELOVL	46q14.1	Elongation of very long fatty acids protein	Autosomal dominant MD (Stargardt-like)
TIMP3	22q12.3	Tissue inhibitor of metalloproteinases-3	Dominant Sorsby's fundus dystrophy
VMD2	11q12.3	Bestrophin; localizes to the basolateral plasma membrane of the RPE and functions as a novel, transmembrane, oligmeric chloride channel	Dominant MD, Best type; dominant vitreoretinochoroidopathy [includes ocular developmental abnormalities]

Abbreviations: MD macular degeneration; AMD, age related macular degeneration.

TOTAL: 11 genes identified as causing macular degeneration. 12 locations containing as yet unidentified genes causing MD have also been mapped. 9 susceptibility alleles have been identified as playing a role in the development of AMD.

The information for this table was taken from: RP web site (http://www.sph.uth.tmc.edu/Retnet/home.htm ,supervised by Daiger SP, Sullivan, LS and Browne SJ of the Laboratory of Molecular Diagnosis of Inherited Eye Diseases at the University of Texas-Houston Heath Science Center, last updated 27th Feburary 2007; Bessant et al (2003)[3]; Brown et al (2006)[4]; Daiger et al (2007)[23].

How many more genes? Several recent studies have tested sets of RP pedigrees in which there is a clear mendelian inheritance pattern to determine the percentage of families in which the causative gene is one of those already identified and listed in the RP gene data banks. These estimates (Maubaret and Hamel, 2005; Sullivan et al, 2006; Daiger et al, 2007)[24][25][23] showed that in the case of adRP only about 50% of families with adRP, is the disease gene one of those already identified. Identified genes account for about 20% of arRP and about 70% for X linked RP (Maubaret and Hamel, 2005)[24]. Maubaret and Hamel, (2005)[24] conclude: "currently known genes do not represent more than 50% of RP cases, suggesting that many genes remain to be discovered. Rivolta et al (2002)[20] reach similar conclusions and provide a web site where estimates of various retinal diseases In the case of one important allied condition, the severe early onset retinal disease Leber congential amaurosis, Allikets (2004)[26] reported that like RP about 50 % of cases were caused by mutations in known genes.

These various screens suggest that a good number of RP genes and genes of other retinal dystrophies remain to be discovered. However the field is moving quickly and new genes are being discovered at a rapid pace and Daiger et al (2007)[23] speculate that in about 5 to 10 years time most of the mutations causing RP and allied retinal disorders such as LCA at least in north American and European populations

will be identified .

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Original Article

Functional and Anatomical Outcomes of Minimal Posture Macular Hole Surgery

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Aim: To determine functional and anatomical outcome of macular hole surgery with minimal postoperative posturing for idiopathic macular holes.

Methods: 46 eyes of 45 patients who underwent. 20g/23g vitrectomy with dye assisted ILM peeling and gas tamponade were analysed. Patients were instructed to lie prone for 3 days only. OCT was done to determine the type of hole closure and assess photoreceptor recovery. Visual acuity was compared pre- and postoperatively.

Results: Hole closure was achieved in 44eyes (96%) – Type-1 closure (69.6%), type-2 closure (28.3%). The mean visual acuity was 1.3 LogMAR units preoperatively and improved to 0.6 log mar units postoperatively. 63% eyes with type-1 closure and 67% eyes with type-2 closure showed vision improvement. 18 eyes received combined primary phacovitrectomy and 8 eyes needed early cataract surgery within 3 months post vitrectomy. Recovery of IS/OS (photoreceptor) layer on spectral OCT was complete in 8 eyes (17.4%) and incomplete (focal, diffuse loss) in rest and correlated with visual outcome.

Conclusions: Macular hole surgery with minimal face-down posturing provides satisfactory anatomical and functional results with no significant complications and therefore may be a more acceptable and less cumbersome option especially in those unable to maintain the traditional prolonged post-op posturing.

Introduction

Several studies have shown that pars plana vitrectomy with gas tamponade for idiopathic macular hole results in hole closure and long-term improvement in visual acuity in most eyes.[1,2] From the inception of this technique by Kelly and Wendell in the early 1990s, face-down positioning has been deemed to be an essential component of the procedure[3]. As surgical techniques have evolved, hole closure rates have risen steadily, with many studies reporting success rates of 90% and above. Internal limiting membrane (ILM) peeling has definitely aided in successful closure of macular holes especially when repair of larger or longstanding defects is undertaken.[4] For many years, there has been debate concerning the optimum duration of face-down posturing following macular hole surgery. Face-down posturing was thought to be essential for hole closure, but recent OCT studies have indicated that a macular hole can close as soon as 1 day after surgery[5] if the tractional forces have been adequately relieved. The speed of hole closure has led some to suggest that face-down posturing is not needed[6]. Most patients find face-down posturing difficult and the prospect of posturing may deter patients from having surgery. Posturing is particularly diffcult for older people, obese and those who live alone or have poor mobility. Posturing has also been associated increase the risk of thromboembolism and other neurological problems[7].

Aim

To determine functional and anatomical outcome of macular hole surgery with minimal postoperative posturing for idiopathic macular holes.

Materials and Methods

This was a prospective study of patients who had undergone minimal posture macular hole surgery at Chaithanya Eye Hospital and Research Institute between November 2008 and December 2010. Patients who underwent the standard 2 week post op positioning were not part of this analysis. All stages and sizes of macular hole were included in study. Data collected from the patient charts included patient age and gender, lens status prior to surgery, preoperative visual acuity, other retinal and ocular diseases, stage of macular hole, postoperative visual acuity, hole closure status after surgery, type of hole closure, whether or not cataract surgery was done during vitrectomy or later during follow-up, list of any complications and final follow-up duration in months. All patients underwent a standard 20 g or 23 g three-port pars plana vitrectomy. Patients who had a significant cataract had cataract extraction with IOL implantation before the commencement of vitrectomy. Significant cataract was defined as more than NS2, any PSCC or cortical cataract involving the visual axis. ILM peeling was done in all cases

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after staining the ILM with brilliant blue dye which was kept in contact for atleast 1 minute. Epiretinal membrane (ERM) peeling was performed whenever required. Fluid–air exchange was performed at the end of surgery and intravitreal 15% C3F8 was injected. Postoperatively, patients were instructed to position their head in a face-down position for 3 days only. Following this, they were instructed to avoid the supine position for 10 days and to sleep on their side at night. Patients who completed a minimal period of 3 months were included in the study. Patients who developed any significant cataract in this period which was responsible for the visual deficit underwent cataract surgery as and when needed. All Snellen visual acuities were converted to logMAR for purposes of analysis.

Results

46 eyes of 45 patients were included in the study. The mean age was 59.7 years (range 51–72). There were 10 males (22.2%) and 35 females (77.8%). 2 eyes (4.4%) had stage 2 holes, 35 eyes (76.1%) had stage 3 macular hole, and 9 eyes (19.6%) had stage 4 macular hole. The mean duration of macular hole evaluated from history was 6.58 mths (range 0.5 to 12 mths). The mean basal diameter of macular hole was 991.01 microns (range 474 microns to 1360 microns). OCT features included CME and SRF in all eyes (100%), incompletely detached posterior hyaloid in 22 eyes, completely detached posterior hyaloid in 13 eyes and no posterior hyaloid detachment in 11 eyes. At baseline, 33 eyes (71.7%) were phakic, and 13 eyes (28.3%) were pseudophakic. 17 eyes (37%) underwent 20g vitrectomy while 29 eyes (63%) underwent 23g vitrectomy. The mean follow-up was 6.2 months with a minimum follow-up of 4 months.

Out of the 33 phakic eyes significant cataract was seen in 18 eyes (54.6%) and these eyes underwent a planned phacoemulsification cataract surgery with the vitrectomy procedure. The remainder of the phakic eyes had their lenses intact at the end of surgery. Out of these remaining 15 eyes, 8 eyes developed significant cataract in the early post operative period and needed early cataract surgery with IOL implantation within 3 months of follow up. In these cases cataract surgery was done at 2 months after the absorption of the gas bubble. Thus out of the 33 phakic eyes, 26 eyes (78.8%) underwent cataract extraction.

Closure of the macular hole was acheived in 44 out of 46 eyes (95.7%). Type 1 closure was seen in 32 eyes (69.6%) and type 2 closure was seen in 12 eyes (26.1%) (Fig 1,3). In 2 eyes (4.4%) the macular hole did not close with persistant subretinal fluid. Both these patients were offered resurgery with repeeling of ILM under guarded visual prognosis but these patients were unwilling for the resurgery.

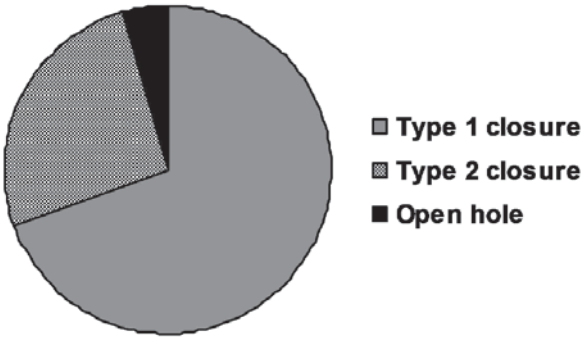


Fig1; Anatomical outcome of macular hole surgery.

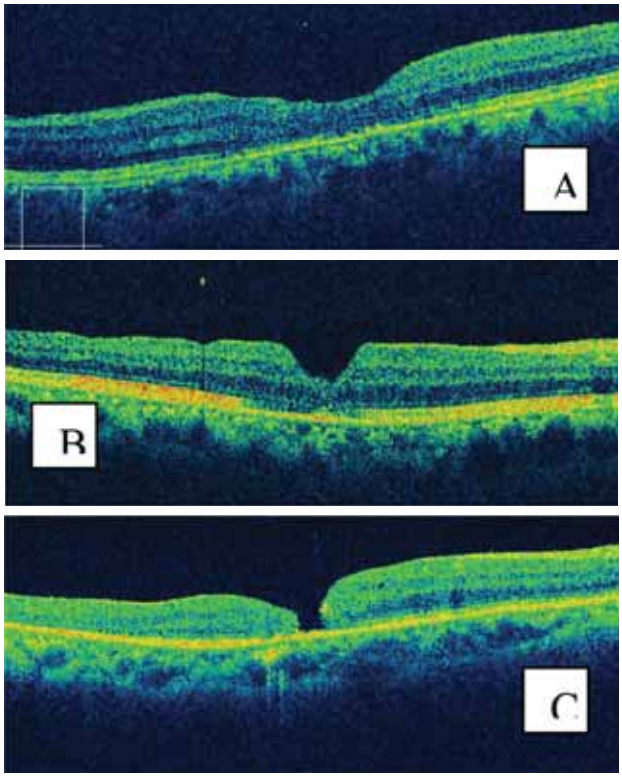


Fig 2;Types of macular hole closure on OCT
A,B- Type 1 closure, C- Type 2 closure

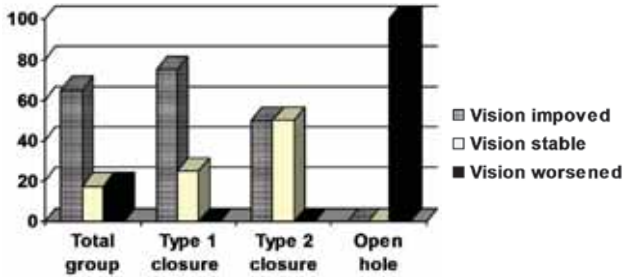


Fig3; Visual outcome after macular hole surgery

The mean preoperative visual acuity was 1.3 logMAR (6/120 Snellen equivalent)- range 6/24 to CF1M). The mean postoperative vision was 0.6 logMAR (6/24 Snellen equivalent)- range 6/9 to 6/60. Out of the 46 eyes 30 eyes (65.21%) showed improvement in vision while in 8 eyes (17.39%) the vision remained status quo and in 8 eyes (17.39%) the vision dropped from baseline. When comparing the type of hole closure with visual outcome it was found that 24/ 32 eyes (75%) with type 1 closure had vision improvement, 6/12 eyes (50%) with type 2 closure had vision improvement. In 25% eyes with type 1 closure and 50% of type 2 closure there was no visual gain. Both the 2 eyes where the hole remained open after surgery (100%) had poor visual outcome (Fig 3). Comparing the baseline hole diameter and visual outcome, though the mean basal diameter was 991.01 microns, eyes which had 6/12 or better had smaller holes at baseline (mean 790.33 microns) compared to eyes with 6/18-6/36 vision (mean 902.71 microns) and eyes with 6/60 and worse vision (mean 1280 microns).

Evaluation of the photoreceptor integrity by studying the IS/OS layer and the ELM was done in all patients at 1 month and 3 months follow up. Recovery of the IS/OS layer and the ELM layer progressed from 1 month to 3 months follow up. At the end of 3 months follow up 8 eyes (17.4%) had normal looking and complete recovery of the ISOS and ELM layer, 22 eyes (47.8%) had incomplete recovery of the ISOS and ELM layer with diffuse loss of the layers, 12 eyes (26.1%) had incomplete recovery of the ISOS and ELM layer with focal loss of the layers and in 4 eyes (8.7%) it could not be determined.(Table 1, Fig 4).

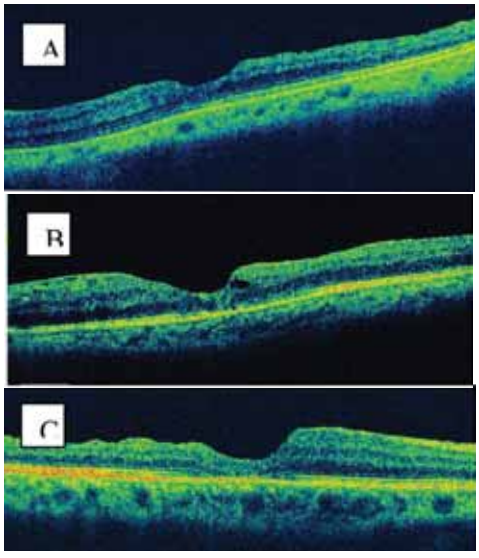


Fig 4; Recovery of photoreceptor after macular hole surgery. A- Complete recovery of IS/OS layer, B- Focal loss of IS/OSlayer, C-Diffuse loss of IS/OS layer

Table 1; Photoreceptor recovery after macular hole surgery

Status of photoreceptor recovery	No (%)
Complete recovery of IS/OS layer	8 (17.4%)
Diffuse loss of IS/OS layer	22 (47.8%)
Focal loss of IS/OS layer	12 (26.1%)
Could not be determined	4 (8.7%)

Eyes with normal ISOS and ELM and eyes with focal ISOS loss showed the best improvement in visual acuity. Among the eyes with diffuse loss of IS/OS some eyes especially those where the foveolar photoreceptors recovered demonstrated vision improvement while others had poor visual outcome.

1 patient with a type 1 closed macular hole developed a subtotal retinal detachment at 3 months due to an iatrogenic hole close to the dominant sclerotomy port and needed scleral buckling with repeat gas injection. The closed macular hole in this patient did not open and needed no intervention. The visual acuity in this patient after RD surgery remained at 6/36 which was the baseline vision. No other ocular complication was seen. None of the patients had any systemic problems due to the posturing and all the patients found this modification of posturing less cumbersome.

Discussion

The present study found that minimal posturing after macular hole surgery with brilliant blue stained ILM peeling and C3F8 tamponade achieves 96% hole closure rate. The mean visual acuity improved by 0.7 log MAR units after surgery. 78.8% of phakic eyes had undergone cataract surgery extraction along with the vitrectomy or in the early post-op period. Visual outcome could be related to the extent of recovery of the photoreceptor – IS/OS layer in majority of the cases.

Positioning patients for shorter periods of time carries with it many theoretical concerns, including (1) decreased hole closure rates, (2) the increase in ''gas-induced cataract'' given the greater duration of contact between the lens and gas bubble and (3) the increase in retinal tear and detachment, since the bubble may exert more inferior peripheral vitreous traction in the upright position. Our current study, however, demonstrates that minimal positioning with use of long-acting gas tamponade results in a 96% initial hole closure rate in this series of macular holes with no attendant increase in complications.

Various authors have reported the effects of shortened postoperative prone positioning in macular hole surgery.[8,9,10] Isomae et al performed macular hole surgery without ILM peeling for small macular holes with symptoms less than 6 months and compared 1 day and 1 week postoperative positioning. They found no difference in hole closure rate (91%). Finally, the same group of authors later studied 1-day postoperative face-down positioning with ILM peeling and air tamponade for recent, small macular holes and found a similar (91%) anatomical success rate8. Various studies have reported a hole closure rate between 88% and 100% with minimal postoperative prone positioning and avoidance of supine positioning[8-10]. Our results compare favourably with these findings.

Initial postoperative positioning regimens longer than 2 weeks were developed at a time when ILM peeling was not commonly employed. The greater relief of traction obtained with this technique may have diminished the importance of prolonged prone positioning. A recent investigation into the physical mechanism by which gas tamponade effects hole closure has revealed that surface tension rather than buoyancy may be the factor most responsible for flattening the edges of a macular hole[11]. Berger and Brucker convincingly argue this point using Archimedes principle to measure the buoyant pressure exerted by an intraocular gas bubble (0.08 mm Hg for a bubble 1 mm in height) [12]. They further note that as long as tangential traction has been relieved with ERM and/or ILM dissection, variation of bubble buoyant pressures is not likely to affect adequate tamponade of macular holes. This would seem to imply that position of the head would not be important as long as the gas bubble is large enough to allow for contact with the hole for a sustained period. This sustained contact is easier to achieve with prolonged prone positioning, but reasonable contact between the hole and the gas bubble could be achieved with strict avoidance of the supine position alone. A larger gas bubble appears necessary for sustained contact to occur in the absence of prone positioning and is facilitated by performing as complete a vitrectomy as possible and taking the time to achieve as complete an air–fluid exchange as possible. In our study, although patients were positioned for 3 days only, with the use of C3F8 gas and avoidance of supine positioning, contact between the bubble and the macular hole would have been present for at least several days.

Another variable which needs closer examination is the role of combined cataract and macular hole surgery. Many advocates of shortened or eliminated face-down posturing have suggested that in patients who are not posturing, cataract extraction is needed.[13,14] Cataract surgery is advocated for two reasons. First, it has been proposed that lensectomy may allow more complete vitrectomy and better gas fill. This may allow support of posterior pole, even with the patient sitting upright, and eliminate need for posturing face-down. This theory is supported by the observation of Guillaubey et al[13] that there was higher success rate in patients having a combined macular hole and cataract surgery compared with those having macular hole surgery alone (96.8% vs 89.8%). The second reason for combined cataract macular hole surgery is that cataract is the most common complication following macular hole surgery, occurring in up to 64% of eyes within 1 year[15]. For the phakic eye, not posturing can lead to an increased rate cataract progression. Tranos et al9 found significantly more cataract progression in non-posturing (5/16, 31%) than posturing group (1/23, 4%, p 0.009). In our study 8/15 (53.3%) of phakic eyes that did not undergo cataract surgery primarily developed cataract early in post-op period which could be attributed to the modification in positioning.

Guillaubey et al[13] found no significant difference in closure rate with or without face-down posturing with surgery for small macular holes. In contrast, for holes >400 microns, the success rate was significantly higher for those that postured face-down (95.1% vs 79.5%, p 0.45). This suggests that perhaps macular hole surgery should be tailored to individual patient with small holes being treated differently to larger holes. Previous studies have also shown that closure rate is related to the initial size of the macular hole[16]. The mean basal hole diameter in this study was 991.01 microns. Though larger this study found 96% closure rate with ILM peeling and minimal posturing.

Visual outcomes are more difficult to assess than closure rates and are more likely influenced by preoperative differences in initial visual acuity, hole size and duration, follow-up period and concurrent cataract surgery. Dhawahir-Scala et al[10] and Simcock et al[13] both had reported that there was no significant difference in patients improving by two or more lines of vision whether posturing for less than 24 h or longer. In our series 65.2% eyes showed vision improvement. This good visual outcome has to be interpreted keeping in mind the fact that 56.5% had also undergone cataract surgery along with macular hole surgery. Comparing baseline hole diameter and visual outcome, eyes which had 6/12 or better had smaller holes at baseline (mean 790.33 microns) compared to eyes with 6/18-6/36 vision (mean 902.71 microns) and eyes with 6/60 and worse vision (mean 1280 microns).

It is reported that despite high anatomical closure rates after macular hole surgery, vision remains compromised in 30–40% of patients[17,18]. Recent OCT studies suggest that defects in outer retina may explain why vision is compromised despite hole closure. Christensen et al[18] reported that attenuation and disruption of foveal photoreceptor layer were present in the majority of patients with surgically closed macular holes and seen whether ILM peeling had been performed or not. They found that postoperative photoreceptor layer thickness >33 mm and photoreceptor layer discontinuity with a diameter of <177 mm was associated with an eye having regained reading vision after macular hole surgery. In our study also eyes with normal ISOS and ELM and eyes with focal ISOS loss showed the best improvement in visual acuity. Among the eyes with diffuse loss of IS/OS some eyes especially those where the foveolar photoreceptors recovered demonstrated vision improvement while others had poor visual outcome. The type of hole closure defined the visual outcome. Kang et al[19] had defined type1 and type 2 closure after macular hole surgery and found 61.3% type 1 closure and 38.7% type 2 closure in their series. The extent of postoperative visual improvement of type 1 closure group was larger than that of type 2 closure group (p=0.002). In this study Type 1 closure was seen in 69.6% eyes and type 2 closure was seen in 26.1% eyes. 75% with type 1 closure had vision improvement, compared to 50% with type 2 closure.

The intravitreal application of brilliant blue dye has been suggested to facilitate macular hole surgery because it has been shown to selectively stain the internal limiting membrane (ILM) . Several advantages compared with other dyes such as indocyanine green or trypan blue have been reported. In particular, BB did not show apoptotic death of retinal cells as it was found in laboratory investigations on indocyanine green and trypan blue[20].

To conclude Macular hole surgery with minimal face-down posturing provides satisfactory anatomical and functional results with no significant complications and therefore may be a more acceptable and less cumbersome option especially in those unable to maintain the traditional prolonged post-op posturing.

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Original Article

Clinical Characteristics and Therapeutic Outcome in Acanthamoeba Keratitis

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Purpose: To report the clinical characteristics, predisposing factors and therapeutic outcome in a series of patients diagnosed with acanthamoeba keratitis(AK).

Materials and Methods: The data was collected from the clinical records of patients admitted with infective keratitis at Regional Institute of Ophthalmology, Trivandrum from December 2012 to May 2013. In this retrospective study, medical and microbiology records of forty consecutive patients with acanthamoeba keratitis(AK) were reviewed and analyzed. All cases with a micro biologically proven acanthamoeba corneal infection either by direct microscopy or by culture following standard protocols were included for analysis.

Results: Among the 40 patients,thirty four patients had coexistent fungal keratitis and four were isolated AK. Sixty percentage of patients had a predisposing factor with history of trauma or contact with foreign bodies. No patients in our series were contact lens users.Twenty two patients (55%) had central corneal ulcers with size greater than 3mm. Twenty three patients (57.5%)had a best corrected visual acuity(BCVA) less than 6/60 at presentation. Majority (80%) of these patients responded well with adequate healing of ulcer and visual improvement(60%) to a combination therapy of Chlorhexidine 0.02% and Neomycin(98%).

Conclusion: Till recently acanthamoeba infections were considered as a rare cause for infective keratitis compared to fungal and bacterial keratitis in this part of the world. This recent report highlights a significant rise in occurrence of Acanthamoeba keratitis among our corneal ulcer patients. Most of the patients in our series lacked the typical clinical characteristics of acanthamoeba keratitis. High index of clinical suspicion helped us in the accurate diagnosis of this co existing mixed parasitic infection. Addition of specific amoebicidal drugs like Chlorhexidine andNeomycin or Poly hexa methylene biguanide to the conventional anti fungal therapy gave very goodresponse with favorable therapeutic outcome in majority of these patients, as demonstrated in our series.

Keywords: Acanthamoeba keratitis, culture, epidemiology, microscopy, risk factors.

Acanthamoeba is an ubiquitous free-living protozoa of the subphyla Sarcodina. [1,15] Because of the wide spread distribution of this parasite in the environment, human contact with the organism is very common[2,3,10]. Ocular infection by Acanthamoeba is reported more from developed countries including USA and UK.[10,13] Acanthamoeba keratitis is a potentially devastating corneal infection leading to severe visual loss. This vision threatening disease shows wide geographic variations and several outbreaks had been reported worldwide mostly through contaminated contact lens solutions or through domestic water sources. However, in developing countries important risk factors are either trauma or exposure to contaminated water[4,7,11]. An understanding of the region-wise epidemiological features and risk factors of Acanthamoeba keratitis will be of great help in the diagnosis, prevention and appropriate management of this disease entity.

The purpose of this study was to determine the clinical features, risk factors, epidemiological characteristics and therapeutic outcome of Acanthamoeba keratitis in a series of patients presenting at a tertiary eye care referral center in the southernmost part of India (Thiruvananthapuram, Kerala).

Materials and Methods

A retrospective case series study of 40 consecutive cases ofmicro biologically confirmed Acanthamoeba infections among the total 264 infective keratitis cases,treated at Regional Institute of Ophthalmology, Thiruvananthapuram,

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Kerala, South Indiaover a period of 6 months from December 2012 to May 2013 were includedfor analysis. Clinical and microbiological data of the study population was collected after obtaining the approval of Institutional Review Board.

A standard protocol of data collection was followed for each patient. Socio-demographic features, duration of symptoms, predisposing factors, clinical features, associated ocular conditions, systemic diseases and previous treatment data were collected.All patients were examined under the slit-lamp biomicroscope. The size of the epithelial defect and depth of the stromal infiltrate were measured with the variable slit beam and recorded in millimeters and documented diagrammatically. The presence or absence of a hypopyon was recorded and the height measured in millimeters. Specific predisposing factors for corneal ulceration including trauma, use of contact lenses, topical steroid use and the nature of domestic water sources were enquired and documented.

Specimens for smear and culture were obtained by scraping the corneal ulcer under aseptic conditions using sterile number 15 BP blade following instillation of 0.5% proparacaine hydrochloride in the conjunctival sac. The material was scraped under slit lamp from the edge and the base of each ulcer,spread onto labeled slides in a thin, even manner to prepare a 10% potassium hydroxide (KOH) or normal saline wet mount, Gram-staining and Giemsa-staining and direct microscopy was performed without any delay in our laboratory. The remaining specimen was inoculated onto the surface of solid media such as 7% sheep blood agar, chocolate agar, Sabouraud dextrose agar and nonnutrient agar with E. coli overlay in a row of "C"-shaped streaks. Acanthamoebae infections confirmed either by direct microscopy and or culture were included for this analysis. Microbiological diagnosis of acanthamoeba was based on presence of specific microscopic features of trophozoites including it's motility and presence of double walled cysts for immobile acanthamoeba cysts under the low-power (X 10) objective using a light microscope. Amoebal migration tracks, bacterial clearing show where the amoeba have been grazing were the other signs considered to be positive for Acanthamoeba growth in culture media. The fungal and bacterial cultures were considered positive if growth of the same organism was demonstrated on more than one solid phase medium and/or if there was confluent growth at the site of inoculation on one solid medium and/or if growth of one medium consistent with direct microscopy findings. All laboratory procedures followed standard recommended protocols.

All microbiologically confirmed acanthamoeba keratitis were treated with combinations of reconstituted chlorhexidine 0.02% and neomycin eye ointment. Propamidine(Golden eye drops) were also added in a few non healing AK cases. Mixed infective keratitis were treated with additional topical antifungal therapy using topical Natamycin 5% and Voricanazole eye drops. Broad spectrum antibiotic eye drops, cycloplegics, antiglaucoma measures, systemic antifungal therapy and other supportive treatment with analgesics were given based on individual case requirements.

For the purpose of analysis, the corneal ulcerswere grouped to mild, moderate and severe according to size of ulcer in millimeters, location and severity ofassociated anterior segment inflammation. Corneal ulcers with a size less than 3mm, peripheral corneal location and less than 2+ cells in anterior chamber were graded as mild, those with a size more than 3 upto 5mm, central or paracentral in location and 3+ or above cells in anterior chamber were graded as moderate in severity. All corneal ulcers above 5 mm in size,located anywhere on cornea with or without hypopyon were graded as severe ulcers.

Therapeutic outcome measures were defined as good or poor according to healing response, course of illness and visual outcome. Ulcers healed with opacificationwith medical treatment were considered as good healing response and those which progressed to complicationsor required surgical intervention while on treatment were considered as poor outcome. Course of illness was graded according to duration of hospital stay as <2 weeks,2-4 weeks and >4 weeks. Best corrected visual acuity(BCVA) at time of admission and after treatment were documented and included for outcome analysis. Cases with prolonged hospital stay for more than 4 weeks and occurrence of complications while on treatment with reduction in final BCVA were reported as poor outcome. Favorable outcome was reported on cases with less hospital stay showing adequate healing with opacification and stable or improved BCVA after treatment.

Results

During the study period, a total of 264 patients were micro biologically evaluated for infective keratitis in our Institute. Among them, presence of acanthamoebae infections were confirmed in 40 patients by direct microscopy (n=24) or by culture (n=16).

Microbiological data analysis showed that among the

40 patients positive for acanthamoeba,majority had co existing polymicrobial infections (n=36). In our series, acanthamoeba infections were coexisting with fungal keratitis in majority of patients. (34/40). Four patients had isolated acanthamoeba keratitis and 2 patients had mixed infections. Among fungal keratitis, fusarium species (19/40) showed predominance over aspergillus infections (11/40). The two cases of mixed keratitis had co existing bacterial infections also.

Acanthamoeba infections were predominant (65%) among males (n=26) compared to females (n=14). Majority of affected patients in our series were adults in the working age group. Twenty six patients in our series (65%) belonged to 30-60 years age group and 13 patients (32.5%) were above 60 years of age.Fifty seven percentage of study population were engaged in outdoor occupations (n=23).

DEMOGRAPHIC FACTORS	Number of cases
GENDER	
MALE	26
FEMALE	14
TOTAL	40
AGE	
<30 yrs	1
30-60yrs	26
>60yrs	13
TOTAL	40

Table 1

A positive history of trauma or contact with foreign bodies was the major predisposing factor in 60% of patients (n=24). Among this group of patients,twelve patients(50%) gave history of contact with vegetative matter, 4 patients with mud and 3 patients with stone particles. (Figure 2). None of the patients in our series were using contact lenses. Seventy five (n= 30) percentage of patients in our series were from rural areas and the rest were from semi urban areas. All patients in our series were using well water for their domestic purposes and a few patients also gave exposure to water from ponds and lakes while at work.

Majority(55%) had severe vision threatening keratitis with involvement of visual axis and stromal ulceration (n=22). Among them, eleven patients had large corneal abscess with hypopyon (27.5%).Among the rest, nine patients had moderate severity (22.5%) with mid peripheral location of ulcer and significant associated anterior chamber inflammation. Nine patients had small peripheral ulcers with minimal anterior chamber inflammation(22.5%).

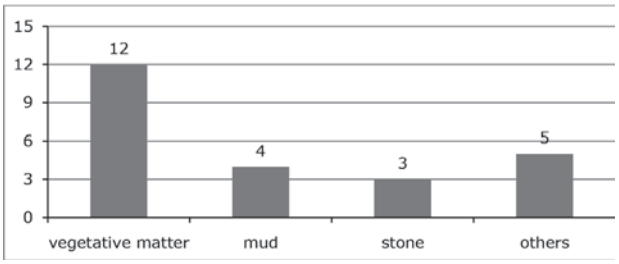


Figure:2 PREDISPOSING FACTORS

Seventy five percentage (n=30) of patients had pre treatment from local hospitals with antibiotic and antifungal eye drops before seeking care from our centre. Also about 60% of patients (n=18) among them were treated at our institute as fungal keratitis initially as scrapings were positive only for fungi. Repeat scrapings from the above 18 poorly responding cases demonstrated acanthamoeba parasites subsequently. In two cases where surgical intervention was needed, diagnosis of acanthamoeba infection was possible only by culture of the corneal button or anterior chamber aspirate.

Once presence of acanthamoeba infections were confirmed by microscopy or culture, all patients were treated with topical amoebicidal drugs.Thirty eight patients (95%)were treated with combinations of reconstituted Chlorhexidine 0.02% eye drops and Neomycin eye ointment. Two patients showing very poor response were given PolyHexaMethyleneBiguanide 0.02% eye drops in addition to above combination. Coexistant fungal and bacterial keratitis were treated with topical Natamycin 5% and or Voriconazole eye drops and fortified or broad spectrum antibiotic drops respectively as per requirement along with other supportive measures.

BCVA was poor in majority of patients at presentation and 23 patients (57.5%) had a best corrected visual acuity less than 6/60 to hand movements, nine patients (22.5%) had vision in range 6/24-6/60 and eight patients had BCVA better than 6/18. (Table:3).

Following treatment, 60% patients (n=24) showed improvement in vision ,20% patients had stable vision(n=8) and 20% patients showed worsening in vision(n=8) (Figure 4)

Chronic course of illness was noted in 40% patients(n=16) as inpatient hospital careand disease course was prolonged for more than 4 weeks, 50% patients (n=20)had adequate healing response within 2-4 weeks and 10% patients(n=4) got cured of the disease in less than 2 weeks.

TABLE 3:VISION AT PRESENTATION

<6/60	23
6/24-6/60	9
Up to6/18	8

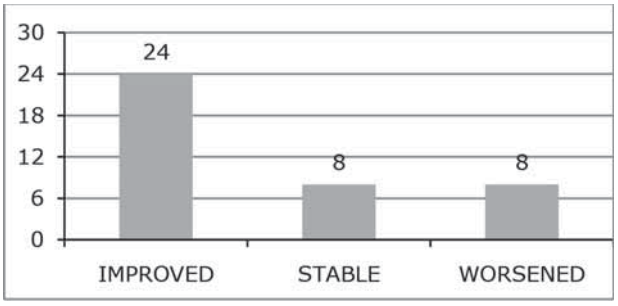


Figure:4 VISION OUTCOME

Therapeutic outcome analysis showed good response with adequate healing and opacification in 80% patients(n=32) with either improvement (n=24)or stabilization (n=8) of BCVA. Eight patients (20%) with poor healingresponse and worsening needed surgical interventions (n=4) or progressed to complications (n=4) including perforation.

Subgroup analysis of theulcerswhich showed poor therapeutic response (n=8)revealed that all of them were of severe grade with stromal ulceration and presented to us very late and had predominant cyst infections on direct microscopy. Among them four patients had to undergo therapeutic keratoplastyfor control of infection. One patient also had recurrence of disease in graft and had to have a repeat tectonic corneal grafting later. Two patients refused any surgical intervention and one patient ended up in perforation and lost the eye.

Discussion

Acanthamoeba keratitis is a growing clinical problem both in developed and developing countries[1,15,17].Indian studies reported a prevalence rate of 1 to 4% for acanthamoeba keratitis among culture positive corneal ulcers [4,7,11,12].

Unlike previous reports from south India, majority of patients with AK in our series had poly microbial infections with super added fungal keratitis in majority (n=36). Mixed parasitic and bacterial keratitis have been reported in literature before[16,14] but co existing fungal and acanthamoeba infections are rarely reported. Published reports from developed countries are mostly acanthamoeba infections associated with contact lens use or on pre existing viral keratitis.[7,13]

Acanthamoeba organisms exist in two forms, the active trophozoite form and the resting cystic form. The cystic form is dormant and is resistant to desiccation, extreme temperature and chemicals. The cysts do not exhibit any movements and may remain viable for many years until they are exposed to a food source, where they again assume the trophozoite form.[7,10,13]

Acanthamoeba is encountered in large numbers where other microorganisms are abundant and it has been reported as a waterborne pathogen. Outbreaks of acanthamoeba keratitis from contaminated water sources has been reported in literature from many parts of the world. [2,3,10]

Higher incidence of fungal keratitis due to the humid conditions in this part of the world may be an important reason for increased number ofmixed infections with parasite and fungi, observed in our study group.

Corneal injury was the most important predisposing factor in our series which is in accordance with earlier reports from other parts of South India [7,11].Interestinglynone of our patients in this series had a history of contact lens use [11]. With an aim to identify the specific predisposing factor for AK, we collected data regarding the source of water for domestic purposes from these patients. Ninety five percentage of our patients were from rural areas and were using ground water(well water) for their domestic purposes. Many patients also gave history of contact with muddy water and water from ponds and lakes. Polluted domestic water sources may be an important source for acanthamoeba infections in our patients. It has been suggested in many earlier studies that co contamination of Acanthamoeba with a bacterial species is capable of supporting amebic growth in any medium [2,3,10].

Anotherobservation we noted in our study group is lack of classic features of acanthamoeba keratitis as described in literature such as peri neural or ring infiltrates [7,15]. Pain was characteristically present in most ulcers in our series. Presence of co existent fungal infections might have masked the characteristic clinical features of acanthamoeba keratitis.

Among many of our patients microbiological diagnosis of acanthamoeba was obtained after repeated scrapings. This highlight the importance of clinical suspicion for this parasitic infection and to look for them in all non healing ulcers where specific anti microbial therapy is not giving expected therapeutic response. The high index of clinical suspicion of mixed infections and if possible discussions with your microbiologist to look for acanthamoeba is recommended even though an organism is isolated earlier. The treatment with combination amoebicidal drugs showed good clinical response with adequate healing with opacification[5,6]. Ten percentage of patients underwent surgical intervention as compared to a western report where35% required surgical intervention.Progression of

ulcer to complications occurred in 20% patients and half among them had surgical intervention.

In our series adequate therapeutic success with medical treatment alone was achieved in majority of patients. High index of clinical suspicion,repeat microbiological examinations, early and accurate diagnosis and execution of appropriate therapy with specific anti parasitic medications helped us achieving good therapeutic results in this otherwise blinding parasitic corneal infection.

Conclusion

Diagnosis and management of acanthamoeba keratitis remains challenging for ophthalmologists worldwide. Till recently AK is considered as a rare cause for microbial keratitis in India. But current report suggest a rising trend and the high possibility of concurrent acanthamoeba infections in patients with fungal keratitis. High index of clinical suspicion and repeated microbiological evaluations in all non healing ulcers will help in identifying this causative organism. Polluted domestic water sources including wells and water storage tanks facilitates the growth of acanthamoebae. This fact highlight the importance of maintaining high water quality standards and proper environmental hygiene in order to prevent this devastating corneal infection.

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Original Article

Endothelial Keratoplasty Combined with Phacoemulsification and IOL: Results of New Triple Procedure- A Pilot Study

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Abstract

In situations where you encounter a patient with cataract who has significant corneal guttata due to Fuch's Dystrophy, it is a dilemma whether to proceed with cataract surgery or to defer the surgery for fear of corneal de compensation. The delay in cataract surgery vice versa increases the risk of corneal de compensation due to surgical manipulations expected in a hard cataract. In this modern era of lamellar corneal surgery, the New Triple Procedure (Descemets Stripping Endothelial Keratoplasty + Phacoemulsification +IOL) allows to tackle this situation in a more refined way with better refractive results expected than in a traditional single stage or combined cataract surgery with corneal transplantation. In this case series, the new triple procedure and its results in patients with coexisting cataract and Fuch's dystrophy is demonstrated.

Aim of the study

The aim of this study is to examine the visual outcome and complication rate of performing New Triple Procedure (Descemets Stripping Endothelial Keratoplasty + Phacoemulsification +IOL) in patients with Fuch's endothelial dystrophy and concurrent cataract.

Materials and Methods

It is a prospective case series of 5 eyes with diagnosed Fuch's endothelial dystrophy who underwent combined surgery of Descemets Stripping Endothelial Keratoplasty (DSEK) with phacoemulsification surgery with IOL implantation. The inclusion criteria included:

1. Diagnosed Fuch's endothelial dystrophy with corneal guttata in both eyes(fig 1)
2. Specular microscopy confirming the poor endothelial status.
3. Coexisting cataract of nuclear sclerosis grade 2 or more
4. Preoperative pachymetry > 600μ
5. Slit lamp signs of epithelial decompensation

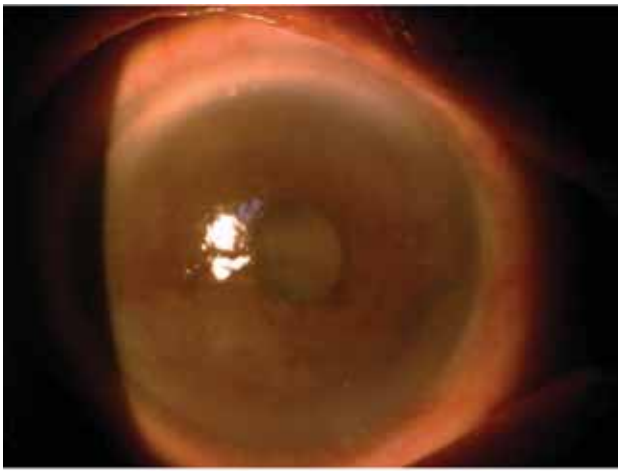


Figure 1: Fuch's dystrophy with cataract- pre op edema

Pre operative evaluation:

Preoperative data collected included UCVA (Uncorrected visual acuity) and BCVA (Best corrected visual acuity) on Snellens Chart, ultrasound pachymetry(central corneal thickness), age , gender and concurrent ocular co morbidity. (Table 1)

	Age	Gender	Pre op CCT	Pre op BCVA
1	53	F	620μ	6/36
2	62	F	612μ	6/60
3	54	M	672μ	1/60
4	68	F	640μ	HMCF
5	62	F	646μ	6/60

Surgical Technique

Combined DSEK with phaco and IOL surgery was performed in all five patients with Fuch's endothelial dystrophy with co existing lenticular changes. All the surgeries were performed by the same surgeon (SN)

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First Stage: Phacoemulsification with IOL implantation
Standard temporal limbal 2.8mm incision phaco emulsification under topical anaesthesia was performed first. A smaller sized (5-6mm)continuous curvilinear capsulorhexis was performed and the nucleus was hydrodissected and phacoemulsification performed using primary chop technique. Epithelial debridement was performed in cases with poor media clarity due to epithelial edema. A dispersive viscoelastic was used during phaco. After performing irrigation and aspiration of cortical matter, the foldable IOL was implanted in the bag. The first stage is thus concluded by leaving the chamber filled with viscoelastic (cohesive). The surface of the cornea is then measured using a caliper and marked with proper centering and adequate sizing. The IOL power was selected with -1.0 to -1.5 D myopic target to compensate for hyperoic shift that tend to happen after DSEK.

Second stage: Donor eye preparation
The donor eye was selectively used from younger age donor (<50years) with a specular count of > 2500cells/mm3. (Table 2).All the donor eyes except one (patient no4) were preserved in MK medium. The eye used for patient no 4 was stored in Eusol medium. All the donor eyes were received as corneoscleral button. The corneo scleral button was placed on the Katena artificial anterior chamber (fig 2) with endothelial side coated with dispersive viscoelastic and storage medium filled in to the tubing of anterior chamber. After securing the button and forming a water tight chamber, adequate pressure is maintained. A 400μ controlled depth blade is used to make an incision at the limbal area and a plane is dissected at that level with help of careful dissection using straight and curved dissectors. The care is taken to maintain same plane and not to perforate the deeper layers. Once limbus to limbus dissection is completed, the corneo -scleral button is removed from the anterior chamber carefully, to prevent chamber collapse. The button is then placed on the Teflon block and punched with a corneal trephine of adequate size (8-8.5mm) which is already marked on the recipient.

Pateint	Donor age	Donor specular count
1	54 yrs	2514
2	42 yrs	2724
3	52yrs	2611
4	9yrs	2604
5	50 yrs	2666

Table 2 : Donor eye details

Stage 3: Descemets stripping and donor lenticule insertion



Figure 2: Katena artificial anterior chamber

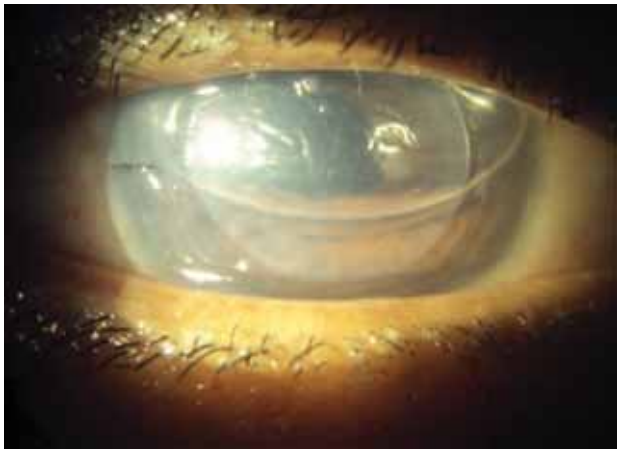


Figure 3: Two hours post op with 50% air fill in AC

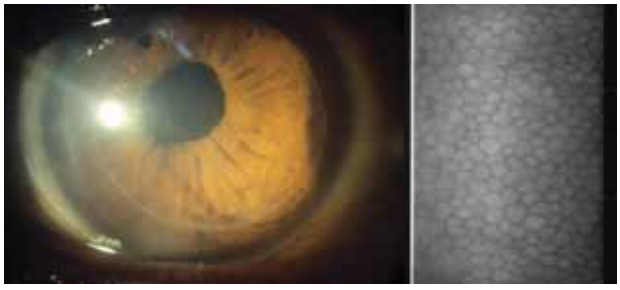


Figure 4: At 1 year follow up with normalised specular microscopy pattern

The incision for phaco is used for this stage as well. Under dilated pupil and cohesive viscoleastic filled anterior chamber, Descemet stripping was performed. Through a paracentesis incision or main incision a reverse sinskey hook with blunt tip is introduced to score the Descemets membrane following the path of the surface marking. This is done360 degree followed by gentle pulling out of the detached Descemets membrane from every corner towards the centre of the eye. In dilated pupil the retro-illumination view helps in easy visibility of the margins of the detached

membrane. The membrane is completely removed from the eye. The viscoelastic is thoroughly washed and anterior chamber filled with BSS.The donor lenticule which is manually prepared using Katena artificial anterior chamber was inserted using needle insertion technique in all cases under healon protection of the endothelial surface. The technique described here is termed ' needle insertion' technique whereby a 26 gauge needle with tip bent slightly is used to push the lenticule into the Anterior chamber . This technique is found to be very economical and easy to learn. A bed of healon is made at the incision site. The button is placed with endothelial side down followed by separation of the dissected posterior lamellae. The tip of incision is held with a colibri and the button is pushed swiftly into the anterior chamber with the needle. The immediate next step is to deepen the anterior chamber with BSS which help the button to float in anterior chamber. An air bubble of moderate size is then injected to attach the button to the posterior aspect of cornea. The wound may be sutured with 2 to 3 sutures of 10.0 nylon, to achieve a water tight chamber. A full tight air fill is then given for 10-15 minutes followed by release of air bubble partially to maintain as much as 50% air fill in anterior chamber (fig 3). The centration of graft can be achieved by stroking over the corneal surface. One or two venting incisions may be given to release the interface fluid to attain better and faster adherence. Supine position was maintained till full adhesion of donor lenticule is confirmed. The eye is pad and bandaged with antibiotic ointment. After 2 hours the bandage is opened to observe the adhesion of the graft and also to look for signs of pupillary block. The post operative medicines included antibiotic drops (moxifloxacin) for 2 weeks, steroid drops (prednisolone acetate) tapered over a period of 8 months to 1 year and lubricating gel preparation.

The outcome measured included any complications in surgery, visual outcome, time for visual recovery, patient acceptance, spherical equivalent and astigmatism at 1 months, 6 months and 1 year.

Results

All 5 patients successfully underwent the procedure under topical anaesthesia. No cataract surgery related complications occurred in any of the cases. The DSEK procedure also underwent without any on-table complications. No cases of primary graft failure occurred. None of the cases required re bubbling for de centered or dislocated graft. The average time taken for the whole procedure was 40-45 minutes. All patients completed 1 year follow up.

The visual acuity (table 3) improved in all the cases with all patients achieving BCVA by 1 month post op. 4 out of 5 patients achieved BCVA 6/9 Snellens acuity with all 5 eyes having less than 1.0D astigmatism at 1 year follow up. The average spherical equivalent at 1 year was +1.65D (+1.12 to +2.38). One patient (no.4) had BCVA 6/24 which was partially attributed to co existing diabetic retinopathy. The refraction at 1 month was maintained at 6 months and at 1 year follow up (fig 4). The glasses could be prescribed at 1 month for 4 out of 5 patients.

The patient acceptance was very good in all the cases which were evaluated based on positive feedback on minimal discomfort postoperatively and early visual recovery. All 5 patients expressed willingness for same procedure in their fellow eye.

Discussion

In the setting of Fuch's corneal endothelial dystrophy and visually significant cataracts, the surgeon must decide which visually rehabilitative surgery is in a patient's best interest namely cataract surgery alone or cataract surgery combined with keratoplasty. Traditionally, a triple procedure denotes cataract surgery, lens implantation and penetrating keratoplasty. Endothelial keratoplasty is an attractive alternative to penetrating keratoplasty especially in combined procedure.

Cataract surgery may accelerate endothelial cell loss; therefore cataract surgery alone in the setting of Fuch's dystrophy should be carefully considered. Although many preoperative factors contributing to decreased endothelial cell count cannot be controlled (age, sex, diabetes, ocular inflammation, trauma), intra operative measures may help preserve the health of the corneal endothelial cells.

Although the triple procedure requires a longer and more involved operative and postoperative course compared to cataract surgery alone its benefits include obtaining more specific treatment for pathologies, one trip to operating room, avoidance of discomfort of a de compensated cornea, avoidance of an insecure feeling for the patient that 'something' more needs to be corrected.

The penetrating keratoplasty exposes eye to higher potentially sight threatening risks of an open sky procedure like endophthalmitis and expulsive haemorrhage. In combination with cataract surgery the penetrating keratoplasty has less predictability in refractive outcome due to technical difficulty in IOL power calculation due to change in ocular surface measurements and also due to

	1 month	At 1 year				
	Preop BCVA	IOL power adjustment	Post op UCVA	Post op BCVA	Refraction	Co existing ocular morbidity
1	6/36	-1.0 myopic	6/12	6/6p	+2.0/+0.75 x1400	Nil
2	6/60	-1.5 myopic	6/24	6/9	+1.0/+0.5 x1800	Nil
3	1/60	-1.5 myopic	6/18	6/9	+0.75/+0.75 x1800	Advanced glaucoma
4	HMCF	-1.0 myopic	6/60	6/24	+2.0 DS	Diabetic retinopathy
5	6/60	-1.5 myopic	6/18	6/9	+1.0/+1.0x 400	Nil

Table 3: Post op data

high suture induced astigmatism. Hence traditional triple procedure is understandably more reserved procedure in Fuch's dystrophy with cataract and tempting for the surgeons to try out the cataract surgery first and go for the keratoplasty as second stage if needed. The option of endothelial keratoplasty in skilled hands offer excellent alternative to penetrating keratoplasty in terms of refractive outcome. The surgical time is considerably reduced as suturing is limited to closing a 5mm wound. As corneal surface is untouched the induced astigmatism is very minimal. This gives the additional benefit of early visual recovery and visual rehabilitation in form glass prescription. The sight threatening complications are avoided to significant level. The whole procedure can be done under topical anaesthesia in experienced hands.

Conclusion

The new triple-procedure, DSEK combined with cataract surgery provides rapid and satisfactory visual recovery and allows selection of an appropriate intraocular lens There is lack of randomised controlled studies comparing new and traditional triple procedures and also those comparing staged versus combined surgery. In the new era of more refined techniques of both cataract and keratoplasty surgeries the indication for each surgery and combined surgery needs to be re investigated and new recommendations should be discussed in the best interest of the patients.

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Original Article

Acute Angle Closure Glaucoma with Capillary Leak Syndrome Following Viper Bite

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Abstract

Ophthalmic manifestation after viper snake bite are CRAO, macular infarction, vitreous haemorrhage, optic neuritis, cortical blindness, endophthalmitis , uveitis, globe necrosis and rarely ghost cell glaucoma and acute angle closure glaucoma. We report 3 cases of angle closure glaucoma with capillary leak syndrome and acute renal failure. Methods: Retrospective, descriptive analysis of snake bite in a tertiary care hospital in rural area during the period of May 12 to May13. Results: Of the 119 snake bites admitted, 15 patients needed hemodialysis for acute renal failure. 7 of them were diagnosed to have capillary leak syndrome. Among them 3 cases with acute angle closure glaucoma on the second day of bite developed capillary leak syndrome and went into acute renal failure and needed hemodialysis.1 patient expired and other two recovered due to timely and appropriate intervention. Conclusion: Acute angle closure glaucoma following viper bites have been reported earlier, but the physician, the nephrologist and the ophthalmologist should be aware of the possibility of capillary leak syndrome and the chance of impending renal failure. If recognised early, timely an appropriate treatment can decrease the morbidity of this major public health problem.

Key Words

SNAKE BITE, HEMOFILTRATION, CAPILLARY LEAK SYNDROME, ANGLE CLOSURE GLAUCOMA

Introduction

Snake bite is a major public health problem worldwide. Epidemiological study on snake bite varies from place to place. Literature review showed the ophthalmic manifestations after hemotoxic snake bites as CRAO, macular infarction, vitreous hemorrhage, optic neuritis, cortical blindness, endophthalmitis,uveitis and rarely acute angle closure glaucoma. The present study focuses on the patients who underwent hemofiltration after snake bite and those who had eye manifestations.

Aim

To find the incidence of angle closure glaucoma among the hematotoxic snake bite cases admitted in the medical ICUs in our hospital during a period of 1 year from May 2012 to May 2013.

Materials And Methods

We did a retrospective chart review and descriptive analysis of snake bite cases who underwent hemofiltration from May 2012 to May 2013 who were admitted in our tertiary care hospital ICUs in rural Kerala. Hematotoxic envenomation was diagnosed using the 20 minute whole blood clotting test and other coagulation profile. Haematological and biochemical analysis of blood in view of snake bite and its complications were done. Assessment of the severity of envenomation was done1. Lyophilised polyvalent enzyme refined equine immunoglobulin (Snake Venom Anti serum. I.P-SAV) was administerd depending on the severity. When necessary, surgery, nephrology, cardiology, pulmonology, ophthalmology and other relevant referrals were done. Patients with severe envenomation and renal involvement who needed dialysis underwent Heparin free hemofiltration in the ICU itself.

Bed side ophthalmological evaluation was done as the patients were not ambulant. Visual acuity, gross colour vision, ocular position, extraocular movements, digital tension, anterior segment evaluation was done.IOP was recorded using Schiotz tonometer. Fundus examination was done after dilating with Tropicamide eye drops 0.5% when possible after physician's approval. Later when fit to shift, detailed evaluation was done . Only patients who were diagnosed to have haematotoxic bite were included in this study.

Results

119 suspected snake bites were admitted in the medical

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ICUs during the study period. 15 patients with severe envenomation with hematotoxic bite needed heparin free hemofiltration for renal involvement (FIG.1). None of the patients without hemodialysis had ocular symptoms and hence ophthalmological referral were not done .Of the 15 patients 7 cases had ocular symptoms (FIG. 2). 5 of them had respiratory distress and 4 needed ventilator support. Local reactions were noted in 14 of them and regional lymphadenopathy in 10 of them.

Whole blood clot time was prolonged (>11minutes) in all the 15 patients. SAV was administered in all patients ranging from 15-40 vials.

Patients under our study ranged between the age of14 and78. Maximum patients ranged in the age group of 30-40. 11 (73%) of the 15 patients were males. Russels viper bite was noted in 5 (30%) patients, viper in 5 others and the rest 5 were unidentified bites .Serum sickness was not reported in any of these patients.

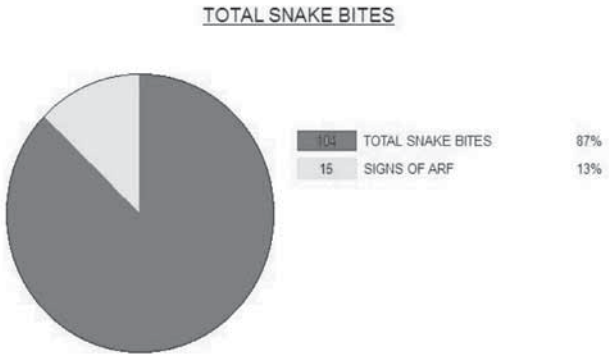


Fig 1

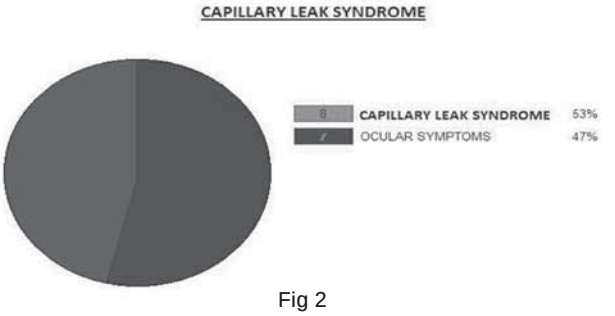


Fig 2

Capillary leak syndrome was diagnosed by the nephrologist in 7 (46%) patients. Ocular symptoms were noted in 3 patients on day 1, same day on 1 patient and day 2 another patient. 4 cases (26% among them had facial puffiness, peri orbital edema and lid edema. 3 (20%) of these patients with facial puffiness and periorbital edema had very shallow anterior chamber and raised IOP. (FIG.3). Visual acuity recorded at bed side in them were less than 6/60. 2(13%) (28%) of them had mid dilated fixed pupil and the cornea was hazy in them.IOP was lowered using hyper osmotic agents and topical anti glaucoma medications. Topical steroids was started hourly in them due to the diagnosis of capillary leak syndrome along with systemic low dose Methyl Prednisolone at a dose of 125mg/ kg body weight 8th hourly. All of them improved with medications,IOP was controlled. Vision improved in 2 patients but the older patient expired in the hospital.

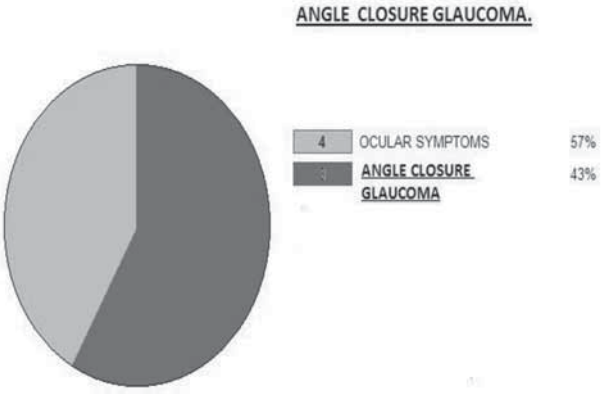


Fig 3

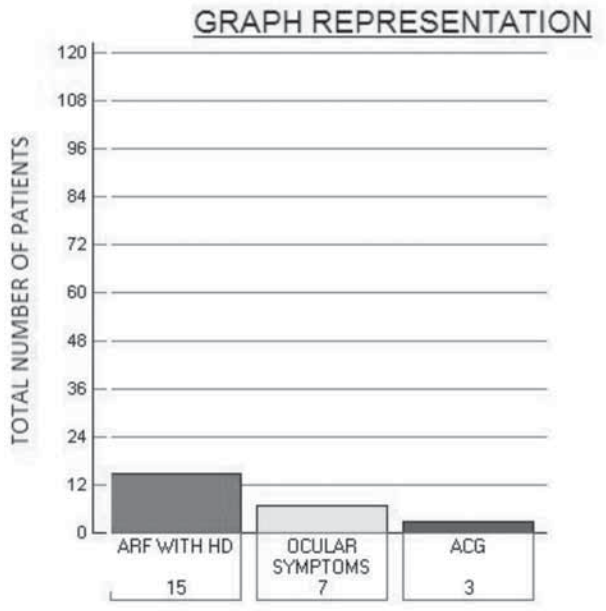


Table 1
ARF-ACUTE RENAL FAILURE, HD-Hemodialisis, ACG-Angle Closure Gluacoma.

Discussion

Although a major public health problem in many countries, the epidemiology of snakebite is still fragmentary, mainly due to lack of statistical data. This is compounded by the fact that the majority of victims wwcome from rural areas, out of reach of the available medical facilities. It is estimated that snakebites may exceed 5 million per year, out of which approximately 100,000 develop severe sequelae.

The incidence also shows a distinct seasonal pattern with a higher frequency in summers and during rains when the reptiles come out of their shelters. Epidemics of snake bite following floods owing to human & snake populations getting concentrated together have been noted in Pakistan, India & Bangladesh.

Snakebite is observed in all age groups, the majority affecting 11-50 year olds with males affected twice more often than females. Most bites occur between midnight and early morning and a large number of bites occur in fields[2]. In our study, age of the patents ranged from 14- 78 years. 11 (73%) were males. Our study showed most bites as in the evenings and night. 10 cases (66%) could identify the snake. Every bite does not result in complete envenomation and more than half the victims escape without serious poisoning, same is the case in our study also.

Srinivasan.R et al [3] had reported two cases of bilateral angle closure glaucoma following snake bite. Appukuttan. A. et al[4] described about 3 patients who developed bilateral angle closure following snake bite and SAV administration. Mohammed Haneef & Veena Verma[5] had reported on acute angle closure glaucoma as a rare complication of viper bite from the same geographical area. Preethi et al[6] had reported on single case of bilateral angle closure glaucoma following snake bite and acute renal failure. Similar to all these reports from South India, we also have 3 cases of bilateral angle closure glaucoma following hemotoxic snake bite . All our patients had received polyvalent SAV. Interestingly all the 4 reports of similar cases are from South India which confirms the geographic predilection of different snakes types

Although Appukuttan et al described patients who were young, our 3 patients were of different age groups, two patients in 30s and 1patient in 50s. All of the patients in this study group had been diagnosed as hematotoxic snake bites and capillary leak syndrome with acute renal failure needing heparin free hemofiltration unlike other reports.

Suchithra . N[7] et al from Kottayam , Kerala had reported on snake bite envenoming with capillary leak syndrome and also acute renal failure but nothing was specified about the ocular involvement in their study group.

Chavan W M & Chavan K D[8] in their report from rural Maharashtra on ocular manifestations in patients with snake bite had reported only 6% snake bites as of viper and had not mentioned of angle closure glaucoma.

Preethi et al posulated that antihemostatic factors present in viper venom can lead to acute fibrinogenolysis, reduction of platelet levels and damage to vascular endothelium. This could lead to break down of blood aqueous barrier which in turn leads to the edema and extravasation of ciliary body. This may be the probable cause for uveal effusion and forward movement of lens iris diaphragm and the shallowing of anterior chamber in our cases too.

Conclusion

Acute angle closure glaucoma following viper bites have been reported earlier but only few. The physician, the nephrologist and the ophthalmologist should be aware of the possibility of capillary leak syndrome and the chance of impending renal failure. Vision threatening complications are reversible if timely treatment is given. If recognised early, timely and appropriate treatment can decrease the morbidity of this major public health problem.

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Original Article

Spectrum of Eyelid Tumors at A Tertiary Eye Care Centre In Kerala

Dr. Rohit Khatri MS, Dr. Reena A Rasheed MS

Abstract

PURPOSE

To study demographic pattern & distribution of various eyelid tumors.

To study clinical profile of eyelid tumors

To evaluate clinic-pathological correlation of eyelid tumors.

Methods

35 Patients presenting to our eye care centre with clinical features suggestive of an eyelid tumor between Jan 2012 & May 2013 were included in the study. Data collected includes age , sex , geographical location , predisposing factors of study population. Provisional diagnosis was made based on clinical features & morphological characteristics of lid swelling , extent of involvement, orbital invasion & associated systemic features. Histo-pathological diagnosis was made from the biopsy specimens obtained. The extent of correlation between the clinical diagnosis & the histopathological diagnosis was analyzed.

Results

35 patients were included for analysis. Majority of the patients(31%) were in the age group of 41 to 60 years. 63% patients were females(n=22). 60% of them were from urban areas(n=21).All the patients presented with complaints of swelling over the eyelid, 11% had mechanical ptosis. 57% of the lesions were located on the upper eyelid.

Histopathologically 17%(n=6) of the tumors were malignant, the rest being benign. Most common tumors were Intradermal naevus 20% , Dermoid cyst 20% & Capillary Hemangioma 20%.Clinical diagnosis was correlating with pathological diagnosis in 91% of cases(n=31).

Conclusions

This study gives us some insight into the spectrum of eyelid tumors presenting to this tertiary referral centre. A reliable clinical diagnosis can be made based on the morphological & associated features of the mass lesion, which in most cases correlates with the histo-pathological diagnosis.

Aim

To study demographic pattern & distribution of various eyelid tumors.

To study clinical profile of eyelid tumors

To evaluate the clinic-pathological correlation of eyelid tumors.

Materials & Methods

Patients presenting to the OPD of this tertiary eye care centre with clinical features suggestive of an eyelid tumor were included in the study. Approval for conducting the study was obtained from the institutional review board. An informed consent was taken at the time of inclusion in the study. A thorough clinical history was taken from the patient with regards to presenting complaints, past & systemic history, medication history, personal history.

General & Systemic evaluation was done whenever indicated to rule out possibility of systemic associations.

Detailed ocular examination was done to assess the best corrected visual acuity, external eye examination, anterior segment examination by slit lamp, posterior segment examination by indirect ophthalmoscopy, intraocular pressure.

Additional investigations like exophthalmometry and external eye photography were done in relevant cases.

A provisional clinical diagnosis was formulated at this point of the work up.

Excisional or incisional biopsy of the tumor was done in all cases depending on the nature of the tumor.

Tissue samples obtained intra-operatively were sent for a detailed histopathological examination to the ocular pathology laboratory at our eye care centre. A histopathological diagnosis was made based on this examination. The correlation between the clinical and histopathological diagnoses was analyzed thereafter.

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STUDY DESIGN: Descriptive
SAMPLE SIZE : 35
STUDY PERIOD : January 2012 to May 2013 (17 months)

Inclusion Criteria

Patients presenting to the OPD of this eye care centre with features suggestive of an eyelid tumor between Jan 2012 to May 2013.

Exclusion Criteria

Patients not willing to be included in the study
Patients not willing for surgical excision of tumor.

Results

A total of 35 patients were included for analysis. Sixty three percent of the patients (n=22) were aged less than 40 years (n=22) [Fig. 1]. Sixty three percent (n=22) of the patients studied were female [Fig. 2].

All the patients presented with complaints of a mass lesion. Fifty seven percent (n=20) of the patients had a mass lesion located on the upper lid; the lower lid & lateral canthus being involved less frequently [Fig. 3]. Twenty percent of (n=7) patients had lid margin involvement. Seventeen percent (n=6) had conjunctival involvement. One patient each had ocular surface complications secondary to the tumor. One patient had lacrimal glandinvolvement.

The most frequent provisional clinical diagnosis was Dermoid cysts (n=9) and Squamous papillomas (n=8). [Fig. 4]

On histopathological examination, the most frequent tumors were Dermoid cysts (n=7)followed byIntradermal naevi(n=7) and Capillary hemangioma (n=7). [Fig. 4]

In the study population, 17% (n=6) were found to be malignant on histo-pathological examination.

The clinico-pathological correlation in this series was found to be 91%.

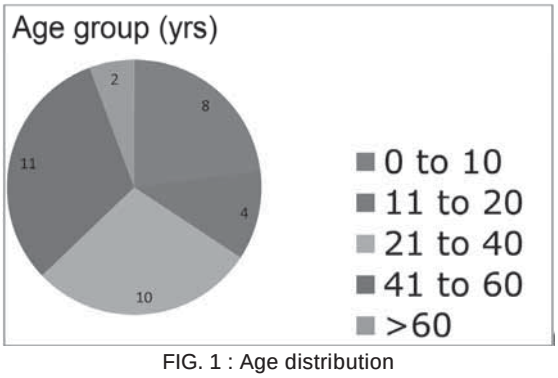


FIG. 1 : Age distribution

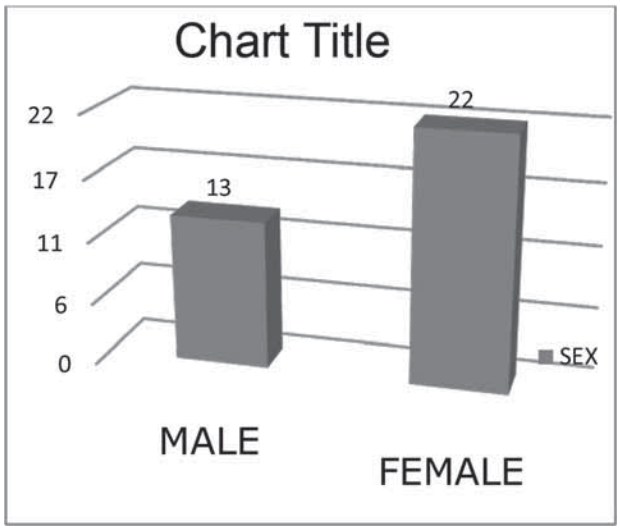


FIG. 2 : Sex distribution

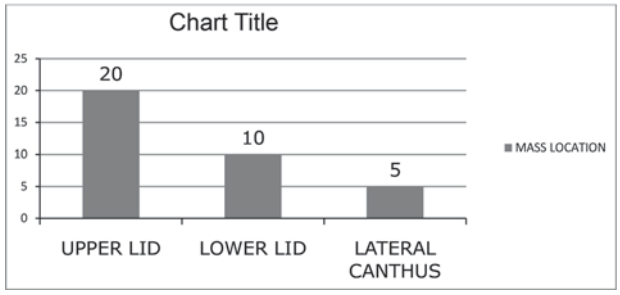


FIG. 3 : Mass location

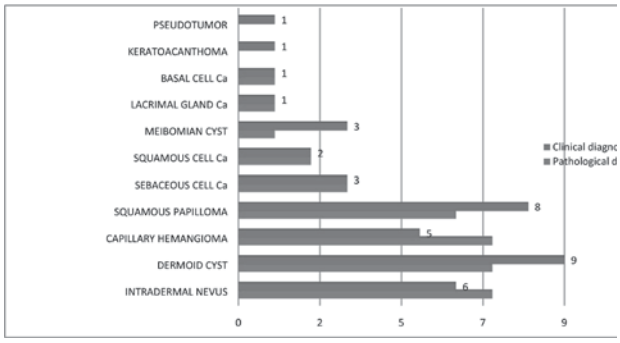


FIG. 4 : CLINICAL & PATHOLOGICAL CORRELATION

Discussion

In this study, majority of the patients were less than 40 years old (63%). Also, majority of the patients in the study were females (63%).

All the patients presented with complaints of a mass lesion involving the eyelids. Some of these patients also had complaints of ptosis. Most of the tumors were seen on the upper lid (57%). Less frequently the lower lid or lateral canthus were involved.

Lid margin involvement was seen in 7 (20%) of the cases

in the study. Cases with lid margin involvement were more likely to have upper lid mass & were more likely to have ptosis as an associated complaint.

Conjunctival involvement was seen in 6 (17%) of the cases. These cases were more likely to have lid margin involvement too. Ocular surface complications secondary to the tumor was seen in 1 case. Lacrimal gland involvement was seen in 1 case.

Of all the cases studied, the common provisional clinical diagnoses were Dermoid cysts(n=9, 26%) & Papilloma(n=8 , 23%). On histo-pathological examination, the most common tumors found were Dermoid cysts(20%), Intradermal nevi(20%) & Capillary hemangioma(20%). A study in North India[1] found vascular tumors(21.3%), neural tumors (18%) & dermoid cysts (16.4%) to be the most common benign tumors of the eyelid. A study in Japan[2] found nevocellular nevi(11%) & Papillomas (9%) to be the most common benign eyelid tumors.

In our study, 17%(n=6) tumors turned out to be malignant on histo-pathological examination, the rest being benign. In a study from Japan[2], 27% of the eyelid tumors were found to be malignant. Another study from Switzerland reported16% of the eyelid tumors as benign.

The malignant lesions were sebaceous cell carcinoma (n=3), basal cell carcinoma(n=1), squamous cell carcinoma (n=1) & lacrimal gland carcinoma (n=1). A study on eyelid malignancies in Central India[4], found basal cell carcinoma (44.5%), sebaceous cell carcinoma (37%) & squamous cell carcinoma (17%) to be common eyelid malignancies. A study in Nepal[5] found sebaceous gland carcinoma (40.5%) to be the most common eyelid malignancy.

There was a 91% correlation between the clinical & pathological diagnoses in our study.

Conclusion

This study gives us an insight into the spectrum of eyelid tumors presenting to our eye care centre. The most common benign eyelid tumors presenting to our centre are Dermoid cysts, Intradermal nevi and Capillary hemangiomas. The most common malignant eyelid tumor seen is Sebaceous gland carcinoma. There is a good amount of correlation between the clinical & pathological diagnoses in these cases.

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Express Glaucoma Implant

Dr. Dhanya Cheriyath MS,DO,DNB; Dr. Muhemmed Swadique DNB,FRCS(Glasgow)

Introduction[1]

The Ex-PRESS glaucoma shunt, made from medical grade implantable stainless steel, 2. 4-3 millimeters long and 400 μm in diameter (Fig.1) is MRI compatible and biocompatible device . It was designed with the intention of offering an accurate, repeatable, and safe alternative to trabeculectomy. Similar to trabeculectomy,the shunt reduces intraocular pressure (IOP) by diverting aqueous humor from the anterior chamber to the subconjunctival space in order to form a filtration bleb. Mitomycin C (MMC) use during the procedure is recommended to prevent scarring. The device's unique flow-modulating design and the scleral flap under which it is implanted, controls postoperative aqueous flow. Filtering surgery with the Ex-PRESS mini-shunt is a safe and standardized procedure compared to classic trabeculectomy[2].

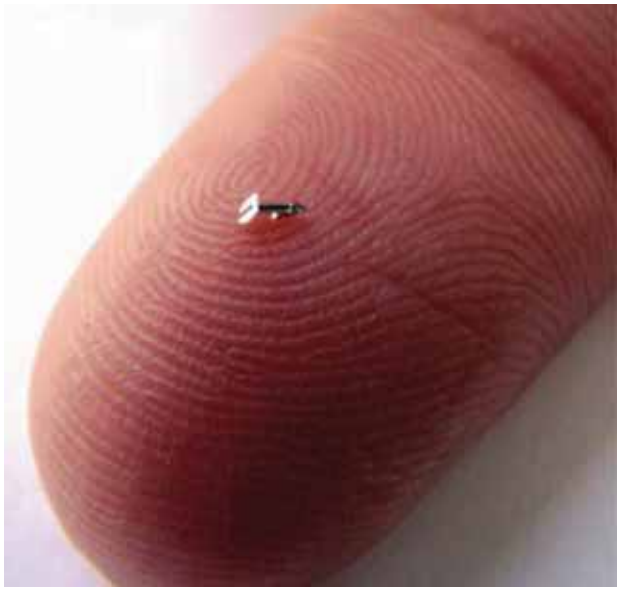


Fig1: Express shunt

Originally the Ex-PRESS manufacturer(Optonol Ltd., a Swiss-Israeli company) recommended placing the device directly under the conjunctiva, but due to excessive hypotony, exposure, and other adverse effects, this technique has been abandoned[3] .

Dahan and Carmichael first recommended implanting

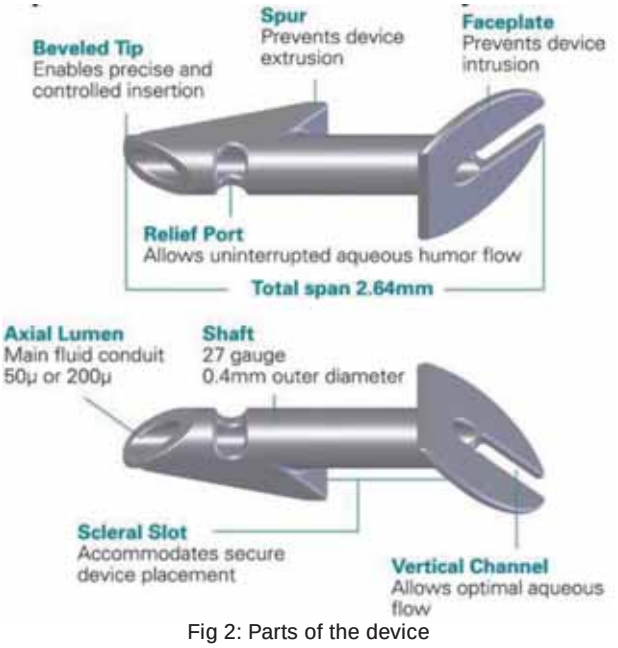


Fig 2: Parts of the device

the Ex-PRESS shunt under a 5 × 5 mm partial thickness scleral flap, similar to a standard limbus-based guarded trabeculectomy4. Placing the Ex-PRESS under a half thickness scleral flap provides resistance to aqueous flow and prevents erosion. No iridectomy is required.

Since 2003, Optonol, Ltd. has recommended all users of the device to only implant the device guarded under a scleral flap.

Ex-PRESS Indications

1. Open Angle Glaucoma refractory to medical and laser treatment
2. Open Angle Glaucoma when a filtration procedure has failed
3. With combined glaucoma and cataract procedure
4. Aphakic glaucoma
5. Sturge-Weber syndrome

Ex-PRESS Contraindications

1. Narrow Angle Glaucoma
2. Congenital or juvenile glaucoma
3. Aniridia and anterior segment dysgenesis syndromes

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MODELS AND FEATURES OF EXPRESS SHUNT[1]

	Ex-PRESS™ R-50 Beveled tip for easy insertion	Ex-PRESS™ X-50 Ex-PRESS™ X-200 Used for excessive flow	Ex-PRESS™ P-50 Ex-PRESS™ P-200 Beveled tip for easy insertion. Vertical split back plate for posterior flow
External body shape	ROUND	SQUARE	ROUND
Device length (mm)	2.96	2.42	2.64
Internal lumen size (μm)	50	50 200	50 200
Tip shape	POINTED	SQUARE & SHORT	POINTED
Back plate shape	UNIFORM	LATERAL CHANNEL	VERTICAL SPLIT
Preincision needle guage	27G	23-25G	25G

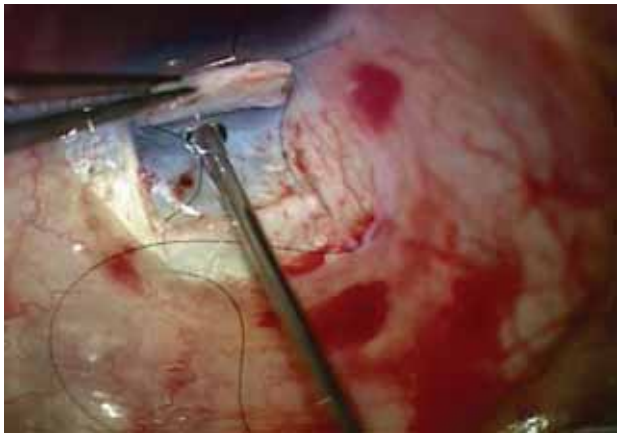


Fig3:The shunt is inserted through a previously made opening with either a 27- or 25-gauge needle (depending on model)

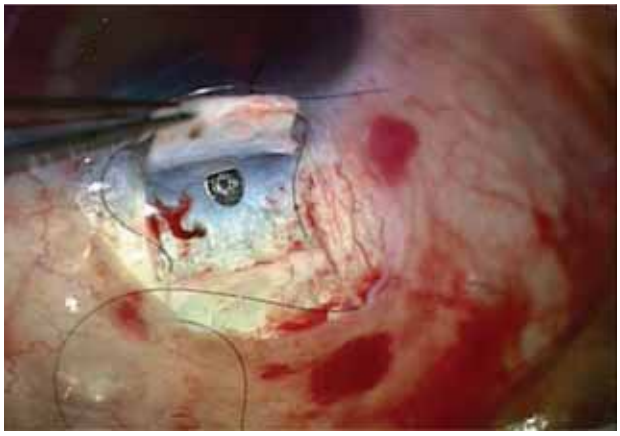


Fig4: The Ex-PRESS external plate should lie flush with the sclera.

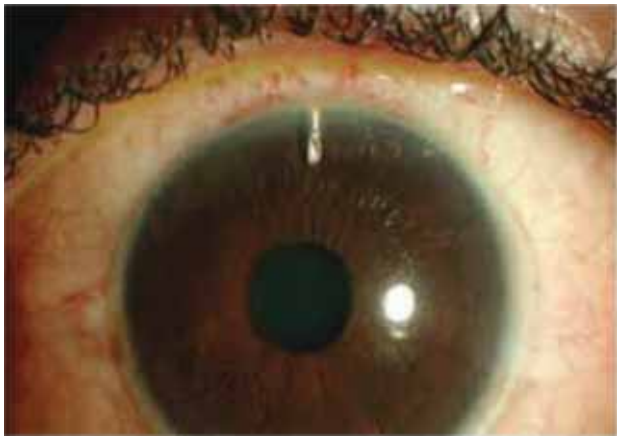


Fig5:Express Shunt in situ

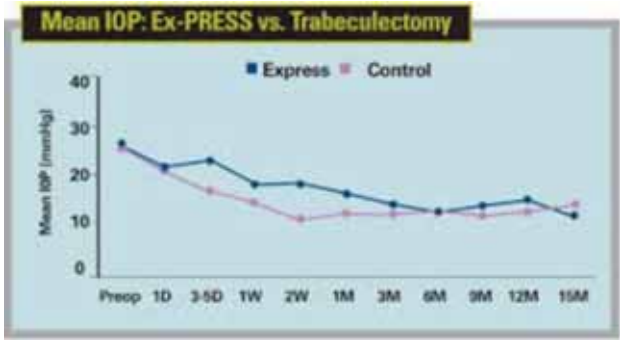


Fig 6: Comparison of mean IOP[2]

4. Neovascular glaucoma
5. Microphthalmia

Surgical Technique[5]

Step 1: A standard fornix or limbal-based conjunctival incision is performed to gain exposure to the scleral bed adjacent to the limbus. Gentle cautery is performed in this area.

Step 2: A scleral flap is created in a similar manner performed with a standard trabeculectomy. Care is taken to dissect the flap up to clear cornea. Anti-fibrotic agents can be applied either before or after the creation of the scleral flap in the usual manner based on the surgeon's preference.

Step 3: A temporal paracentesis is created through the cornea.The scleral flap is lifted and care is taken to identify the center of the "blue line" adjacent to clear cornea which corresponds to the location of the trabecular meshwork. A 26 gauge needle is inserted into the anterior chamber through the center of the "blue line" at an angle parallel to the iris plane.The needle is removed. There must not be any lateral movement of the needle as this will cause aqueous to flow around the implant.

Step 4: The Ex-Press shunt is preloaded on an injector.The shunt is then placed in the anterior chamber through the ostium created with the needle. The angle of entry with the shunt is the same as the angle used to make the ostium. The shunt is inserted all the way into the wound making the plate flush with the scleral bed. In a similar fashion as a standard punctual plug inserter, the injector has an area on the shaft that is then depressed which retracts the metal rod in the lumen of the shunt. This allows the injector to be free from the lumen of the shunt.

Step 5: The scleral flap is then sutured in place using a 10-0 nylon suture with a spatulated needle. One to three sutures are typically required depending on the flow which can be tested by inflating the anterior chamber with balanced salt solution with a 27 or 30 gauge canula through the temporal paracentesis.

Step 6: The conjunctiva is then meticulously closed with the surgeon's suture of choice. (8-0/9-0 polyglactin suture in a running or interrupted fashion). A fluorescein strip is used to make certain the wound is water tight.

Complications[1]

Complications typically seen with a trabeculectomy can also be observed following implantation of the Ex-PRESS implant. Immediate postoperative hypotony,shallow or flat anterior chamber, hyphema, and choroidal detachments do occur, although to a lesser extent because of the small 50 μm drainage orifice . The usual directive on how to avoid these complications in other filtration procedures is also applicable to filtration surgery with the Ex-PRESS.

In terms of toxicity of the material, no adverse reports have been published to this date and the shunt is MRI compatible[6]. Moreover, interpretation of MRI scans of the orbit and brain are not affected by EX-PRESS shunt artifacts. There have been rare reports of erosion when inserted directly under the conjunctiva, and therefore have the implant extrude after direct trauma and the shunt when improperly placed can dislocate into the anterior chamber . On occasion, the implant will need to be safely removed.

Conclusion[1]

Glaucoma surgery is constantly evolving. The perfect glaucoma procedure has yet to be invented. However,the desire to minimize complications while maximizing outcomes continues to move surgical technology forward. Prospective randomized studies comparing Ex-PRESS implantation with standard trabeculectomy and other drainage implants are warranted to define the optimal treatment modality for complicated glaucoma[7].

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To view this video, visit www.ksos.in

Disclosure: The authors do not have any financial interest in the products mentioned in the article

Choosing the Right Gonioscope for Your Practice

Dr S Deepthi DNB, Dr S J Saikumar MS, DNB

Glaucoma is a leading cause of irreversible blindness in the world. Population based studies estimate prevalence of glaucoma in India to be about 11.9million.[1] Primary angle closure glaucoma (PACG) constitutes a significant proportion of those with glaucoma. The Vellore Eye study reported prevalence of PACG of 43.2 per 1,000 population.[1] The Aravind comprehensive Eye survey estimated the prevalence of PACG to be about 0.5%.[2]

Gonioscopy is a very useful tool in understanding the mechanism of glaucoma. However many general ophthalmologists do not give it due importance in their practise. The Chennai Glaucoma study reported that, in patients classified with glaucoma 40% were misdiagnosed with open angles.[3]

Deciding on a gonioscope can be a difficult task, especially for the practitioner without much experience. One of the most fundamental decisions to make when choosing a gonioscope is deciding on the basic design. The two basic varieties are the Goldmann type lenses and the indentation lenses. If you seldom perform gonioscopy, or are just starting out in practice, you may wonder which of the two main lens styles to use. However, by prioritizing your needs, it becomes a bit easier to choose a goniolens.



Fig 1:Goldmann lenses have larger base diameter and larger radius of curvature, and hence need a coupling agent

The best view of the angle is obtained through a Goldmann style three-mirror lens. The Goldmann lens is also easier to use and master than the indentation lens. These lenses include Goldmann, Allen/O-Brien, Allen-Thorpe, Ritch and the Magna View lens. They have larger base diameter (12-mm diameter and a radius of curvature of 7.38 mm) and require a coupling agent to fill the gap between the lens and the cornea. (Fig1) A major advantage of this type of lens is the fact that it can be held squarely on the eye without distorting the cornea, resulting in a clear view of angle structures and hence used for surgical procedures of the angle such as trabeculoplasty.[4,5] The high clarity of image in 3 mirror lenses helps to examine for angle foreign bodies and fine new vessels. However the coupling fluid makes it difficult to do perimetry or fundus photography afterwards and is more uncomfortable for the patient. It is also cumbersome to rotate the lens while maintaining contact with the eye.



Fig 2 :Goldmann 3 mirror lens

The 3 mirror Goldmann lenses incorporate mirrors at precise angles which help in viewing the iridocorneal angle, the equator and the periphery of the retina. (Fig 3) Central part of the gonioscope is used to visualise the central portion of the fundus. Those who prefer the Goldmann type of lens but are only interested in the iridocorneal angle, may opt for a one or two mirror lens. Such lenses include Ocular Instruments Two Mirror Magna View, which offers 1.45x gonio magnification and Laserlight® HD anti-reflective coating for maximum light transmission and image brightness, and Volk's G-1 trabeculum, which offers 1.5x

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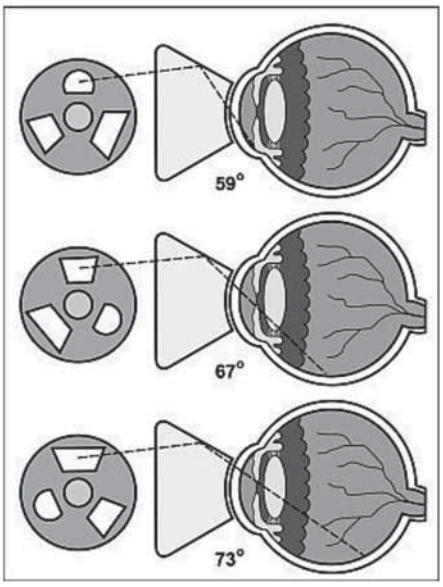


Fig 3 : Goldmann 3 mirror lens – smallest mirror visualizes angle, next bigger mirror visualizes up to fundus equator. Largest mirror visualizes fundus periphery. Posterior pole can be visualized through the central portion of the lens.

magnification and a single 62° mirror.

The technique of using an indentation gonioscope is more difficult to master but it can be performed quickly without causing much discomfort to patient. These are smaller lenses, have four mirrors and a 9-mm diameter corneal surface (radius of curvature 7.72 mm) so there is no need to apply a coupling agent before placing it on the cornea.[6](Fig 1) This not only simplifies the process of performing gonioscopy, it also leaves the anterior segment clear for later viewing of the posterior pole. In these lenses, all four mirrors point toward the iridocorneal angle. This allows quick view of all segments of the angle without much rotation of the lens, significantly cutting down on examination time, thus making it the lens of choice for regular screening of patients. By indentation gonioscopy, we can also determine if angle closure is appositional or synechial. Pushing too firmly on the lens can create corneal folds, hampering view and artificially opening up the angle. Makes of the four-mirror variety

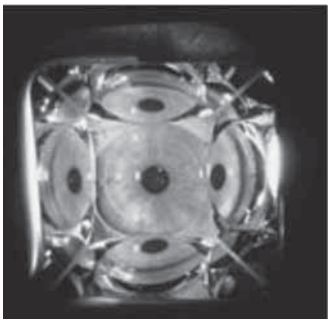


Fig 4: Gonioscopic image with Zeiss 4 mirror showing all segments of the angle

include the Zeiss, Volk G, Posner, and Susmann lenses.

Volk's G-4 series is available with a variety of options, including large and small rings to fit a variety of facial features, adjustable handles, and flanges for stability. In addition, some manufacturers, such as Volk, offer designs that eliminate the need for a coupling solution altogether with their Advanced No Fluid (ANF+) contact option.

Once you have chosen the basic design of your lens, there are still choices to make. Some manufacturers, including both Volk and Ocular Instruments, offer the option of a handle on their lenses. While some like the convenience offered by a handle, others, especially taller physicians may find the handle awkward. In addition, it can be more difficult to stabilize the gonioscope without bracing your hand against the cheek.

Another option to consider is whether to choose a lens with a flange. A flange will provide stability compared to those with a flat contact surface. This is especially useful when performing laser procedures involving the angle. However, they will require the use of a viscous fluid medium. In addition, the flange can make the lens difficult to seat in patients with small fissures and in patients who resist the lens by squeezing. Ocular Instruments' Mini Gonio Laser has a small diameter flange that is convenient for eyes with small palpebral fissures.

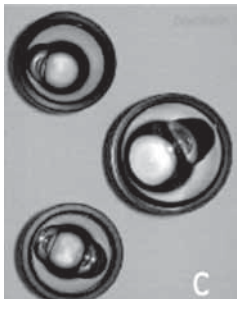
Finally, it is important to consider the materials used to manufacture the lens. Although acrylic lenses are generally less expensive than their glass counterparts, glass lenses are seen to offer better optics, clarity, and durability.

Commonly Used Gonioscopes



GOLDMANN 3 mirror

The smallest mirror visualizes the angle, next bigger mirror visualizes up to fundus equator. Largest mirror visualizes fundus periphery. Posterior pole can be visualized through the central portion of the lens.



GOLDMANN 1 AND 2 MIRROR

Ideal for patients with small interpalpebral fissures. The mirrors are smaller producing a more minified view of the anterior chamber. Gonioscopy lens with 2 mirrors needs to be rotated once to observe all quadrants while the one

mirror lens needs to be rotated three times in order to view all angles.



SUSSMAN

Four 64° mirrors for complete anterior chamber angle viewing with minimal lens rotation. Directly hand held for easy handling and stability. Small diameter contact surface allows static or dynamic gonioscopy without methylcellulose. Advanced technology, multi-layer polymer coating protects mirrors and is compatible with most disinfecting methods.

VOLK



4 Mirror High Magnification Goniolens delivers crisp, clear views. Four mirrors equally angled at 64°. Image magnification of 1.5x. Large or small ring options are available to suit personal handling preferences. For additional flexibility, the 2-in-1 handle can easily be adjusted to create a straight or 45° angled grip.



POSNER

Four 64° mirrors for complete anterior chamber angle viewing with minimal lens rotation. Choice of 3 handles set at 17° for ease of use. Smaller area of contact allows for indentation gonioscopy. Advanced technology, multi-layer polymer coating protects mirrors.



RITCH TRABECULOPLASTY

Designed with two 59° (round on top) and two 64° mirrors (flat on top). A 1.4x magnifying button is placed over one each of the 59° and 64° mirrors. The magnifying button reduces the laser spot size by 30% and increases the laser power by 2x. The 64° mirror is best for treating the superior 180° of the angle, while the 59° mirror is best for the inferior 180°.



LATINA TRABECULOPLASTY

The Latina SLT Gonio Laser Lens was designed specifically for Selective Laser Trabeculoplasty. 1.0x magnification maintains laser spot size and 1 to 1 laser energy delivery. Tilted anterior lens surface corrects astigmatism to maintain circular laser beam profile and give sharp images. Suitable for standard laser trabeculoplasty. Large 63º mirror yields bright image for angle photography.



VOLK 6 MIRROR LENSES

Six closely aligned mirrors eliminate gaps providing a true 360° panoramic view. Enhanced lens body design improves utility: Tapered profile less prone to patient squeezing off the eye. A taller, narrower body easier to hold within the orbit.

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Disclosure: The authors do not have any financial interest in the products mentioned in the article

Therapeutic Challenge: Strabismus

Dr.Sanitha Sathyan DNB

Case

A 11 month old girl presented to us with complaints of deviation of eyes noticed since birth. The deviation has remained constant and there was no history of defective vision observed by the parents. The developmental milestones were appropriate for age.

On examination, she was fixing and following uniocularly, with fixation central, steady and maintained. The patient was not co-operative for preferential looking testing. The right eye was hypotropic in primary position with -4 limitation of elevation, both in abduction and adduction. There was variable esotropia. Other ocular movements were normal and there was no ptosis. Cycloplegic retinoscopy, anterior segment and fundus examinations were otherwise within normal limits.

Questions for discussion:

How would you manage this case?
What is the ideal timing for surgical intervention?
Will early surgery prevent the occurrence of amblyopia?

Responses

Dr Elizabeth Joseph,
Chief, Pediatric Ophthalmology and Strabismus,
Little Flower Hospital, Angamaly

The salient points I gathered from the photographs shown and the synopsis written are that the child has Right Hypotropia with gross restriction of elevation in adduction and an esotropia which is alternating. Although it is written that elevation in abduction is also equally restricted in the right eye (RE), it is not so evident in the photo. The absence



Clinical Photographs:

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of ptosis and absence of abnormal head posture are two important points noted.

This could be a primary vertical deviation with a secondary esotropia due to absence of fusion. The absence of abnormal head posture in the presence of a vertical deviation points to the absence of fusion. The vertical deviation is most likely a Browns syndrome of the right eye (RE), and less likely a monocular elevation defect[double elevator palsy] which can be differentiated by doing a Forced duction test under General Anaesthesia (GA) and looking for foveal intorsion present in Browns.

Regarding the management, alternate patching of each eye has to be commenced as soon as possible to prevent any amblyopia and abnormal sensory interaction.

Surgical management depends on the result of FDT.

FDT positive for Browns - Bimedial recession will correct the esodeviation. If FDT is positive for Browns, the best surgical option is Superior Oblique Silicon Band Expander technique. The chance of a late Superior Oblique (SO) paresis and Inferior Oblique (IO) overaction 6 months or even more later is there and may require additional procedure 1-2 years later. In the mean time patching has to be continued. Even if that is the case, The ultimate result will be definitely better after surgical correction than leaving the patient without surgery.

If FDT is negative, the management is different. We will opt for Knapps procedure to correct the hypotropia [vertical transposition of Medical Rectus (MR) & Lateral Rectus (LR)] with recession MR – resection LR to correct the esodeviation in the right eye as a first stage surgery. If there is residual vertical deviation after Knapps procedure, Ipsilateral Inferior Rectus (IR) recession or contralateral Superior Rectus (SR) recession may be needed.

Regarding the timing of treatment , FDT should be done as early as possible and surgery at the first convenient date. No point in postponing.

Dr.Leila Mohan
Comtrust eye hospital, Calicut

This child presents with features of monocular elevation deficiency with no ptosis. The pathology may be a restrictive one, the restrictive component usually being in the inferior rectus. So an MRI of the orbit and brain will be useful to point to any pathology . An FDT helps planning surgery which can be done before surgery. Abduction seems to be restricted too in the photo which is in favour of a restrictive pathology. In this case a mild widening of palpebral fissure is there in RE which also suggests a restrictive component showing a retraction of lower lid(which may be exaggerated in depression and is not shown here).

Here, the eye is markedly hypotropic and there doesn't seem to be any attempt of chin elevation for binocularity. So patching left eye for 2 hours a day can be started for preventing amblyopia-since she seems to have central, maintained, steady fixation with both eyes now. A revisit may help assessing the esotropia and abduction restriction after patching for a month. Surgery must be undertaken as early as possible, since this is the age where we can attain binocularity.

Counselling the parents is very important and the FDT procedure which will be done before surgery, must be explained and the fact that the surgical plan depends on it and the possibility of second surgery, either for this eye or in the other eye if necessary to attain binocularity must be explained.

I would plan for a recession of 5-7mm with temporal displacement of inferior rectus (IR) for full width of the muscle of course, assuming the IR to show a positive FDT.If the inferior rectus is fibrotic and short, more dissection may be required. If there is considerable improvement of hypotropia and esotropia, child can continue patching and look for periods of binocularity. If the eye is still hypotropic by more than 15 pd SR resection of 5mm may be done in the same eye. Esotropia if persisting, can be corrected with a medial rectus recession during the second surgery. Aim is to have orthotropia in primary position and depression. If orthotropia is not achieved by 2 muscle surgery, contralateral SR can be recessed by 5mm. Close follow up of binocularity and patching if necessary, has to be continued.

Dr. Meena C.K.
Senior Consultant in Pediatric Ophthalmology and Strabismus, Little Flower Hospital, Angamaly

The child appears to have RE- Monocular elevation deficit with variable esotropia.

The diagnosis can be confirmed only after Force duction test of the inferior rectus muscle. If the IR is found restricted/ fibrotic this is more in favour of a monocular elevation deficit. Also associated esotropia has to be tackled as it is more

amblyogenic. FDT of the medial rectus also has to be done as fibrosis of MR is also common.
Birth trauma causing fracture of inferior orbital wall is another possible cause. Imaging may be useful to rule out this possibility.

My line of management would be as follows:
-part time occlusion of the left eye to prevent amblyopia.

First stage surgery:
FDT OF IR and MR.
Bimedial recession to correct esotropia

If IR is found to be restriced, IR recession to tackle hypotropia
-continue part time occlusion and follow up the patient

If there is residual hypotropia, Knapps procedure can be attempted in the right eye

If there is cosmetically bothersome lid retraction (which is common after IR recession), oculoplasty procedure for lid retraction can be done.

Dr.Binu Balan
Consultant in Pediatric Ophthalmology and Strabismus
Dr. Tony's eye hospital, Ernakulam

An 11 month old girl with deviation of eyes noticed since birth, fixing and following uniocularly, having central, steady and maintained fixation with right eye, hypotropia in primary position , -4 limitation of elevation(both in abduction and adduction) having other ocular movements normal with no ptosis points to the diagnosis of Monocular Elevation Deficiency (MED).

Elevation deficiency present equally in adduction and abduction rules out Browns syndrome .Vertical Duanes syndrome is ruled out in the absence of globe retraction in down gaze. Absence of cranio facial anomalies goes against the diagnosis of Congenital absence of Superior rectus or Inferior oblique muscles .Congenital III nerve palsy is less likely as other ocular movements are normal , pupil is not involved, exotropia is absent.

As none of the photos is showing chin up posture ,(chin up posture signifies fusion in down gaze)and patient has uniocular fixation we can conclude that the non fixing eye is amblyopic . Amblyopia treatment needs to be started in the form of occlusion of the fixing eye till Amblyopia is treated.
All cases of MED do not require surgery. Observation is recommended in patient with mild hypotropia. Surgical internvention is needed if there is vertical deviation in primary gaze and if deviation is causing suppression or amblyopia .The goal of surgery is to reduce the vertical deviation in primary gaze thereby increasing the field of binocular vision. Pre operatively the family needs to know that the surgery will not cure MED only reduce the deformity , multiple surgeries will be needed and the affected eye will not elevate as well as the unaffected eye post op.

Bells phenomenon , saccade testing , Forced duction test will help in finding the cause of MED and deciding on the surgery. Lab tests may be needed for GA purpose . Imaging is normally not needed in Congenital MED.

Bell's phenomenon is preserved in Supranuclear elevation deficiency, saccades are slow or floating ,FDT is negative. In these cases if hypotropia is less than 10Pd – Partial tendon Knapp procedure is done . For hypotropia 20-35Pd the Knapp Procedure (transposition of medial rectus and lateral rectus to superior rectus needs to be done. More than 35 Pd needs augumtation with Faden suture.

In Primary inferior rectus restriction, FDT is positive, saccades are normal. If hypotropia is small then Inferior rectus recession is done. If deviation is large the Inferior rectus recession + sup rectus resection is done.

In Secondary IR restriction due to SR palsy, FDT+, Saccades floating - In this case Inferior rectus recession is done as 1st stage and after 4-6 months Knapps procedure is done (vessel sparing if possible).

Esotropia needs Medial rectus recession +/- Lateral rectus resection in the unaffected eye.

Q 2: The ideal time for surgery is as soon as you treat the amblyopia and if there are no other contraindications for General anaesthesia.

Q3: Early surgery may not prevent the occurrence of Amblyopia but it can help in achieving some fusion in down gaze and primary gaze which will go a long way in managing Amblyopia.

Dr. Neena R Menon
Consultant in Pediatric Ophthalmology and Strabismus, Giridhar eye hospital, Ernakulam

The child in the picture has Monocular elevation defect OD with possible fibrosis of IR(due to presence lid retraction rather than ptosis).

1. a) A thorough clinical examination to assess any preference for any eye/resistance to occlusion of any eye should be noted.
b) MRI Brain & Orbits to be done to rule out absence of SR muscle / Fibrosis of IR on right side.
c) FDT to be done intra operatively to rule out restrictive / paralytic cause and to plan IR Recession / Knapp's procedure respectively.
d) Prism Bar Cover Test (PBCT) / MK prism test to assess amount of deviation.

2) Surgery should be planned as early as possible (at least by 3 months of age) as eye is hypotropic in primary position. Also, patient has no chin elevation posture and may develop amblyopia soon.

3) Early staged surgery with alignment of eyes and occlusion of other eye will help in preventing amblyopia.

Conclusion

All the authors have a consensus regarding the need for FDT for the diagnosis of Moncular elevation deficit or Browns syndrome.

MRI orbit cannot provide more clues than FDT regarding the management, hence it is not mandatory. However it may advised for documentation and completion sake.
Occlusion is very important for preventing/ treating amblyopia.

Early surgical treatment has been advised by all the authors. Regarding the surgical management, all the authors agree that IR has to be tackled first if FDT is positive for IR and esotopia has to be tackled by horizontal muscle surgery.

Knapps procedure is an option but its timing is a choice of personal preference as per the discussion.

Faden Procedure for Abnormal Convergence in Congenital Fibrosis of Extraocular Muscle

Dr. Piyali SenM.B.B.S, Dr. Abhipsha Saha M.B.B.S, Dr. Anuradha Chandra M.S,FAICO

Introduction

Congenital fibrosis of extraocular muscle (CFEOM) is a rare, congenital, and non-progressive disorder with multiple extra ocular muscle restrictions. It is characterised by congenital non-progressive ophthalmoplegia with or without ptosis affecting part or all of the occulomotor nucleus and nerve, trochlear nucleus and nerve and thus the muscles supplied by them. These individuals have severe limitation of vertical gaze (usually upgaze) and variable limitation of horizontal gaze.

Case Report:

A 11 year old female patient first visited our hospital on 11/9/2013 with complaint of dimness of vision. Patient had a family history of convergent squint. Her BCVA 6/60 (RE),6/9 (LE). On examination of anterior segment and ocular movements, patient had restriction in upgaze, anomalous convergence on attempting upgaze with A pattern.Posterior segment examination showed CD ratio 0.4: 1, healthy neuroretinal rim and normal macula. She was advised - retinoscopy followed by Glasses, occlusion therapy in left eye 4 hours daily along with near work for 1 hour. Gradually her BCVA improved to 6/36 (RE), 6/6 (LE). Also, reduced dark and light response was found on ERG. In order to correct her esotropia and hypotropia she was advised 5.5 mm medial rectus recession with faden and 4.5 mm inferior rectus recession (till FDT is free) under general anaesthesia.In order to correct the perverted convergence a retro - equatorial myopexy (Faden) of 16mm behind the limbus was performed on right eye medial rectus.



Figure 1: 9 gazes of the eye showing significant hypotropia with esotropia with increased esotropia in upgaze with A pattern

Surgical steps: Forced duction test intraoperatively shows moderate to severe restriction of inferior rectus with moderate restriction in the medial rectus. Lateral rectus was free and superior rectus was also free. Therefore we proceeded to do 6 mm inferior rectus recession with hemi hangback of 1 mm. Medial rectus recession 4.5mm with post equatorial myopexy at 16mmm from limbus was done. At end of surgery the FDT was free for all the muscles



Figure 2: Intraoperative picture of inferior rectus recession with hemi hangback using 5-0 ethibond suture.

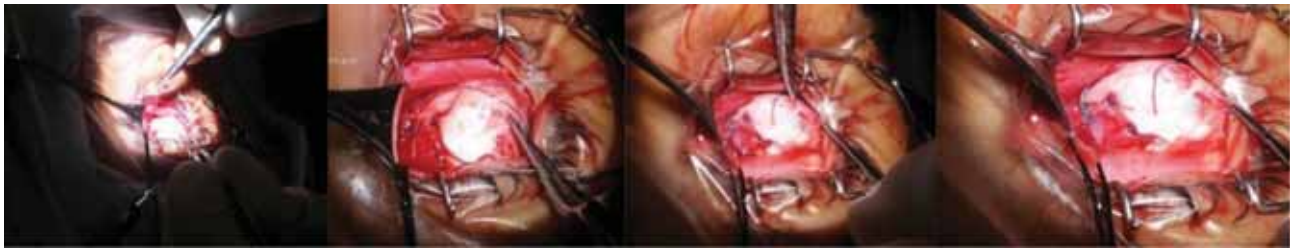


Figure 3 : Intraoperative picture showing faden operation with recession of medial rectus.

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Figure 4: Post operative day 7 pictures showing improvement of esotropia and hypotropia with absence of perverted convergence and no esotropia in upgaze.

Discussion:

Review of literature shows a few articles describing the large recessions in cases of CFEOM. Ahmad Yazdan MD, Elias I Traboulsi, MD in their study on classification and surgical management of patients with familial and sporadic forms of congenital fibrosis of the extraocular muscles concluded inferior rectus recession improved hypotropia and Bell's phenomenon in the patients with infraducted eyes and chin elevation. Horizontal muscle recession, sometimes combined with opposite muscle resection, corrected horizontal strabismus satisfactorily in most cases. Hatem A Tawfik and Mohammad A Rashad conducted a study on surgical management of hypotropia in congenital fibrosis of extraocular muscles presented with pseudoptosis. There was a highly significant improvement from preoperative mean hypotropia angle of 30 prism diopters (PD) to 9 PD mean postoperative angle (P = 0.006) by single-stage adjustable strabismus surgery (SSASS), followed by a frontalis sling if needed.

There is no article which specifies the remedy of abnormal perverted convergence which is a significant abnormality affecting the patients of CFEOM. The abnormal convergence which manifests during the attempted upgaze is a neurological input which is not controlled voluntarily and can be described as abnormal innervation to medial rectus as opposed to normal innervation which should be presented to the elevators of the eye.

Faden operation was first described in control of abnormal AC/A ratio which causes excess convergence when the patient attempts to see near.Later it has also been used in paralytic squints and CCDS. Faden operation is able to reduce the force of convergence while not affecting the position of the eye . Therefore faden operation is good option in cases of abnormal convergence.

This is the first time faden operation is described in cases of abnormal convergence in CFEOM. Usually CFEOM has large restrictions in inferior recti and medial recti which is negated by large recessions. However each case has to be treated individually. Since the child had a moderate amount esotropia, large recession was not warranted in her case as the lateral recti appeared to be acting normally.

Conclusion

Faden operation can be effective in cases of CFEOM with abnormal convergence in attempted upgaze with moderate esotropia with moderate restriction.

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Brief Report

Atypical Mycobacterial Keratitis

Dr. David Pudukadan MS, Dr. Seema K.M DO,DNB, Dr. Karthika MBBS

Introduction

Atypical Mycobacterial corneal infections are rare, but have devastating complications. Although rare, they pose a diagnostic and therapeutic challenge as these organisms show poor response to antibiotics. Hence high index of suspicion is required in cases which do not respond to conventional antibiotics. Here we present a case of atypical mycobacterial keratitis with no predisposing factors in history which eventually required surgical intervention.

Case

A 30 year old male who is a manual labourer presented with a 1 week history of moderate pain, redness, watery discharge & defective vision of right eye. He had consulted his local ophthalmologist and was using topical medications (antibiotics and antifungals) for past 3 days but had no improvement.

There was no past history of ocular trauma, surgeries, contact lens usage, prolonged use of topical medications or pond bathing. No significant past medical and family history. General examination was normal.

On ocular examination his unaided visual acuity in the right eye was 6/36, which improved to 6/18 with pinhole. Anterior segment examination of the right eye showed a 2x2 mm corneal epithelial defect with raised greyish white infiltration with fluffy margins. The infiltrates reached up to midstroma. Surrounding Descemets membrane folds were present. Anterior chamber reaction was present with 4+ flare and 4+ cells. 0.5 mm hypopyon was also present. Digital tension was found to be high.

Right eye syringing was free. All the blood investigations including RBS were normal. Corneal scrapings (gram stain and KOH preparations) & culture on blood agar, chocolate agar and sabarouds dextrose agar was negative. As the clinical picture resembled fungal keratitis, the patient was empirically started on fluconazole and natamycin 5% eye drops 1 hourly along with cycloplegic and lubricant eye drops.

At 1 week, patient had worsening of symptoms. The infiltrate had increased in size and depth(3.5X3.5 mm) size extending to mid stroma and few satellite lesions appeared. Debridement and scraping was done after discontinuing antifungals for 24 hours but results were again negative. Topical voriconazole was also added. Even after 3 weeks of treatment and proper compliance on the patient's side the ulcer worsened. Unaided visual acuity Right Eye (OD) diminished to CF @ ½ meters.

By the end of 4th week the infiltrate progressed more and satellite lesions coalesced with the main lesion. (Fig.1) As the response to antifungals was almost nil and since the clinical picture did not resemble bacterial keratitis and the multiple negative scrapings prompted us to think of rarer organisms. On repeat scraping and Zeihl Neilson staining many acid fast bacilli were seen. Hence a diagnosis of atypical mycobacterial keratitis was made and he was started on topical Amikacin eye drops and Moxifloxacin eye drops 1 hourly round the clock & oral Clarithromycin 500 mg bd.

But the ulcer did not respond satisfacorily to medical management. Initially the patient was reluctant for surgical

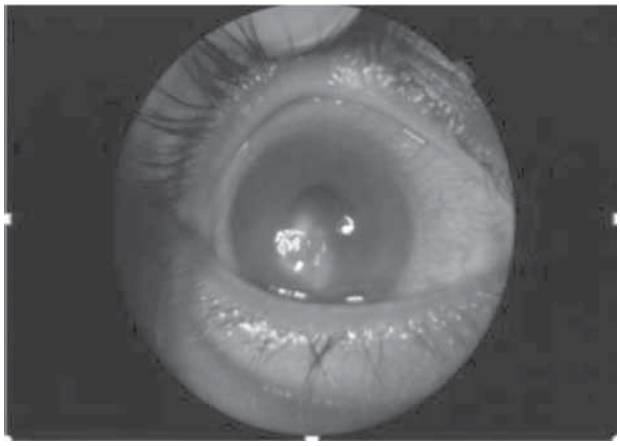


Figure 1

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intervention. After 6 weeks, as there was no improvement, therapeutic keratoplasty was done. Post operatively initially topical amikacin, moxifloxacin, cycloplegics and timolol eye drops were used. Topical steroids were started later. He is on regular follow up with us. Currently the graft remains clear, all sutures intact (FIG 2). Now after 9 months post op his visual acuity OD considerably improved to 6/18, best corrected visual acuity was 6/9 with -3.00DC X 180^{o} and he is free of any symptoms.(Fig.2)

Discussion

NTM or atypical mycobacteria are wide spread in the environment and were once thought to be non pathogenic, but are now known to cause a variety of human diseases including ocular infections.

They are implicated in ocular diseases as early as 1965 with the first report by Turner et al. of a case of chronic keratitis caused by Myc. Fortuitum following the removal of a corneal foreign body.

The first classification proposed by Runyon was based on growth rate and pigment production. Groups 1 to 3 are slow growers and group 4 is the rapid growers. Slow growers are further classified as Photochromgens, Scotochromogens, and Nonchromogens. The most common agents Myc.chelonae & fortuitum belongs to group 4, non-chromatogens,rapid growers.

Clinical Features

Non tuberculous mycobacterial keratitis most often occurs after corneal trauma, corneal foreign body removal, refractive surgeries, lamellar keratoplasty[2], dry eye syndrome[3] and clear corneal phacoemulsification[4]

Keratitis by NTM has a relatively indolent course which fails to respond to common medications. Corneal stromal infiltrates may show feathery margins, satellite lesions,

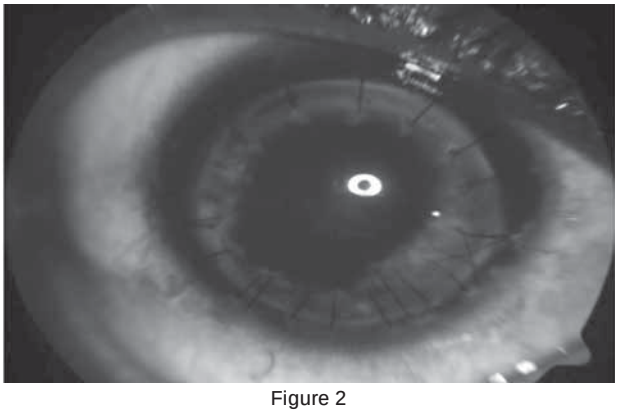


Figure 2

crystalline keratopathy or a ring pattern, cracked wind shield appearance, hypopyon etc. Clinical appearance can mimic fungal keratitis.

In the present case, lack of eye injury, absence of any surgical trauma, the appearance of whitish infiltrate with fuzzy borders and the relative rarity of NTM keratitis prompted us to think of fungal keratitis as the first differential diagnosis and antifungal therapy was instituted. Fungal keratitis and Nocardia keratitis are the 2 principal differential diagnoses of NTM keratitis. AFB staining could have been done in the second scraping, but we had doubts about his compliance to therapy as he was not willing to be inpatient and was following up on an outpatient basis in a lax manner. Hence we continued to think in terms of fungal keratitis and added topical voriconazole.

Laboratory Diagnosis

Corneal scraping, biopsy or culture of contact lens of the patient is required for confirming the diagnosis. Nontuberculous mycobacteria are aerobic acid fast bacilli. The bacilli appear as bight thin rods on Ziehl- Neelson acid fast stain [5]. The flurochrome method is also equally sensitive A positive culture is necessary to confirm the diagnosis. Lowenstein-Jensen media, MacConkey agar, blood agar or Middlebrook 7H11 agar may be used for culture.

Treatment

Aminoglycoside Amikacin at concentrations of 8mg/ml to 50 mg/ml has been found to be effective in treating microbial keratitis. Studies have shown that treatment with amikacin alone has success rate ranging from 30 to 40%. Fluroquinlolones like gatifloxacin and moxifloxacin are also effective against nontuberculous mycobacteria

Clarithromycin which is a macrolide antibiotic is effective in treatment of nontuberculous mycobacterial keratitis. Oral concentration of 500 mg twice daily is used in treatment. Topical preparation is not commercially available but can be prepared from granules used for oral suspension. Topical azithromycin and polymyxin B[6], is also reported to be effective against nontuberculous mycobacteria.

Therapeutic keratoaplasty may be required in unresponsive cases and patients not tolerating medical therapy due to antibiotic toxicity. Some studies have reported Therapeutic lamellar keratoplasty to be effective in management of non responding cases with upto 80% stromal involvement.[7]

Literature review has shown a recent trend of increase in the frequency of these rarer infections. Hence good alertness

and knowledge of this condition would help our patients. High index of clinical suspicion with early diagnosis and prompt combined medical and surgical intervention seem to be the best measure to decrease ocular morbidity.

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Brief Report

Oculsive Retinal Vasculopathy- An Uncommon Presentation

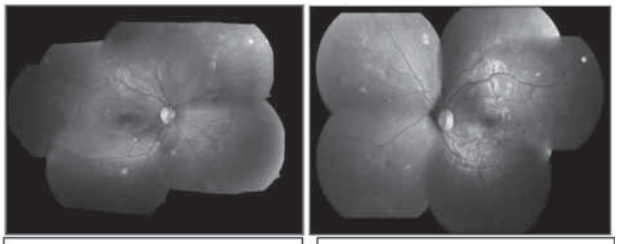
Dr Sandhya N MS, Dr. Mahesh G. MS, FRCS (Ed)

Introduction

The two main stereotypical subgroups of herpetic uveitis are chronic anterior uveitis and acute herpetic retinitis[1]. The classic and the most common presentation of Varicella Zoster (VZ) related retinopathy is Acute Retinal Necrosis (ARN) in immunocompetent patients and Progressive Outer Retinal Necrosis(PORN) in immunocompromised patients. Atypical manifestations of ARN and non necrotizing type of atypical posterior uveitis are being reported with increasing frequency recently. Reported retinal vascular involvement in VZV infection include vasculitis, transient retinal arteriolitis, occlusive vasculopathy and recurrent multiple branch retinal artery occlusions all occurring in eyes with signs of inflammation.

Case report

18 year old female presented to us with defective vision, 3 months after chicken pox. 5 days after the onset of cutaneous eruptions the patient developed unsteadiness and reportedly became disoriented. Magnetic resonance imaging showed pituitary microadenoma with hemorrhage. Rest of the brain study was normal. Visual evoked potential was also normal. With a diagnosis of post varizella zoster encephalitis and cerebellitis, she was given a course of intravenous Methyl Prednisolone and intravenous Acyclovir by the neurologist. When she regained orientation the next day after IV Acyclovir and Methyl prednisolone she noticed defective vision. On her initial visit to us 3months after the onset of chickenpox with history of blurring of vision of both eyes she had healed chicken pox scars. On examination, her best corrected visual acuity in the right eye was 3/60, N36 and left eye was 6/18, N8. Anterior segment and intra ocular pressure were normal in both the eyes. Dilated fundus examination of both eyes showed similar features. The media was clear. There was a well demarcated area of retinal whitening in the posterior pole in both eyes. There were multiple cotton wool spots all over the fundus. The optic disc and retinal vessels were normal. There were a few hemorrhages in the posterior pole in the left eye.

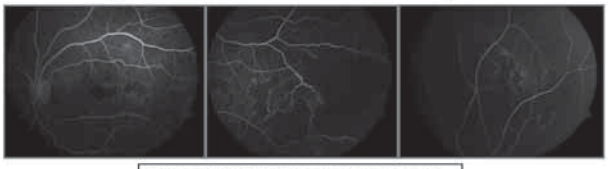


FUNDUS PHOTO OF RIGHT EYE | FUNDUS PHOTO OF LEFT EYE

Interestingly Fluorescein Angiography features were also similar in both the eyes . The foveal avascular zone was clearly increased and there were multiple areas of patchy capillary drop outs in the periphery and posterior pole with numerous micro aneurysms at their edges. Strikingly there was no staining or leakage from the retinal vessels at any phase of angiogram. The optic disc was also normal and there was no cystoid macular edema.



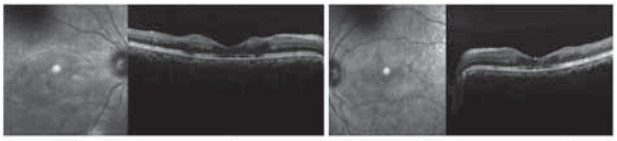
FLUORESECIN ANGIOGRAPHY OF RIGHT EYE



FLUORESCEIN ANGIOGRAPHY OF LEFT EYE

Spectral Domain-Optical Coherence Tomography scan of both eyes through the fovea showed thickening of inner retinal layers corresponding to the area of capillary drop out around the fovea with shadowing of outer retinal layers due to the thickened inner layers. The external limiting membrane (ELM), inner segment-outer segment (IS-OS) junction and Cone Outer Segment Tip (COST) line were disrupted at the fovea. There was a clear demarcation line on OCT at the edges of capillary drop out around the fovea as seen on Fluorescein Angiography.

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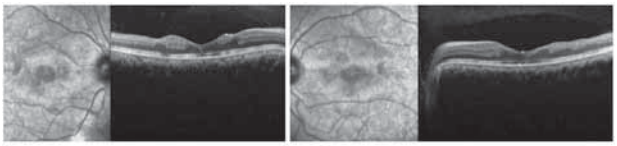


OCT OF RIGHT EYE | OCT OF LEFT EYE

Fundus Autofluorescence of both eyes showed decreased Autofluorescence at the macula which was more pronounced in the left eye. This is due to the blockage of normal RPE Autofluorescence by the thickened swollen inner retinal layers due to ischemia[2].

A thorough vasculitic work up (ANA RF, dsDNA, mantoux tests,VDRL, angiotensin converting enzyme, cANCA, pANCA, Toxoplasma IgG and IgM) proved negative.

With a diagnosis of chicken pox related retinal occlusive vasculopathy she was given oral acyclovir 600mgs 5 times daily for 2 weeks and then 400mgs 2 times daily for another 4 weeks. Oral prednisolone was started at 1 mg/kg body weight and was tapered and stopped over a period of 4 weeks. When she came to us after 6 weeks her BCVA in both eyes was 6/18, N6. The retinal whitening remained the same even after 6 weeks but the cotton wool spots had reduced in number (though not completely disappeared). FA was repeated then which had features exactly similar to the initial one. On SD-OCT inner retinal layers looked the same. However the outer retinal layers (ELM, IS-OS junction and the COST line) had started regaining their original structure. The improvement in VA is most probably due to this because the area of capillary non perfusion on FA remained the same even after 6 weeks.



OCT OF RIGHT EYE AFTER 6 WEEKS | OCT OF LEFT EYE AFTER 6 WEEKS

After 5 months her BCVA in both eyes improved to 6/9, N6 and she had a near normal fundus except for mild residual retinal whitening at the posterior pole.

Discussion

The hallmark of acute herpetic retinitis is full thickness retinal necrosis. Though uncommon there are reports of Non Necrotising Varicella related retinopathies and vasculitis. Wickeremasinghe et al[1] reported 4 patients with transient retinal arteriolitis occurring as a complication of typical chronic herpetic anterior uveitis. None of these patients had significant leakage or vascular occlusion on FA. PCR for VZ was positive in 2 of their patients. Bodhagi et al[3] described 5 patients who were either steroid dependent or resistant, with posterior uveitis along with "bird shot" like choroiditis or retinal vasculitis. None of these patients showed staining of vessels on FA. 3 of these patients were PCR positive for VZ virus. In these patients use of antiviral drugs controlled the ocular inflammation and allowed tapering of corticosteroids. Kuo et al[4] reported a case of retinal vasculitis 2 weeks following chicken pox who also had anterior uveitis and vitreous cells. FA of this patient showed staining of vessel without much leakage or occlusion. Wensing et al[5] described 7 patients presenting with vitritis, vasculitis, and/or papillitis or as pan uveitis without any retinal lesions following VZV infection. Zamora et al[6] had reported earlier, a case of multiple recurrent branch retinal artery occlusions and mild vitritis in a patient with PCR confirmed varicella zoster infection. Monifer et al[7] had reported choroiditis occurring as part of acute systemic varicella infection in a child. There are also other case reports of atypical variants of ARN and all of them had features of uveitis[8,9,10].

In contrast in our patient multiple cotton wool spots all over the fundus and retinal whitening at the posterior pole were the characteristic features. She had no features of anterior or posterior uveitis. There was no evidence of vascular sheathing, disc edema or cystoid macular edema. FA demonstrated capillary drop outs at the macula and periphery without any staining or leakage from the vessel wall. Unfortunately the patient did not have an ophthalmic examination before 3 months and it is possible that the patient might have had vasculitis initially. However at presentation patient did not have any evidence of old anterior or posterior uveitis (like pigmented keratic precipitates, posterior synechae, iris atrophy, pigments in the vitreous or fibrosis around vessel walls) and the angiogram did not show features of old vasculitis like staining or CME. We did not do PCR of ocular fluids for VZV but the temporal association of VZ infection and onset of defective vision and presence of healed chicken pox scars point to the etiology of VZV.

The exact mechanism of vascular occlusion remains speculative. When patient was seen first (that is 3 months after chicken pox) she had retinal whitening which remained the same even after 6 weeks but the cotton wool spots had reduced in number (though not completely disappeared). When the patient was seen last after 5 months she had a near normal fundus except for mild residual retinal whitening at the posterior pole. The fluorescene angiography pictures were exactly same at the initial visit and after 6 weeks. In arterial occlusions (as in Central retinal artery occlusions)

the retinal whitening and FA pictures usually revert quickly. In our case the pathology may be different and a post viral immune mediated reaction which produces longer lasting changes within the vessel wall may be responsible for the occlusive vasculopathy which would have been present initially. Bodhagi et al3 also suggested a similar mechanism for the vascular changes in post Varicella Zoster infection.

Conclusion

Here we report a case of chicken pox related purely occlusive retinal vasculopathy without features of vasculitis, optic neuritis, anterior or posterior uveitis or cystoid macular edema. To the best of our knowledge, non necrotizing purely occlusive vasculopathy without any other signs of ocular inflammation following chicken pox has not been reported earlier.

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Vitreous Substitutes

Dr. Rani Nanda MBBS, Dr. Ashok Nataraj MS, DNB

Vitreous Humour

Its a gelatinous structure that fills the space between lens and retina. Until recently function of vitreous was thought to be only mechanical and optical presence, but now it is understood that it plays an important role in maintaining intraocular pressure & nourishment of the eye.

What are vitreous substitutes

They are substances injected into the vitreous cavity during a vitrectomy.

Main Purpose:

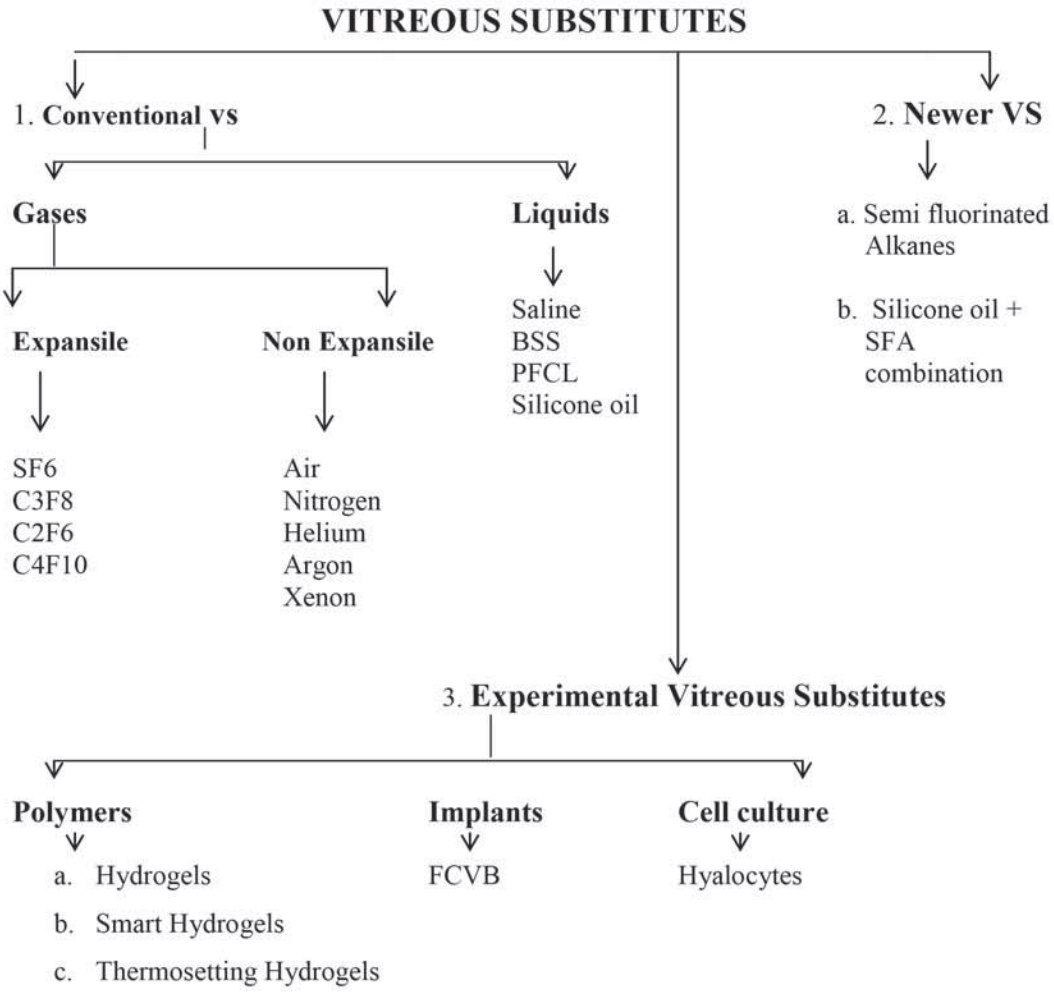
Volume replacement

Retinal tamponade

Characteristics of an Ideal vitreous substitute[1]

1. Clear / Transparent
2. Inert / Non toxic
3. Biocompatible
4. Low viscosity / Elastic
5. Immiscible with water
6. Durable / Slowly absorbed

The use of 1st intraocular vitreous substitute was reported by Ohm : 1911, who introduced air into vitreous cavity.[2]



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GASES

1. Biomechanical Properties

Physical properties

1. Properties of ideal substitutes
2. Highest surface Tension 70 dynes/ cm^2
3. High Buoyancy/ Low specific gravity

Dynamic properties

1. Expansion
2. Equilibrium
3. Dissolution

2. Comparsion of Air, SF6, C3F8

Gas	Duration	Time of Maximal Expansion rate	Time of Maximal Expansion	Expansion Volume	Non Expansile Concenteration
Air	5 days	-	-	1 x	-
SF6	2 weeks	6-8 hrs	24-48 hrs	2 x	20%
C3F8	2 months	6-8 hrs	72-96 hrs	4 x	12-14%

Classification Of Vitreous Substitutes

1. Functional classification (as referred to as in surgical application)

1. Vitreal substitutes as temporary fillers of vitreous cavity during surgical procedure to maintain the ocular tone..

Ex : Air – in Fluid Air Exchange

2. Vitreal substitutes used as surgical tools themselves during different phases of vitreoretinal surgery, requiring short intraocular permanence.

Ex : PFCL

3. Vitreal substitutes left inside eye after vitreoretinal surgery with different permanence time.

3. Complications[3]

1. Glaucoma during max. rate of expansion 6-8 hrs. CRAO *K*
2. Cataract Posterior Subscapular Cataract.
3. Bullous Keratopathy
4. Subretinal seepage
5. Enlargement / New breaks
6. Proliferative vitreoretinopathy (PVR).

4. Disadvantages

1. Cannot be used for long tem tamponade and Inferior tamponade.
2. Due to low refractive index compared to comea & aqueous humour. Hence fundus examination is difficult.
3. Advised against air travel / High altitude & Scuba diving
4. Head down posturing is needed.

5. Poor visual acuity in the early post operative period.

LIQUIDS

Balanced Salt Solution(BSS)[4]

- Most commonly used vitreous substitute – as irrigating solution intraoperatively
- No tamponade properties due to low surface tension
- Also used as vehicle to carry drugs for hemostasis, pupillary dilatation & antiinflammatory effects.
- Recently Low Molecular Weight Heparin and 5 Fluorouracil added to infusion fluid to prevent post – op PVR.

Perfluorocarbon liquids(PFCL)[5]

- Completely fluorinated, synthetic, carbon containing compounds.

Properties

- Clear, Colourless, Odourless
- High density, Low viscosity & Refractive index similar to water
- Hydrophobic, Lipophobic & Immiscible Ex : Perfluorodecalin (PFD), Perfluoro-n – octane (PFO)
- Perfluoro tetradecahydrophenanthrene

Uses

As Temporary Tamponade to unfold and stabilize retina intra – op and displacing subretinal fluid anteriorly.

Complications

They are removed at the end of surgical procedure due to potential complications : -

1. Retinal toxicity
2. Intraocular inflammatory reactions Epiretinal membrane(ERM) formation and intraretinal layer disruption

3. Silicone Oil

Polymer of polydimelthyl siloxane[6].

Properties

Properties of ideal substitutes

2. High viscosity (1000-5000 Centistokes)
3. Lighter than water (0.93G)
4. Refractive index close to vitreous (1.4)
   - Acts plus lens in aphakic eyes
   - Acts as minus lens is phakic eyes

Advantages

1. Currently the only substance accepted for long term tamponade.

2. Intra - operative[7]

- Better intra – op visualization.
- Easier retinopexy.
- Control of hemorrhage & effusion.
- More useful in complicated cases like giant retinal tear, retinal detachment(RD) with PVR.
-

3. Post – operative

- Better immediate visual acuity (so indicated in One eyed patients)
- Less posturing needed (so better in old age / children)
- Air travel/ scuba diving not contraindicated.

4. Reduces the movement & compartmentalizes cytokines and cellular factors between anterior and positive segment.

Complications

1. Glaucoma –
   Angle closure glaucoma (from pupillary block – needs inferior iridectomy).
   Open angle glaucoma (from emulsification)
2. Cataract
3. Cornea – Filamentary keratitis, Bandshaped keratopathy.
4. Emulsification of silicone oil
   - Uveitis
   - Subretinal seepage
   - Subconjuctival cyst formation
5. Silicone Retinopathy (ERG & EOG detected abnormal)
6. ERM
7. Macular edema
8. Recurrent RD

Time of Silicone Oil removal - 3-6 months – when retina is attached & retinal traction absent.

Anatomic outcomes & visual acuity remains stable from 6-24 months.

During removal, problems faced are hypotony and persistence of diffused small emulsion particles on retina causing chronic inflammation.

NEWER VITREOUS SUBSTITUTES

1. Semi Fluorinated Alkanes (SFA)[8]

- They are partially flourinated alkanes with perfluorocarbon chain attached at one or both ends.
- Colorless, physically and chemically inert, immiscible with water.
- Lower viscosity and density than PFCL so that pressure

on choroidal capillaries is less and so can be used as intraocular tamponade beyond surgical time (up to 3 months).

- Soluble in PFCL, Hydrocarbons & silicone oil.
- Refractive index = 1.3

Complications[9]

1. Early emulsification.
2. Early cataract formation.
3. ERM formation.
4. Toxic & inflammatory reaction.

2. Silicone Oil + SFA Combination

This combination takes advantage of the high viscosity of silicone oil and high specific gravity of SFA to produce a vitreous substitute of good tamponade & less emulsification. 10 Solubility of SFA in silicone oil depends on viscosity of silicone oil and molecular weight of SFA. Higher viscosity of silicone oil and higher molecular weight of SFA makes it less soluble. The combination of both produce either a homogenous clear solution (Heavy Silicone Oil) or separated solutions (Double fills) depending on the ratio of the two liquids.

HEAVY SILICONE OIL (HSO)

Homogenous mixture of silicone oil + SFA11
Ex : Densiron 68, Oxane HD, HWS 46 – 3000

Properties

Heavier than water, viscous, stable, better tolerated, longer tamponade (complex RD with inferior PVR) , lesser emulsification .
Good anatomical & visual outcome.

Problem

Requires strong active aspiration during removal (Sticky Oil phenomenon).

DOUBLE FILLS

Since both SFA & silicone oil are hydrophobic, it produces a single bubble with two layers – one layer providing upper support (silicone oil) and other providing inferior support (SFA).[10]

MAGNETIC SILICONES

Dispersion of nanoparticles of metal (Nickel, Iron, Cobalt) increases surface tension of oil and therefore tamponade effect. This is carried out with positioning of encircling scleral magnetic band.

EXPERIMENTAL VITREOUS SUBSTITUTES

POLYMERS

a. Hydrogels

They are hydrophilic polymers that form a gel network when cross linked and are capable of absorbing several times their weight in water & swells.[12]

Ex:- Polyvinyl alcohol (PVA), Polyacrylamide (PAA), Poly (2-hydroxy ethyl methacrylate) PHEMA

Properties[13]

Biocompatible
Clear
Viscoelastic dampner
Enable diffusion of ions & small particles – so can be used as drug delivery devices.
Allows diffusion of O2, Nutrients & Growth factors.

Problem

They shear thin upon injection into eye and lose their elasticity and become fluid like. Now over come by injecting hydrogel in aqueous form and transformed into gel insitu using disulfide crosslinker.

b. Smart Hydrogel

There are hydrogels which are stimulus sensitive pH, temperature, light, pressure, electric fields or chemicals.[14]

c. Thermosetting Hydrogel

There are hydrogels that gelate at 360c and retains transparency upon gelation. Ex : WTG – 127

Limitation of Hydrogel

1. Bioincompatability [15]

Trigger immense relation leading of inflammation & phagocyte mediated disappearance of gel within weeks of injection
2. Drying of gel under retinal scar.

Implants

These are implantable devices that support retina and control intraocular pressure without the need of intravitreal injected solutions.[16]

Ex : - Foldable capsular vitreous bodies (FCVB)

Consists of thin, vitreous shaped capsule made of silicone rubber elastomer with silicone tube valve system filled with BSS or silicone oil.

Advantages

1. Good Biocompatibility.
2. Easy implantation & removal.
3. No corneal opacity.
4. No intraocular inflammation.
5. No vitreal opacity.

Disadvantages

High incidence of cataract

Cell Culture

It is the artificial generation of vitreous in-vitro, by hyalocyte culture which produces Hyaluronic acid and other vitreous components.17 Hyalocyte proliferation done with ascorbic acid in a dose dependant manner by increasing collagen production and m- RNA expression of cells in-vitro and regulated by specific grown factors – bFGF (stimulates) & TGF – ß 1 (inhibits).

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Photo Essay

3 Unusual Foreign Bodies

Dr. Thomas Arun Varghese MS, FRCS, MRC Ophth, FAICO(Glaucoma)

We all see patients with foreign bodies day in day out. Most don't need any history as they are obvious. We present a few unusual ones where the history gave significant clues.

Case 1: A 75 year old Caucasian man was referred for left cataract surgery. Examination showed a deep corneal foreign body and cataract in the left eye (fig 1). On questioning, he said he used to be a coal miner (in Wales, UK)and gave a history of something going in his eye during his working life and the eye being red and sore for a week. Slit lamp examination showed the foreign body to be at deep stromal level (fig 2), most likely a piece of coal. As he was asymptomatic and the fact that probably the foreign body had been there for several years and not causing any problem, it was decided not to remove it. The patient underwent uneventful phacoemulsification and the foreign body was left undisturbed. Postoperatively he had best corrected visual acuity 6/6. The patient was given a photograph of his eye to keep with him so that he can advise any eager doctor to leave his foreign body alone. It is worth remembering that inert intracorneal foreign bodies, namely perspex fragments from cockpit windshields were the origin of IOLs.

Case 2: A 35 year old Caucasian lady presented with a complaint of foreign body sensation in her right eye and sharp pain on trying to look up. She said she had trimmed her fringe herself and her symptoms started soon after that. Examination showed the tip of a hair in the upper punctum(fig 3). This was removed with immediate symptomatic relief (fig 4). The history of symptoms starting after the 'hair cut' gave a clue to look for something 'hairy'.

Case 3: A 55 year old Caucasian man developed foreign body sensation while on a transatlantic flight with redness and watering of the eye. He came to the eye clinic the next day. Examination showed staining of the cornea and a concretion on the lower lid corresponding to it, which had eroded through the conjunctiva and caused the abrasion (fig 5,6 &7). The concretion was removed and the patient was prescribed Chloramphenicol ointment for a few days. As the symptoms started while the patient was inside the plane, we looked for an 'internal' cause rather than 'external'.

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Fig 1

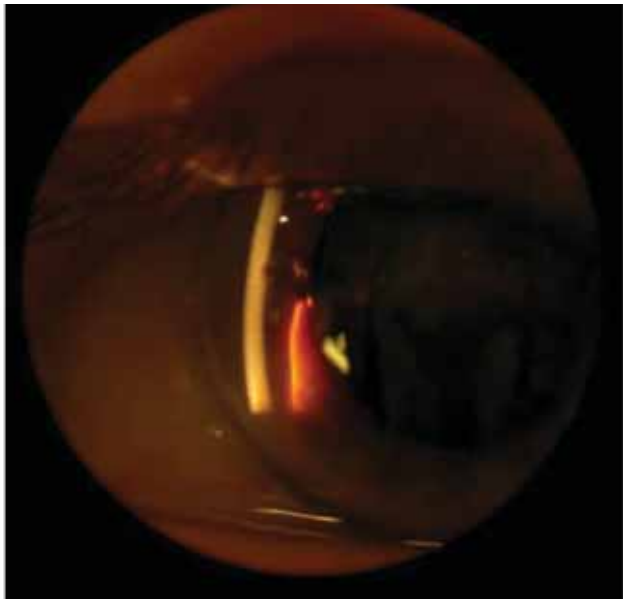


Fig 2



Fig 3



Fig 4



Fig 5

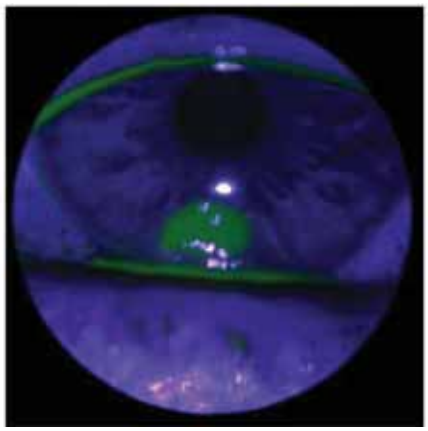


Fig 6

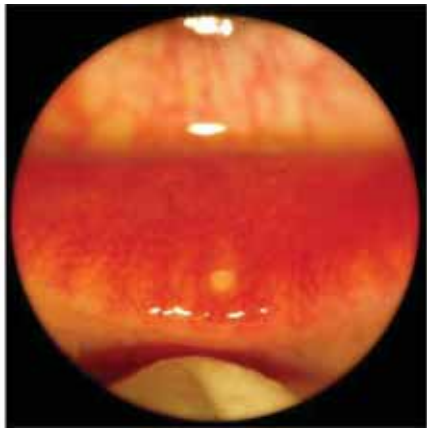
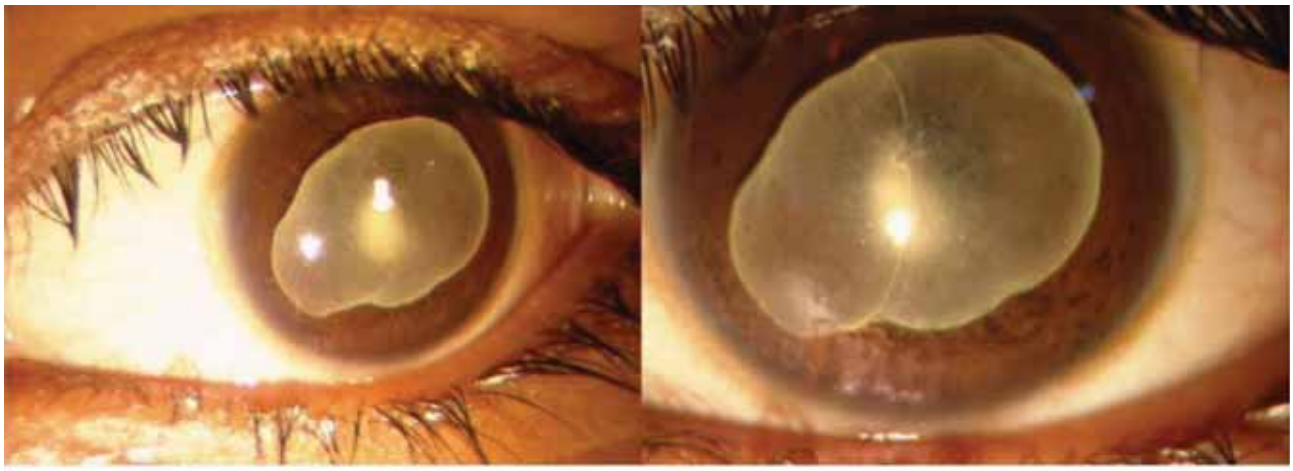


Fig 7

What is the diagnosis?
What additional investigation will you recommend?
What will be the line of management?



16 yr old girl presented with complaints of progressively decreasing vision of 4months duration with whitish discolouration of cornea in left eye. No history of injury/ surgery. Visual acuity in left eye was 1/60. Fellow eye within normal limits.

Send your answers to: drashok.eye@gmail.com

The answer for the question in the last issue is

Diagnosis: Optic nerve glioma (with involvement of optic canal, chiasm, optic radiation, temporal lobe, cerebral peduncles and brain stem) Syndrome associated: Neurofibromatosis Type: 1

Courtesy: Dr. Sujith Nayanar, Vasan Eye Care, Calicut.

Dr. Sumi Lukose DNB

Glaucoma diagnostic value of the total macular thickness and ganglion cell-inner plexiform layer thickness according to optic disc area.

Myung Hun Yoon, Sang Jun Park, Chan Yun Kim, Hee Seung Chin, Na Rae Kim.

Br J Ophthalmol.2014; 98(3): 315 - 320.

The aim of this study was to evaluate the diagnostic value of perimacular Ganglion Cell Inner Plexiform Layer (GCIPL) thickness in the detection of glaucoma according to optic disc area.

This was a cross sectional study of 96 glaucoma patients and 87 normal subjects who underwent complete ophthalmological examination including standard automated perimetry and cirrus HD - optical coherence tomography.One randomly selected eye from each subject was included.

Cirrus HD – OCT was used to acquire one macular and one optic disc scan in each eye. The macular cube protocol included macular thickness analysis and GCA.The optic disc cube protocol included ONH and RNFL analysis.

The diagnostic accuracy of GCIPL, macular thickness, RNFL and ONH were determined using the area under the receiver operating characteristic curve .Optic disc areas of $\leq$ 1.9, $\leq$2.4 and $>$ 2.4 mm2 were chosen and area under curves and sensitivities at fixed specificities were compared for each.

The mean GCIPL thickness and RNFL showed similar ability to diagnose glaucoma (p= 0.911).
The mean GCIPL thickness had higher diagnostic ability than the central retinal subfield thickness(p=0.001) comparable with that of retinal cube volume. (p= 0.840) and mean retinal cube thickness(p=0.840).The mean RNFL , minimum GCIPL and the inferior and inferotemporal disc had the highest Area Under Curves (AUCs) for small, medium and large discs respectively.

The macular GCIPL thickness, total macular cube thickness, circumpapillary RNFL thickness and disc rim area showed similar performance in diagnosing glaucoma , irrespective of optic disc size.

Glued Trans-scleral Intraocular Lens Exchange for Anterior Chamber Lenses in Complicated Eyes: Analysis of Indications and Results.

Divya Ashok Kumar, Amar Agarwal, Athiya Agarwal

Am Ophthalmol 2013;156 (6): 1125-1133

This study was done to evaluate clinical outcomes after glued trans-scleral posterior chamber intraocular lens (IOL) exchange for anterior chamber (AC) IOL.

This is a retrospective case study of patients who underwent glued IOL in exchange for ACIOL from January 2008 to December 2012.38 eyes were studied. Preoperatively Corrected Distance Visual Acuity (CDVA), intraocular pressure, slit lamp biomicroscopy , dilated fundus examination, AC cellular reaction by OCT, central macular thickness, potential visual acuity, corneal thickness, gonioscopy, specular microscopy, AC depth were evaluated.

The mean follow-up was 24.1 $\pm$ 15.4 months. The indications were corneal decompensation (39.4%), malpositioned AC IOL (28.9%), uveitis (15.7%), glaucoma (13.1%), and broken haptic (2.6%). There was significant improvement in the postoperative CDVA (P = .000) and central corneal thickness (P = .000) after AC IOL removal. CDVA better than 20/60 was obtained in 65.7% eyes. Thirty-four (86.8%) eyes showed an increase in the CDVA after IOL exchange. The mean endothelial cell loss was 3.4 $\pm$ 2.4%. There was significant correlation between the CDVA and the central corneal thickness (P = .000). There was significant change in the AC depth (P = .000), the intraocular pressure (P = .005), and the AC inflammation (P = .000) after IOL exchange. The preoperative macular edema in 3 eyes resolved after surgery (mean central macular thickness, 205.6 $\pm$ 7.2 μm).

Glued IOL exchange for ACIOL can be an excellent alternative in eyes with ocular complications related to ACIOL.

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Long term outcomes following the surgical repair of traumatic cyclodialysis clefts.

P Agarwal, P Shah

Eye.2013; 27 (12): 1347 – 1352

This study was done to evaluate the long term visual prognosis and intraocular pressure control following direct and indirect cyclopexy for surgical treatment of traumatic cyclodialysis clefts.

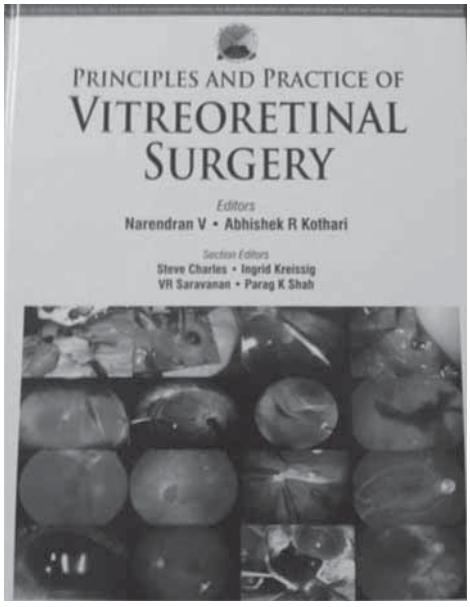
In this study retrospective review of clinical data of 17 eyes of 17 patients who underwent surgical cyclopexy ± cleft cyclocryotherapy for traumatic cyclodialysis was done . Direct cyclopexy was done in all cases where initial management with atropine and cryotherapy was unsuccessful in cleft closure. Cyclopexy was done by suturing ciliary body to sclera spur under a double lamellar limbus based sclera flap.

The main outcome measures were IOP, BCVA and postoperative complications.

In all 17 eyes cyclodialysis clefts extended for 2.1 ± 1.6 clock hours.The mean follow up was 43.7± 24.6 months.Preoperatively mean IOP was 6.9 ± 4.0 mm Hg. Postoperatively , painful reversible IOP spikes of upto 70 mm Hg developed in 13 eyes. The final mean postoperative IOP Was 12.2 ± 4.1 mm Hg with no cases of secondary glaucoma . Preoperatively BCVA was 6/12 or more in 24% (4) eyes, which rose to 71% (12) at final follow up.

There were no serious postoperative complications. Successful cyclodialysis cleft repair can lead to good longterm visual prognosis and stable IOP control.

Principles And Practice of Vitreoretinal Surgery
Dr. Narendran and Dr. Abhishek Kothari



Comprehensive book updating the reader on the current practices in vitreoretinal surgery. The book is very systematically compiled with sections contributed by distinguished vitreoretinal surgeons who are masters in their own fi elds. The practical pearls in each chapter are very valuable. The transition from basics to advanced techniques is gradual and easy to comprehend. The sections on emerging techniques provide insight into future trends and give better perspective of the present practices. All major topics are precisely covered in one volume which makes this book handy. I recommend this book for core learning by the trainees and a quick reference for the practicing surgeons.

Dr. Shalini Singh
Consultant Vitreoretina
Dr. Shroff's Charity Eye Hospital
Daryaganj, New Delhi.

Descemet's Stripping Automated Endothelial Keratoplasty
Different strokes with DVD ROM
Authors: Dermot Cassidy, Namrata Sharma, Vishal Jhanji, Rasik Vajpayee
Publisher: Jaypee Highlights, New Delhi
First edition 2013, 179 pages,
Price: Rs.1595

The book describes the evolution of DSAEK, indications, preoperative evaluation, the instruments used and various methods of graft insertion. The book is divided into five sections. Various techniques like manual dissection technique of Descemet's stripping endothelial keratoplasty and DSAEK techniques like suture pull through technique, hitch suture technique, Tan EndoGlide technique, Sheet Glide technique and sutureless DSAEK has been described in detail with coloured photo illustrations. In addition DSAEK in special situations like aphakia, cataract extraction, floppy iris syndrome, pediatric eyes, glaucomatous eyes and failed grafts are given in detail. The "different strokes" in DSAEK include the use of various methods of donor lenticule placement such as the sutures, forceps, glides, inserters and catridge. The usual complications and pitfalls corneal surgeons come across and their solutions are also highlighted. These innovative techniques given by the pioneers in this field if used correctly can ensure atraumatic donor insertion and adhesion without jeopardizing the corneal endothelium. This book will help the beginners as well as the corneal surgeons to improve their techniques.

Dr. Remya K.
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Little Flower Hospital
Angamaly

Address for Correspondence:

Dear Editor,

We read with interest the article by Menon R et al[1]. I congratulate the authors for the hard work that has been done to do this case control study. The authors have found a high serum Homocysteine (Hcy) value in their elderly male Primary Open Angle Glaucoma (POAG) patients (although not statistically significant) and a negative correlation between serum levels of Hcy and that of serum Folate and B12.

I would like to make the following observations and comments on this article.

The role of Hcy in cardiovascular disease was first highlighted by McCully[2]. Several studies have since shown the role of Hcy in apoptosis, extracellular matrix remodelling, ocular vascular disease and glaucoma[3]. Consistently elevated Hcy levels have been shown in Pseudoexfoliation Glaucoma (PEXG) and a pathogenic link is now proposed with exfoliation material containing laminin, elastin and fibrillin, components of extracellular matrix metabolism under the influence of Hcy.

The association between POAG and Hcy is divided with equal number of studies showing correlation and lack of it. The present study is one of the largest studies looking at this although the small number of controls (case 44, control 10) is a drawback . The authors have enforced strict exclusion criteria but it is practically impossible to rule out variations in diet which can influence B 12 and Folate levels directly and Hcy indirectly. It would also have been interesting to know the severity of glaucoma and whether there was any correlation between the severity and the Hcy level.

The Folate box plot in Fig:1 and the B12 level in Fig:2 show higher levels in the glaucoma patients and this is repeated in Table 1.There is some confusion as a negative correlation has been found between B12/ Folate levels and the level of Hcy and the high levels of Hcy are being attributed to the 'low' levels of B12 and Folate. This is either an error or the small number of controls unfortunately have low B12 / Folate levels and a group of cases with high B12/ Folate values have resulted in the mean B12/ Folate values of the cases being high. As mentioned by the authors, among the cases 9/ 25 males and 6/ 19 females had very high Hcy values. A few of these could be cases of Pseudoexfoliation, without clinically visible exfoliation material (as it is well documented for the exfoliation material to appear several years down the line), thus appearing clinically as POAG initially.

With increasing life expectancy and greater chance of malnutrition due to changing social circumstances, the role of B12 and Folate supplementation in the elderly is certainly an option although a meta-analysis of randomized controlled trials showed no difference between intervention and control groups[4]. As Hcy causes apoptosis through N-Methyl-D-Aspartate (NMDA) mediated pathways, blockage of NMDA receptors is an exciting option on the horizon[5].

The authors' efforts have certainly kindled interest in this relatively unexplored area.

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Authors reply,

We sincerely thank Dr. Thomas Arun Varghese for appreciating the study and his critical evaluation on the results of the study.

Table 1 and figures 1 and 2 are not just a repetition. Figure 1 is with mean value of Hcy and folate in the control (n=10) and glaucoma patients (n =44) (for further clarification find the legend to the figure 1 and 2). Table 1 provides the gender vise value of Hcy, folate and B12 in the control and glaucoma groups.

Regarding the 'confusion of negative correlation', we would like to point out that this is not an error in analysis. We request you to see the results section (last paragraph) of MS to know about the negative correlation. However, we agree with the comments of Dr Thomas Arun as the negative correlation that was found in the control group may probably due to the low sampling (n=10). We had mentioned the limitations of this study in the discussion part of the MS as 'This study failed to take the dietary habit of the subjects and the size of the aged control group population was too small to suggest a normal biological reference value.

Another point raised pertains to the severity of glaucoma in relation to the levels of Hcy. All our patients were established cases of POAG with moderate to severe field loss. As Dr. Arun has suggested a multi centeric prospective study would be a better way to know this relation.

Once again, we thank Dr. Arun Varghese for showing a keen interest in our study and this article.

Sincerely,

Dr. Rani Menon
Dr. Sobha Ramesh
Dr. Rani Menon's Eye Clinic
Thrissur

Dear Editor,

The discussion on CSCR was read with great interest. Very often we come across such case scenarios in our practice. OCT is a great tool in educating the patients regarding the disease and convincing them about the progress. In this discussion, the time to start treatment for different practitioners varied from 1 to 4 months. Can we reach a consensus with regard to the time of starting investigations and treatment?

It is heartening to note that all participants in the discussion agreed to the role of PDT in treating the cases of non resolving CSCR with foveal leak, even though the dose is still under investigation. It was pointed out in this discussion that unlike thermal laser, PDT helps to prevent recurrences also. The discussion has proven beyond doubt the ineffectiveness of Anti-VEGF therapy in the treatment of such cases.

Dr. Mahesh has arranged a splendid occasion to share the views and ideas of many experts on a very common subject. It is really useful for any practising retina specialist and we are thankful to him.

Dr. Teena Ann Varghese
Consultant , Medical Retina
Alphonsa Eye Hospitals

Authors reply,

Thank you very much for the comments. When to do intervention in CSCR is a question that is still not answered. CSCR was once considered to be self limiting. But it can cause secondary RPE damages and final outcome may be suboptimal. So retinologists have started treating CSCR little early. Most of the specialists treat CSCR 1-3 months after onset. This can be decided by monitoring using OCT. If the fluid is reducing in sequential OCT it can be managed conservatively. If there is no reduction of fluid and there is secondary degenerative changes happening in RPE treatment can be planned. So this decision may be individualized based on case to case scenarios. Considering the cost effectiveness, still thermal laser remains primary treatment for CSCR with non foveal leaks.

Thank You

Dr Mahesh G
Giridhar Eye Institute
Cochin

Dear Editor,

I would like to congratulate the authors of the article 'Retinal pigment epithelial tears (rips) in the era of anti vegf- when and why?' It is indeed a meticulously conducted study and a well written article.

The article unveils a comprehensive data on RPE tears following anti VEGF injections which is an important condition that has not featured much in the scientific literature. Chang et al has large irregular PED associated with CNV has a higher risk to develop RPE tears in the course of anti VEGF therapy. The major clinical data in this study correlates with that of the available international literature.Estimates for the incidence in RPE tear in eyes with neovascular AMD are 2% to 6% among AMD cohorts overall and 12% to 25% in patients with a pre-existing PED.

Retrospective nature of the study increases the likelihood of bias or confounding, but given the relatively rare occurrence of RPE tears, it is highly unlikely that a clinical trial will be conducted on outcomes after RPE tear. The mean time to tear after injection was mentioned to be 8 days to 12 weeks and > 63.63% tears occurred within 2 weeks. But the study method says that as per the post injection protocol, the patients were first seen only after 2 weeks. This data requires a clarification. More over few questions that arises from the data analysed are

1. Higher incidence of RPE tear among bevacizumab injected eyes?
2. Fibrovascular PED's are at high risk for tears?
3. PED height and the diameter are the best predictors of RPE tears?

The information regarding the risk factors for developing RPE tears will be of great value to the retina physicians. A sub group analysis would have unveiled the single most Important predictor of RPE tears but the small sample size denies this. This importance of close follow up after the injection for eyes with PEDs has been nicely described in the discussion. A larger series with a longer duration of follow up will address many valuable queries on this condition.

Dr Rameez N Hussain
Giridhar Eye Institute, Cochin

Authors reply,

We would like to thank Dr. Rameez N Hussain for his interest shown in our article Retinal Pigment Epithelial Tears (Rips) in the era of anti VEGF- When and why?

As pointed out by Dr.Hussain, it is possible that because of the retrospective nature of the study, capture of certain relevant data could have been overlooked. However as rightly discussed conducting a prospective study in such a relatively less common pathology may not be feasible.

Regarding the queries put forth by Dr.Hussain, of the 11 cases of RIP eyes, 7 rips developed within 2 weeks- 6 cases out of 7 detected at first routine follow up at 2 weeks and 1case presented on the 8th day post injection with sudden severe drop in vision. This case revealed massive sub-retinal haemorrhage with development of RPE tear. (Case illustrated in Fig 1 & Fig 2). As part of the protocol all patients who receive an intravitreal anti VEGF agent in our setting are seen on the first day after the injection and advised to review after 2 weeks. However patients are adviced to report to us if they experience sudden worsening of vision or symptoms like severe congestion or pain. Out of the 7 RIPS one patient had a massive subretinal hemorrhage and significant decrease in vision and hence presented early. It is also possible that among the other 6 patients a few of them would have had RIPS earlier than 2 weeks but preferred to wait till the scheduled follow up visit as they had no significant drop in their pre-existing vision. Ronan et al [1] had reported RPE tears to occur within 4 days to 8 weeks of injection in their series involving 1455 injections of bevacizumab while others have reported later RIPS[2,3].

It was an observation that a higher incidence of RPE tears was seen among the Bevacizumab eyes in our series. Rips developed in 1/20 of Ranibizumab injected eyes (5%), 9/54 of Bevacizumab injected eyes (16.67%) and in 1/21 of combination with PDT eyes (4.7%). Many authors have reported RIPS in eyes receiving intravitreal Bevacizumab[1,2,3]. Only a few studies have reported the relative frequency of RPE tears among the various anti VEGF agents[4]. It is also likely that because of the relatively larger number of patients who receive Bevacizumab compared to Ranibizumab, there could be a higher reporting of these events in the literature. Chan et al[2] also have suggested that the exclusion of patients with preexisting RPE detachments in the pivotal pegaptanib and ranibizumab trials may explain the very low occurrence of RPE tears in these trials. However whether Bevacizumab eyes have an increased propensity to develop RIPS needs to be investigated. Subgroup analysis from the CATT and IVAN trials may throw some light.

Among the 11 RIP eyes, 7 had fibrovascular PED, 2 had haemorrhagic PED and 2 had serous PED in our series.The increased risk of fibrovascular PED'S and PED'S associated with choroidal neovascularisation in causing RIPS has been discussed by various authors[2,4]. Recently Fundus autofluorescence and spectral-domain optical coherence tomography findings have been reported suggesting tissue remodelling in fibrovascular PED's leading to retinal pigment epithelium tear[5].

The minimum PED height among RIP eyes was 485 microns and the minimum PED diameter was 1629 microns. Chan et al[3] have also reported a PED height of >400 μm as a significant risk factor for RPE tears while Chiang et al[6] reported a mean value of 394 μm height and 3200 μm basal diameter on FFA as critical for RIP. Applying the principles of physics it is prudent to assume that larger and tense PED's may have a higher risk of developing RIPS. However whether a critical value as mentioned in the discussion above is relevant needs further large studies.

Thus though RPE rips may be a rare occurrence a knowledge of possible "at risk eyes" may help in anticipating this complication and explaining to the patient.The significant risk factors that have been identified to cause RPE tears in our retrospective series include the presense of vascularised PED, larger PED (>1600μm), high PED (>400μm) and use of intravitreal Bevacizumab. We agree with the fact that a multivariate analysis of the risk factors may not yield necessary conclusions due to the relatively small numbers involved. A larger series will probably address many valuable queries on this condition and identify more "at risk" eyes. It is therefore imperative that close follow up after intravitreal anti VEGF injection for eyes with PEDs is essential in order to identify and manage this complication at the right time.

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