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Delhi Journal of Ophthalmology (DJO), once called Visiscan, is a quarterly journal brought out by the Delhi Ophthalmological Society. The journal aims at providing a platform to its readers for free exchange of ideas and information in accordance with the rules laid out for such publication. The DJO aims to become an easily readable referenced journal which will provide the specialists with up to date data and the residents with articles providing expert opinions supported with references.

Contribution Methodology

Author/Authors must have made significant contribution in carrying out the work and it should be original. It should be accompanied by a letter of transmittal. The article can be sent by email to the Editor or a hard copy posted. Articles receive will be sent to reviewers whose comment will be emailed to the author(s) within 4-6 weeks. The identity of the authors and the reviewers will not be revealed to each other by the editorial team. Detailed instructions to the contributors and for advertisement are included at the end of the journal.

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## Contents

### Editorial
3. The old order changeth…..  
*Dr. Rohit Saxena*

### Major Review
4. Implants in Anophthalnic Sockets  
*Ruchi Kabra, Nitin Trivedi, Deepak Mehta*
8. Persistent Fetal Vasculature  
*Neha Goel, Vishaal Rajesh Bhambhwani, Gauri Bhushan, Meenakshi Thakar, Usha Kaul Raina, Basudeb Ghosh*

### Preferred Practice Pattern
13. Understanding Amblyopia  
*Aarti Nangia, Digvijay Singh*

### Case Reports
16. An Unusual Presentation of an Epithelial Iris Cyst Attached to The Corneal Endothelium  
*Jacob Koshy, Gurvinder Kaur, Satish Thomas, S.M. Bhatti*

### History of Ophthalmology
19. Professor David Peter Choyee  
*Suresh K. Pandey, Vidushi Sharma, David J. Apple*

### Instrument Scan
26. Emerging Trends : Role of Functional Magnetic Resonance Imaging In Ophthalmology  
*Anoop Kishore Gupta, Senthil Kumaran, Rohit Saxena, Shikha Gupta, Vimla Menon, Pradeep Sharma*

### Original Article
29. Incidence of Ocular Complications of Orbital  
*S.M. Farooq, M.Q. Keng, Shabana Khan, Ahsan Dar, Afroz A. Khan*
34. Mutation screening of α-crystallin mutations  
*Manoj Kumar, Rima Dada, Tushar Agarwal, Sudarshan Khokhar*
38. Importance of LVAsin Blind School  
*Abhishek Purohit, Namrata Gaikwad, Ulka Srivastava, Pushpa Varma*
41. Genotype-phenotype correlation : Clinical implications of CYP1B1 analysis in primary congenital glaucoma  
*Mukesh Tanwar, Tamaj Dada, Ramanjit Sihota, Rima Dada*

### Instructions to Authors
Dear friends,

This is my last communication to you as Editor of the Delhi Journal of Ophthalmology and though these past two years as Editor of the DJO have been the most challenging yet they have filled me with a feeling of satisfaction and achievement that is hard to explain. I wish to express my sincere gratitude to the President Dr P V Chadda, the Past President Dr Sharad Lakhotia, the Secretary Dr Amit Khosla and the entire executive for their constant support and encouragement given to me to enable me to perform my duties and responsibilities properly and on time.

In this term of 2 years we have achieved the rare distinction of publishing all the 8 issues in full colour with rich academic content. We were able to get articles from the best in India and abroad and had a highly qualified Editorial Board. I am grateful to the Editorial team that had worked tirelessly to ensure high quality in the scientific content and in printing. Also I am grateful to the Editorial Board that has responded to all the demands I had placed upon them however unreasonable. However the maximum credit of making this effort successful lies with all the members of the DOS who have overwhelmingly supported us by sending their articles to the journal. Without active involvement and contribution from the members it would not have been possible to achieve this.

As change is the only permanency there is, I wish the incoming Editor Dr Rajesh Sinha and his team all success and hope that the journal achieves greater milestones under him. With many thanks for giving me the responsibility of serving as the proud editor of the DJO and for your constant support.

Dr Rohit Saxena
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Major Review

Implants in Anophthalmic Sockets

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HISTORY
Since long removal of eye in intractable painful blind eye, traumatic disfigured eyes and intraocular malignancy has traditionally been the definitive treatment of choice. The removal of eye for treatment of ocular disease was first described by George Bartisch in 1583[1]. This procedure was done without anesthesia and has been described as the most severe and repulsive operations in surgery[2]. This painful and crude procedure proceeded with little change for 265 years. The socket thus left behind was unsuitable for any implant. It was in 1885 when Philips Henry Mules introduced a glass sphere after enucleation with satisfactory result[3]. Frost in 1887 introduced a similar hollow glass sphere in tenon’s capsule post enucleation[4].

Introduction of implants in orbit was a major breakthrough in anophthalmic socket surgery. This was the beginning of a new era in anophthalmic socket surgery where the problems of cosmesis could be addressed. Mules sphere began to be used extensively and simultaneous search for better material continued. This implant though replaced the lost orbital volume but it had a tendency to migrate within tissues and even sometimes extruded out of the cone. Implants progressed from nonintegrated to partially integrated to integrated implants. Rudeman in 1941 introduced the first exposed integrated implant and an acrylic prosthesis [5]. Cutler developed a partial exposed integrated implant similar to Iowa implant. These implants did have excellent motility but infection and extrusion finally occurred and these implants fell into disrepute. The high extrusion rates upto 90% with these partially integrated implants emphasized the need for epithelization of wound to decrease extrusion and infection. Attention again was then directed to bury implants.

Then it was Allen who discovered a buried nonspherical polymethylmethaacrylate (PMMA) implant[6]

NEWER IMPLANTS
It was Perry in 1985 who introduced the hydroxyapatite (HA) implant after enucleation and evisceration[7]. HA was a coral derived natural substance mainly comprising of calcium phosphate and had pores resembling Harvesian system of normal lamellar bone[8]. Porous implants favour fibrovascular ingrowths and this decreases the late extrusion and migration of implants [12,14]. HA soon became popular as they gave good motility even after being integrated implants. A good structural framework also supported pegging. Till 1992 HA accounted for 56% of implants and became the material of choice[2]. Synthetic HA implants with slightly different pore uniformity and interconnectivity was also introduced. Due to the rough surface HA implants needed different wrapping material. Various materials used for wrapping are the polygalactin mesh, donor sclera, fascia lata, temporalis fascia. Even though HA had a brittle nature HA was also used as secondary implants in orbits[8]. The next major introduction was the porous polyethylene implants. This material was used in craniofacial reconstruction. These implants were porous in nature and had smoother surface. The pore size varied from 150-400 micron and muscles could be directly sutured to the implant hence decreasing the need for wrapping material as in HA [10,15]. These implants can be carved according to shape required. This implant incites less fibrosis and tissue reaction than HA[13].

Another emerging implant is the Aluminum oxide implant also referred to as the bioceramic implant as it is made of ceramic biomaterial similar to that used in orthopedics and

Enucleation and Evisceration still remain the definitive treatment in end stage eye diseases where nil visual prognosis is the expected outcome. Implants in anophthalmic sockets mark the beginning of a new era in anophthalmic socket surgery. The marked improvement in aesthetic outcome addresses the important issue related to psychological trauma the patient undergoes postenucleation. In this article we review, in short, the history of introduction of implants in anophthalmic sockets, the evolution of newer material, designs, and major complications associated with them.
dentistry[13]. Expandable implants with osmotically active gel which expand in vivo and stimulate orbital growth were recently introduced especially for congenital anophthalmos. The latest implant introduced is the Alpha Sphere. It is the first poly-Hema (2-hydroxyethyl methacrylate) implant. The majority of alpha sphere composition is water and this closely resembles that of natural globe. The long term result of this porous implant is awaited. With the use of various implants over the years, now motility of implants and prosthesis has also become an important issue.

The first prosthesis or artificial eyes as they were then called were developed by Venetians around 1580 and these were very thin glass shells. In 1880 Snellen developed the modified eye design which was hollow glass with rounded edges. It was only in late 1960, the modified impression method was developed by Allen. This method accurately duplicated shape of individual sockets as well as addressed the anterior lid problems due to prosthesis placement. Motility of prosthesis which is a very important issue depends on various factors as prosthesis-implant interface, weight of prosthesis, state of fornices, stability and muscle attachment to implant, placement and coupling of peg to the prosthesis. The most common material used in pegging is polycarbonate and titanium.

**COMPLICATIONS**

- Placement of porous polyethylene implant postevisceration
- Healthy Socket post implant placement
- Posttraumatic staphylomatous eye in 18 year male
- Post implant and prosthesis placement
- Conjunctival thinning and implant exposure
- Post implant discharge and conjunctival gaping
With the long term use of implants complications gradually surfaced and came to light. The published rate of complications vary from one series to another[18]. Reported complications include exposure, conjunctival thinning, cyst formation, discharge, pyogenic granuloma formation, migration and extrusion of implant[18]. Serious complications like infection and extrusion may call for implant explantation. Surgical technique, materials used in implants, size of implant, hygiene of the sockets, pegging all determine the ultimate success rate of surgery. Proper assessment of the size of an orbital implant along with proper placement is a very important step towards the success of surgery. We recommend preoperative BScan of the eye and the use of orbital sizers intraoperatively to determine the exact size of implant to be placed. Prosthesis is generally placed 4-6 weeks later after the edema subsides and the socket hygiene is taken care off. It is not the motility of implant that is the main problem now, it is the transfer of this motility to the prosthesis that is the main concern nowadays. To peg or not to peg is absolutely surgeon’s decision as pegging though definitely improves motility but invites their own series of complications. In our cases we donot generally peg the implant because in our experience though by not using peg system there is definitely a compromise on the motility aspect but most certainly the chances of infection, irritation and exposure of the implant also decrease.

The journey of implants in anophthalmic sockets have gone through various stages like from solid to hollow spheres, from nonintegrated to integrated, from plain to porous, from nonpegged to pegged implants. In general an ideal implant is being sought for which should have the following characteristics. It should be lightweight, nonantigenic, inert, biocompatible, affordable. It should mimic the motility of the normal globe, and should have minimum complications like infection, extrusion and migration. Presently all implants are broadly classified as nonintegrated, semi-integrated, fully integrated, biogenic.

Nonintegrated implants are the ones which are nonporous and are not integrated and have no direct muscle attachment. Examples are the silicon and acrylic implants.

Semiintegrated implants allow attachment of muscle in tunnels on anterior surface for better motility. Examples include Allens, Iowa BioIntegrated implants-these allow fibrovascular ingrowth in the porous channels and result in direct biological integration with orbital contents. Examples include HA, porous polyethylene implants, aluminium oxide, alpha sphere.

Biogenic implants- An autograft or allograft of natural tissue with direct biological integration with orbital structures but not prosthesis. Examples include dermis fat graft, mucous membrane graft.

The most difficult aspect in finding an ideal orbital implant and prosthesis is that it has to match a fellow eye which is not static and has constant dynamic motion. It is still a matter of debate as to which implant is best suited for anophthalmic sockets. In our experience porous implants are presently the material of choice as vascularisation leads to integration of implants. But porous implants are significantly more expensive than acrylic and silicon implants. Younger cosmesis oriented patients may be the most ideal patients for implants in anophthalmic surgery. Aesthetic results have definitely improved with the use of orbital implants but still patients have to be cautioned about the likelihood of problems and potential need for additional surgeries. Proper implant selection and a well executed technique helps a lot in restoring cosmesis and decreasing complications in patients. It seems that the journey of using implants in anophthalmic sockets is to continue and its scope for use in anophthalmic sockets is to be limited only by the innovative capabilities of its surgeon.

References
Major Review

Persistent Fetal Vasculature

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Persistent Fetal Vasculature (PFV), also known as Persistent hyperplastic primary vitreous (PHPV), is a rare congenital developmental malformation of the eye, caused by the failure of regression of the primary vitreous. It can occur in isolation, in association with other ocular disorders and rarely as a part of systemic disorder. Most cases of PFV are sporadic, but it can be inherited as an autosomal dominant or recessive trait. PFV is divided into anterior and posterior types. Characteristic features include microphthalmic eye, white vascularized retrolental tissue with or without a persistent hyaloid artery, centrally dragged ciliary processes, an anteriorly shifted and (or) swollen lens, and varying degrees of lenticular opacification. Radiological investigations (ultrasound, computerised tomography, magnetic resonance imaging) aid in the diagnosis and differentiation from other causes of leucocoria. Although visual potential is limited in PFV, with modern vitreoretinal techniques, aphakic rehabilitation, and aggressive amblyopic therapy, useful vision can be obtained in selected patients. This article presents a current review of PFV, including the pathogenesis, genetics, clinical features, differential diagnosis, and management.

Introduction
Persistent hyperplastic primary vitreous (PHPV) is a congenital anomaly caused by failure of regression of the primitive hyaloid vascular system first described by Reese[1]. Goldberg later renamed the entity persistent fetal vasculature (PFV)[2] since this term more accurately describes the anatomic and pathologic features of the disease.

Embryology
Primary or primitive vitreous is a vascular structure, predominantly of mesenchymal origin, having the hyaloid system of vessels, seen during the first month of gestation. The hyaloid vessels emerge from the optic nerve and course anteriorly to nourish the developing lens and anterior segment structures. From the second month of gestation onwards, the primary vitreous is normally replaced by the definitive or secondary vitreous, an avascular structure made up of hyalocytes in an extracellular matrix. Primitive vitreous is thus reduced to a small central space called the Cloquet’s canal which courses between the optic nerve head and the posterior surface of the lens[1,2].

Pathogenesis
PFV is a disorder related to the persistence and secondary fibrosis of the primitive hyaloid vascular system. A fibrovascular stalk emanates from the optic disc to join the posterior lens capsule. At the posterior capsule, the stalk fans out to form a white fibrovascular membrane that covers the posterior lens (Figure 1). The extent of this membrane may be variable which is responsible for the spectrum of disorders like Mittendorf’s dot, persistent anterior fetal vasculature, persistent posterior fetal vasculature and combined anterior and posterior persistent fetal vasculature[3-5]. PFV membranes have been found to contain dense connective tissue (collagen, polysaccharides) with numerous inflammatory cells. Histopathology and immunohistochemistry has demonstrated numerous vascular channels, smooth muscle cells, nervous cells and epithelial cells. Proliferating cell nuclear antigen (PCNA) positive and terminal deoxynucleotidyl transferase-mediated deoxyuridine 5-triphosphate nick-end labeling (TUNEL) positive nuclei are widely found in PFV membranes. The cell types found in PFV membranes are similar to those of the primary vitreous[6].

Figure 1  A schematic illustration of the various parts of the eye showing the normal eye (a) and hyaloid artery as well as its branches covering the posterior part of the lens (b) in persistent fetal vasculature (PFV).

Genetic predisposition
Although most cases of PFV are sporadic, it can be inherited as an autosomal dominant or recessive trait. Inherited PHPV also occurs in several breeds of dogs and cats. In a limited number of cases, Norrie disease and FZD4 genes are found to be mutated in unilateral and bilateral PFV. These genes when mutated also cause Norrie disease pseudoglioma (NDP) and
familial exudative vitreoretinopathy (FEVR) that share some of the clinical features with PFV. Experiments indicate that abnormalities in normal apoptosis may be responsible for the pathogenesis of PFV[7]. Identification of other candidate genes in the future may provide a better understanding of the pathogenesis of the condition that may lead to a better therapeutic approach and better management.

**Association with other disorders**

PFV can occur with other disorders such as Axenfeld Rieger syndrome, Peter’s anomaly, myopia, osteoporosis pseudoglioma syndrome, morning glory syndrome, megalocornea, bilateral retinal vascular hypoplasia, neurological abnormalities, neurofibromatosis, Aicardi syndrome[7,8]. These studies imply that: (i) the failure of hyaloid vasculature regression is associated with several ocular pathologies, or a number of diseases can lead to PFV; (ii) the condition can be caused by many genes; and (iii) there is a relationship between the genes of other disorders and PFV phenotype.

Bilateral PFV has been reported in association with severe protein C deficiency. It has been hypothesized that thrombosis of the fetal hyaloid arterial system at a crucial developmental stage may cause intraocular ischaemia in utero that could lead to the compensatory upregulation of angiogenic stimuli and hence persistence of fetal vascular structures[9].

Bilateral microcornea, posterior megalolenticonus, PFV, and chorioretinal coloboma (MPPC) syndrome is a distinct syndrome recently reported notable for dramatic lens morphologic features, which the authors have termed posterior megalolenticonus[10].

A careful history of maternal drug abuse during the prenatal period is essential, as cases of unilateral PFV have been reported with cocaine and LSD use[11].

**Clinical features**

PFV is usually unilateral (90%) and typically associated with microphthalmos. Bilateral PFV is uncommon, with only few case series being reported in the literature[8]. PFV has been classified into 3 types – anterior (most common), posterior or a combination of both (Figure 2-4).

1. **Persistent anterior fetal vasculature**

   In this case the abnormality is confined to the anterior segment and usually involves the lens in the form of a retrolental plaque. It typically presents with unilateral leucocoria. Contraction of the fibrovascular membrane produces circumferential traction which pulls the ciliary processes centrally thus making them visible through the pupil (Figure 2).

   Over time the contraction of the membrane pushes the lens iris diaphragm anteriorly leading to shallowing of the anterior chamber. Also, the lens is often clear at first and later develops a posterior opacity following a break in the posterior capsule and swells causing further shallowing of the anterior chamber. If left untreated angle closure glaucoma results and eventually over several years the eye will be lost.

   Other abnormalities include prominent blood vessels on the iris and occasionally intralenticular hemorrhages. In some cases the lens cortex and nucleus may undergo spontaneous absorption through a break in the posterior lens capsule.

2. **Persistent posterior fetal vasculature**

   In this case the abnormality is usually confined to the posterior segment and the lens is usually clear. It may present as leucocoria, strabismus or nystagmus. There is often a fold of condensed vitreous and retina running from the disc to the ora (Figure 3). Preretinal membranes at the base of the stalk are common. Membrane contraction in the posterior segment may lead to retinal detachment including tractional macular detachment which is often associated with a poorer visual prognosis.
Mittendorf’s dot
It is a small white opacity on the posterior capsule of the lens. A small remnant of the hyaloid artery may extend from the optic nerve to the opacity. It is found in approximately 2% of normal individuals. Mittendorf’s dot with hyaloid artery remnant may represent a very mild form of PFV. Unlike PFV, Mittendorf’s dot is not progressive and does not interfere with vision.

Bergmeister’s papilla
It is a small tuft of fibrous tissue present at the centre of the disc (Figure 5). Usually observed as an incidental clinical finding as visual acuity is preserved; it is a remnant of the hyaloid artery fibrous sheath.

Investigations
An ocular ultrasound supplies essential information for the diagnosis of PFV as it determines the presence of the lesion, its extension and retinal and optic nerve head involvement (Figure 6).[12] There is usually a retrolental band which may be thick or thin, with evidence of increased posterior capsular echogenicity. A combined ultrasound study consisting of an ocular ultrasound with colour doppler to examine the blood supply to and hemodynamics of the hyaloid system has been recommended for indicating the possibility of hemorrhagic complications (hyphema, hemophthalmos, hyaloid vascular bleeding), as well as the optimal time of surgical treatment[13]. A case of bilateral PFV diagnosed by prenatal ultrasound in a fetus of 23 weeks gestation has also been reported[14].

Figure 5 Bergmeister’s papilla – picked up as an incidental finding in an asymptomatic adult male.
Persistent Fetal Vasculature

Computerised Tomography (CT) findings of PFV are absence of calcification, increased density of the entire vitreous, tubular intravitreal density (Cloquet’s canal or nonattached retina), decubitus positioning showing a gravitational effect on fluid-fluid level, microphthalmos, enhancement of abnormal intravitreal tissue, and small or irregular lens (Figure 7) [2,15,16]. Use of intravenous contrast agents accentuates the persistent fetal fibrovascular tissue.

Magnetic Resonance Imaging (MRI) findings of PFV consist of a tubular structure, representing the hyaloid vessel, fluid-fluid level due to the presence of hemorrhage in the subretinal space, a retrolental mass, microphthalmos, enhancement of abnormal intravitreal tissue, and small or irregular lens (Figure 7) [2,15,16]. Use of intravenous contrast agents accentuates the persistent fetal fibrovascular tissue.

**Differential Diagnosis**

PFV must be suspected when unilateral leucocoria is observed in a microphthalmic eye with elongated ciliary processes, and can be confirmed on ultrasound or CT scan. The following conditions also present with leucocoria and must be ruled out clinically and by appropriate investigations where necessary:

1. Uncomplicated congenital cataract
2. Retinoblastoma
3. Retinopathy of prematurity
4. Retinal dysplasia (NDP, FEVR)
5. Posterior uveitis, Toxocariasis

**Treatment**

Controversy exists as to which patient should undergo surgery especially because visual results are often poor and the fellow eye is usually normal. However the natural course of severe anterior PFV culminates in angle closure glaucoma and intraocular hemorrhage seen most frequently in the first 3 years of life, often occurring suddenly. Consequently many have advocated early surgical intervention to preserve the globe[18,22].

On the other hand, mild PFV can run a relatively benign natural course without surgery. Surgery may be avoided if the visual axis is clear, anatomical anomalies are not progressive, and the anterior chamber angle is not compromised[1,19].

Recent advances in surgical techniques have improved the prognosis of PFV. Surgery usually consists of lensectomy, 3-port vitrectomy, or both, through a limbal or pars plicata/pars plana approach. Authors who favor a limbal approach argue that the peripheral retina and the ciliary body can be dragged anteriorly and centrally, making iatrogenic injury to these structures more likely. Other authors advocate a pars plicata approach for less disturbance of the cornea and anterior chamber angle, improved ability to remove the entire lens cortex, and reduced anterior traction on posterior retina intraoperatively by earlier transection of the persistent hyaloid stalk. The choice of surgical approach, however, does not have a statistically significant effect on final visual acuity or rate of complications.20 Surgery aids in the maintenance or restoration of vision, prevention of angle closure glaucoma and intraocular hemorrhage and avoidance of phthisis bulbi. Intraocular lens implantation may be a favourable and beneficial option for the management of children with unilateral PFV and avoid the complications of glaucoma and amblyopia[21].

Surgery for severe posterior PFV is rarely undertaken. Although the fibrovascular tissue can be dissected and the accompanying retinal detachment may approximate to the retinal pigment epithelium (RPE), visual outcomes are quite poor. This is a result of the associated retinal dysplasia, and most critically, the normal fellow eye causing dense amblyopia.

**Figure 6** Ultrasound scans of 2 full term infants with unilateral cataract and microphthalmos showing retrolental echogenic bands suggestive of PFV.

**Figure 7** Axial CT scan showing an enhancing channel extending throughout the vitreous anteriorly with thickened retrolental membrane in the right globe. The left globe is comparatively small in size with increased vitreous attenuation likely due to bleed from PFV. Bilateral PFV is rare, encountered in less than 10% of patients.

Magnetic Resonance Imaging (MRI) findings of PFV consist of a tubular structure, representing the hyaloid vessel, fluid-fluid level due to the presence of hemorrhage in the subretinal space, a retrolental mass, microphthalmos and vitreous hemorrhage. Both T1-weighted and T2-weighted images show hyperintensity of the vitreous compartment or of the subretinal spaces, probably caused by the presence of proteinaceous fluid or old blood[17].
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Understanding Amblyopia

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Introduction
The word amblyopia is derived from the Greek word ambluōpia where its oldest use in literature has been documented in 1706. It is composed of amblus meaning dull or dim and ὤps meaning eye[1]. Today the neolatin counterpart refers to it as lazy eye or amblyopia.

It is defined as a reduction in the best corrected visual acuity (BCVA) as a result of defective central visual processing. It is a disorder of visual development caused by various mechanisms including imperfect optics, abnormal ocular alignment and sensory deprivation during childhood. No organic pathology involving the visual receptors or pathways can be elicited on examination though an impaired functionality is documented in the form of poor visual acuity in one or both eyes which usually reduces to 6/12 or less with a difference of 2 lines between the eyes[2].

The term functional amblyopia is used to describe amblyopia which is potentially reversible by treatment while organic amblyopia refers to visual loss of on organic origin such as: optic nerve hypoplasia, retinopathy of prematurity etc. and is considered to be irreversible. It has been known though that functional amblyopic could coexist with organic amblyopia and some improvement may be seen in such cases with occlusion therapy[3].

Prevalence
At a prevalence of 1-5%, amblyopia forms an important cause of visual morbidity. Since it affects children, the disability adjusted life years are significantly higher than for an equivalent visual loss in adults[4,5]. The potentially reversible cause becomes irreversible with increasing age and depth of disease. It is becoming an important public health problem and is finding therapeutic measures in the vision 2020 programs through setup of 50 pediatric vision centres in India.

The commonest cause of unilateral amblyopia is strabismus in 50% of the cases followed closely by anisometropia.2, 5 It is four times as common in premature and small for gestational age infants or who have a 1st degree relative with amblyopia. A six fold greater found in infants with neuro-developmental delay than healthy full term infants.

Pathophysiology
The pathophysiology involves a pattern deprivation or severe blurring through [1-3] postnatal months which produces profound and permanent reductions in spatial acuity in the affected eyes. The ocular dominance columns show suppression in the area belonging to the affected eye. It is postulated here that strabismic amblyopia is initiated as a maladaptive differentiation in the ocular dominance columns, whereas the non-strabismic amblyopia may be initiated from the ganglion cell population of the amblyopic eye[6]. Lateral geniculate layer's subserving amblyopic eyes are shrunken & atrophic while normal cells are expanded. The amblyogenic risk is maximum in early childhood and lessens after 3 years of age though it may be seen up to teenage years. The response to therapy is maximum between 30 months to ten years of age.

Clinical types
Amblyopia may be divided into strabismic and non strabismic types with differing characteristics between these two groups.

Strabismus Amblyopia
Strabismus-ocular misalignment deprives visual cortex of synchronous stimulus of corresponding images from the two foveas. Half of such cases have amblyopia at the time of presentation. Amblyopia is a risk factor to develop strabismus and vice versa by reduction in binocularity. If a child adopts alternating fixation (without binocularity), then both eyes receive focussed image at some time averting amblyopia.

Cases with strabismic amblyopia exhibit crowding phenomenon with linear optotype acuity worse than singular optotype acuity. On the neutral density filter test, strabismus amblyopias do better with them compared to normal eye.

Non Strabismus Amblyopia
This primarily includes anisometropic and stimulus deprivation amblyopia.

Anisometropic Amblyopia
This includes presence of a refractive error, unilateral (anisometric) or bilateral (ametropic) which causes an optical blur and consequent weakening of vision.

The risk of amblyopia is 100% in hyperopes with 4D ametropia and myopes with 6D ametropia. It is 50% in hyperopes with 2.5 D ametropia and myopes with 4D ametropia. This form of amblyopia has a milder affection and is amenable to treatment.

Stimulus Deprivation Amblyopia
This form of amblyopia is seen in children with congenital cataracts, leukomas or any other form of media haze leading to obscuration of visual stimulus. This form behaves very similar to ametropic amblyopia but has more depth and worse prognosis if not treated early.

Prevention and Early Detection
- Identify factors that predispose to amblyopia in early in child' life to improve treatment outcomes.
- Screening for amblyopia and strabismus conducted at the level of primary care physicians, nurses and health care professionals or school nurses.
- Referrals to be sent to ophthalmologists by 6 months age:
  - premature birth –(28 wks of gestation or less)
  - low birth wt(<1,500gms)
  - perinatal complications involving CNS.
- Referrals by 18 mths to be sent for:
  - neurological disorders ,neurodevelopmental delays
  - relatives with amblyopia or strabismus ,childhood eye disorder.
  - Genetic syndromes with mental retardation or motor delays.

**Diagnostic Evaluation [7]**
- History:
  - Demographic data.
  - Chief complaints for eye examination .
  - Current eye problems.
  - Ocular history of patching.
  - Eye surgery.
  - Systemic history.
  - Family history.

Amblyopia is a diagnosis of exclusion with the common symptoms ranging from asymptomatic patient to strabismus with loss of stereopsis and occasionally closing one eye during reading and attention deficit or poor concentration.

- Examination:
  - VA Assessment & Refraction.
  - Fundus evaluation
  - Ocular motor deviation : Corneal light reflex, Cover /uncover test
  - Sensorimotor fusion :
  - Accomodation.
  - Ocular health and systemic health.
  - Supplemental testing: electrodiagnostic testing.

**Table 1: Usual refractive error Required to produce amblyopia**

<table>
<thead>
<tr>
<th>Type of error</th>
<th>Subtype</th>
<th>Power in diopters</th>
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<tbody>
<tr>
<td>Anisometropia (asymmetrical)</td>
<td>Hyperopia</td>
<td>1.5</td>
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**Treatment [7]**

Aim of therapy: Restore normal or near normal visual function by eliminating eccentric fixation and/or developing extensive synaptic input to visual cortex. Therapy improves deficits of visual acuity, monocular fixation, accommodation and ocular motility. It finally develops binocular vision.

**Nonsurgical Treatment of Amblyopia:**
- Refraction
  Refraction alone improves amblyopia in 1/3 of cases. In refractive amblyopia, a progressive improvement in VA upto 16-22 wks after refractive correction is encouraged prior to implementation of other measures
- Vision therapy:
  Vision training, a method to correct presumed ocular visual processing and perceptual disorders, encompasses a wide variety of nonsurgical methods:
  - Orthoptic vision therapy or orthoptics: improves binocular vision disorders and is for strabismus and diplopia.
  - Behaviour vision therapy or behavioural optometry: improves difficulty of visual attention and concentration.
- Occlusion / patching:
  A common treatment for amblyopia is to patch the strong eye; the weak eye is strengthened because the child is forced to use it.
  Physiological benefit is to produce greatest decrease in neural signals from dominant eye.
  Types of patch include direct adhesive dark patch on skin (best), elastic band, part of lens patch or a dark contact lens.

Improve Compliance by:
- Parents and child should be equally motivated & convinced of the need for treatment
- Demonstrate on a doll, explain to teacher ,who will explain situation to classmates .
- Use patching diaries with stickers

Patching should begin as early as possible with a frequency
dependent on the age of the child eg. for a 3 year old child, 3 days of good eye patched followed by 1 day of amblyopic eye, or a 4 day old child, 4:1 and so on. It is ideal to patch for all the waking hours but on the basis of individual situation, it may be done after school hours or during some active play/watching TV etc. For anisometropia, patching should be done after giving proper refractive correction. For severe stimulus deprivation amblyopia such as unilateral cataracts, long term full time patch until age 7 or a longer period may be needed as there is risk of relapse. The initial followup should be frequent especially in infants and younger children to look or occlusion amblyopia. Initially 2-4 weekly follow-up and later 2-6 monthly can be considered. After equalization of visual acuity of both eyes, 3 months of patching should continue followed by once a week maintenance patching. Reasons for patch failure include poor cooperation and compliance, underlying organic defect, Late start of treatment, uncorrected refractive error, microtropia and latent nystagmus.

**Side effects of patching:**
- Occlusion amblyopia : decrease frequency of patching or stop
- allergy to constituents of patch or adhesive : stick patch on spectacle
- sore skin: leave patch off at night or change shape & size of patch
- precipitation or increase in magnitude of strabismus & diplopia
- Increased risk of accidents.

**Penalization**
- Pharmacological blurring
  - Principle: blur vision of of fixation eye by palsy of accomodation and dilatation of pupil both for distance and near and increase use of amblyopic eye.
  - 1% atropine sulphate, a topical muscarinic antagonist blocks action of acetylcholine causing palsy of sphincter and pupil dilatation along with palsy of ciliary muscle reducing accomodation.
  - Method : used as ointment once a day ,with punctal occlusion in good eye with no optical correction and amblyopic eye left with full accomodation & optical correction.
- Optical blur:
  - high power contact lens /elevated bifocal segments in sound eye.

The advantages of penalization include comparable results to patching without the cosmetic blemish and adverse effects mentioned above. Also, there is a higher compliance. The disadvantages are difficulty in monitoring; occlusion amblyopia and medication related side effects (flushing, hypersensitivity, tachycardia).

**Pleoptic:**
It is an old modality of treatment started in the 1950’s but losing its popularity now in view of time and human recourse intensive methodology having limited results. It could follow Cupper’s or Bangerter’s methods and involves occlusion with auto flashing on synaptophore or the use of a pleoptophore and eutyoscope.

**Surgical Treatment of Amblyopia:**
This involves surgery for strabismus and removal of any media opacity such as cataract surgery, ptosis surgery, corneal transplantation etc.

**New Advancement of treatment:**
Neurovision:
- Clinically proven nonsurgical risk free treatment of adult amblyopia.
- US FDA approved
- > 2% world’s population are adult amblyopes.
- Age –9 - 55yrs who are motivated to see sharper clearer with “lazy eye”.
- Improves quality of life.
- Patented system which trains brain to see sharper:
  - 40 sessions in personal computer, 1.5 mts away from " monitor for 20 mts everyday for 10 wks.
- Home based near vision activities:
  - a hand eye coordination programme which uses conditioning & behaviour modification to appropriately alternate stimuli ,targets become smaller ,improves resolution and VA and hand eye coordination mo-noocularly.

**Medical therapy:**
- Drugs such as levodopa/carbidopa are showing promise in the treatment of amblyopia.

**References**
Case Reports

An unusual presentation of an epithelial iris cyst attached to the corneal endothelium

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An iris cyst attached to the endothelium causing decrease in vision is extremely rare. A twenty year old gentleman presented with painless progressive decrease in vision in the right eye for four months. Anterior segment evaluation revealed a 3.5 mm circular mass, brown in colour attached to the corneal endothelium but free from both iris and lens. It was removed through a clear corneal incision and histopathological examination was consistent with a benign epithelial cyst of the iris.

Introduction
Iris cysts are uncommon and their ectopic presentation is rarer still. We present a case of primary epithelial iris cyst, not attached to the iris but attached to the corneal endothelium in the centre leading to decreased vision which to the best of our knowledge has not been reported in literature so far.

Case report
A twenty year old male presented to the out patient department with painless progressive decrease in vision in the right eye for four months. No other relevant ocular or systemic history was present. Unaided visual acuity was hand movements close to the face and there was no improvement in vision on refraction. Anterior segment evaluation revealed a 3.5 mm circular mass, brown in colour in the anterior chamber (Figure 1, 2). The rest of the anterior segment was within normal limits. Intraocular pressure and gonioscopy were normal. On dilatation, the mass was seen even more clearly attached to the endothelium of the cornea but free from both iris and lens (Figure 3). The fundus on examination was normal. A probable diagnosis of ectopic iris cyst in the right eye was made. The vision in the left eye was 6/6 and both the anterior and posterior segments were normal. Surgical removal of the mass was planned in view of the mass leading to decreased vision in the right eye. A clear corneal section was made. Viscoelastic assisted cyst separation done and the cyst removed by viscoexpression (The video of this surgery can be viewed at http://youtube/dLbrlsOHlRA ). The mass was sent for histopathological examination that revealed a cyst wall comprised of fibro lamellar material and scant pigmented epithelial cells, consistent with benign epithelial cyst of the iris (Figure 4). Post operatively the patient regained 6/6 vision in the right eye (Figure 5).

Figure 1: Iris cyst in the right eye

Figure 2: Temporal view of the cyst
Iris cysts being relatively uncommon, not much is known in literature about its clinical characteristics, natural course and complications. In general, iris cysts are of the pigment epithelium or of the iris stroma. Iris cysts have been reported to be of surface ectodermal origin[1]. Most iris epithelial cysts remain stable and do not progress. They therefore rarely require treatment.

If the cyst is located in an area of iris pigment epithelium, the cyst will fail to transilluminate. In contrast, if the iris cyst is more peripheral and located near the ciliary body nonpigmented epithelium, the cyst may allow transillumination. As its name implies, a cyst of the pigment epithelium is lined by the iris pigment epithelial cells. On the other hand, cysts of the iris stroma are lined by stratified squamous epithelium with goblet cells and may resemble conjunctival epithelium. These findings and the fact that stromal cysts are usually found in infants support the idea of a congenital rest of ectopic surface epithelium as the source of these lesions.

In a review of two hundred thirty-four patients by Lois et al, primary iris pigment epithelial (IPE) cysts were classified as central in 6 patients (3%), midzonal in 50 patients (21%), peripheral in 170 patients (73%), and dislodged in 8 patients (3%). Central (pupillary) IPE cysts were found only in males, peripheral IPE cysts were found most often in females (69%), and no gender predilection was detected for midzonal and dislodged IPE cysts. Central and peripheral IPE cysts occurred in young patients (mean age, 20 and 33 years, respectively); whereas midzonal and dislodged IPE cysts were seen in slightly older patients (mean age, 52 and 45 years, respectively). Dislodged IPE cysts appeared as a brown oval lesion, free floating in the anterior chamber (12%) or in the vitreous (12%), or fixed in the anterior chamber angle (75%). None of these patients had cysts attached to the corneal endothelium leading to decreased vision[2].

In a review of 57 iris cysts in children by Shields et al, 53 were primary and four were secondary. There were 44 primary cysts of the iris pigment epithelium, 34 of which were of the peripheral or iridociliary type, accounting for 59% of all childhood iris cysts. Among the secondary iris cysts, two were post-traumatic epithelial ingrowth cysts and two were tumour induced cysts, one arising from an intraocular lacrimal gland choristoma and one adjacent to a peripheral iris naevus[3].

Most iris cysts of childhood are primary pigment epithelial cysts and require no treatment. However, the iris stromal cyst, usually recognized in infancy, is generally an aggressive lesion that requires treatment by aspiration or surgical excision. In a review by Haller et al anterior chamber epithelial cysts can be managed conservatively in selected cases with good results [4]. In our case even though the patient had a primary pigment epithelial cyst surgical excision was required because the cyst was in the visual axis causing decreased vision.
Pupillary pigment epithelial cysts of the iris have been shown to have an autosomal dominant heredity pattern [5]. Complications associated with IPE cysts included lens subluxation in one case (1%), iritis in one case (1%), focal cataract in two cases (2%), glaucoma in two cases (2%), and corneal touch in five cases (4%) [2].

Conclusions
Most cysts have a benign clinical course, and treatment is rarely necessary. An iris cyst attached to the endothelium causing decreased vision is extremely rare. In the present case because of the location of the cyst a simple surgery was required leading to immediate gratification for both the patient and the surgeon.

References
The story of Sir Harold Ridley’s invention and first surgery implanting the intraocular lens at London’s Saint Thomas’s Hospital on 29 November 1949 is well-known. Choyce’s first contact with Sir Ridley was in 1950 at Moorefield’s Eye Hospital, where he was fortunate to witness Ridley’s early implant. This article addresses several achievements and innovations of a protégé of Sir Harold Ridley, Mr. David Peter Choyce in the field of intraocular implant and keratorefractive surgery, which are mostly forgotten.

David Peter Choyce and Contemporary Ophthalmic Pioneers

Professor David Peter Choyce, FRCS, DOMS, MS, (Figure 1) passed away at a hospital near his home at Southend-on-Sea on August 8, 2001 at the age of 82. He was often mentioned in association with 4 of his contemporaries who were also pioneers of anterior segment surgery and intraocular lens (IOL) implantation. These are Sir Harold Ridley of England, Syvatoslav Fyodorov of Russia, Cornelius Binkhorst of Holland, and Edward Epstein of South Africa (Figures 2A-D). For each of the latter, a specific and well-defined role and legacy has been established [1-5]. While Sir Ridley, invented the IOL[5]. Fyodorov, pioneered several IOL designs. He was also an innovator in the field of corneal/IOL refractive surgery, including radial keratotomy and phakic silicone plate posterior chamber (PC) IOLs. Binkhorst was an early lens designer, but, more importantly, was an early advocate of extracapsular cataract extraction (ECCE), and capsular (in-the-bag) fixation of IOLs. Although routine now, these specific surgical procedures were very controversial in his time, and remained so until the early 1990s. Binkhorst was also a leader in developing formal laboratory (wet lab and hands on) training of eye surgeons. Epstein was another early disciple of Sir Ridley, an early lens designer, a pioneer in IOL implantation in children, and an early advocate of “soft”-biomaterial foldable IOLs[3]. Unfortunately with the passing of Fyodorov in 1999, Sir Harold Ridley and Peter Choyce in the year 2001, of these 5, only Epstein remains with us today. We provide details of innovations, achievements and contributions of David Peter Choyce after a careful revisiting of Choyce’s published [6-15] and non-published work that leads to the conclusion that he is one of the 20th Century’s most underrated pioneers.

Innovations, Achievements and Contributions of David Peter Choyce

A. Anterior Chamber and Phakic Refractive Implants

Peter’s foray into the field of IOLs began when he was a registrar (resident) at Moorfield’s Hospital in London at precisely the same time that Ridley did his first implant at Saint Thomas’ Hospital on November 29, 1949. He immediately saw the value of Ridley’s device and procedure and he became an ardent supporter of Sir Harold. Peter was 12 years Ridley’s junior and he once remarked that, since he had lost his own father, a prominent general surgeon who died when Peter was only 18, he longed for a father figure. During his years of training he subsequently had two. Sir Stewart Duke Elder was his father figure on what Choyce considered the academic/research side. Harold Ridley (of course not yet...
They are now being researched and applied as possible phakic IOLs [19]. One of the best attributes of Choyce’s AC-IOL design was the broad haptic or footplate fixation element. Such haptics are “tissue-friendly” when properly fitted into the anterior chamber (AC) angle recess. A good lens emerges when one combines this haptic with the most important feature of the Kelman series of AC-IOLs, namely, flexibility. This helped move this lens type towards, but probably never exactly to a “One size fits all lens”[16-18].

The reputation of AC-IOLs as a group was particularly blighted in the 1970s and 1980s as several disastrous models flooded the market. Of importance for this discussion is the fact that, other than the site of fixation is the AC angle recess, virtually all of these bore almost no resemblance to the Kelman-Choyce designs. They caused myriad complications. These were of course not the fault of Choyce. When properly sized and implanted (which indeed was often difficult and required a combination of skill and luck, Choyce’s licensed lens, and the flexible Choyce-Kelman multiflex designs originally manufactured with expertise and excellent polishing techniques by Rayner, Ltd., U.K., provided good results. Unfortunately there were badly made, razor-sharp edged, non-licensed copies of his lens made in the United States, as well as a myriad of other defective designs that we often rated as being better suited as “IUDs” (Intrauterine devices) rather than “IOLs”—lenses that had nothing to do with Peter Choyce—that nevertheless inappropriately gave him and AC-IOLs a disproportionately bad name.

To understand Choyce as a person is to understand that this degradation of his lifetime pet project was extremely discouraging and disappointing to him. It was an occurrence from which he really never recovered—leaving extreme bitterness within him to the end.

As our specialty now speeds forward into a new era of refractive surgery with both kerato-and IOL-refractive procedures, it is ironic that phakic IOLs that now are being researched in order to provide high precision designs to be presented to the world’s huge population of patients with ametropia. Lenses intended for placement into the AC, most of which are based on Choyce’s principles, are now being seriously considered for phakic IOLs [19,20]. Many leading IOL manufacturers are intensely researching these AC-IOL designs in a race to enter

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Professor David Peter Choyce

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this market with the first and best candidates. We can’t predict what will happen but it would be an interesting dose of poetic justice and a nice enhancement of Peter Choyce’s legacy if these lenses did have some resurgence. It is unfortunate that if this resurgence does occur, he will not see it.

Secondly, another common criticism of Choyce that appears to be of little importance to the big picture regarding his legacy, but apparently was a strong source of irritation to some was that he failed to admit to complications of his IOL and his surgical procedures. There are indeed several anecdotal stories from colleagues in local London hospitals or at meetings who had seen Choyce’s patients who, implanted with his IOL, had complications that he purportedly did not report. So be it. However, if one reviews his writings [6-15] it is clear that he did not deny or hide the existence of such complications; they are clearly spelled out in some of his publications. What he probably did was to understate them, a common practice from beginning of time and still today. This was certainly not unique to Choyce. For example, in the large series of IOL explants accessioned in our Centre (over 9,000 at the time of this writing), many of the catalogued complications came from operations performed by some of the best surgeons in the field. The overwhelming majority of these complications was unknown to the surgeon or, if known, was not always reported.

Proof of Choyce’s innovative nature exists in reports he published in the refereed literature, in unpublished manuscripts and in records of many oral presentations. There is a single, now-almost-forgotten, obscure writing that warrants special attention here. It is a remarkable thesis that he wrote in the late 1950s through the early 1960s in partial fulfilment of the Degree of Master of Surgery, University of London. At the university, it was rejected by the above-mentioned Sir Stewart Duke Elder, but was later subsequently accepted by other reviewers. Peter had numerous papers that were submitted to refereed, peer-reviewed journals that were rejected, in part, because many of his ideas were considered “radical” for their time. This thesis, replete with innovations, contains patches of several rejected manuscripts. It was subsequently published in 1964 as a monograph entitled “Intraocular Lenses and Implants, London, HK Lewis & Co., Ltd.” [6] It has long been out of print but a small limited edition was recently reissued by Rayner Intraocular Lenses, Ltd., Hove-Brighton, U.K. Rayner is, of course, the manufacturer who very competently fabricated Sir Harold Ridley’s original lens and with whom both Ridley and Choyce worked for many years during the evolutionary process of these IOL designs. A perusal of the topics discussed in this monograph summarize some of his work on IOLs done up to that time (1964), including forerunners of what we now consider new high technology devices. Some may seem routine now, but were bombshells then and showed foresight for that time.

B. -Paediatric Intraocular Lens Implantation

To our knowledge the first paediatric IOL implantation was performed in 1951 by Edward Epstein who implanted Ridley lens in a 9-year-old child with traumatic cataract. This patient is alive today and the implanted eye has 20/20 vision 46 years after the surgery[21]. According to our search of literature Peter was the second surgeon to implant an IOL in a child. His first case was an 8-year-old implanted with Mark I design in 1957 (Figure 3 A-B) [6,12-14]. This daring foray into the then absolutely unknown field of paediatric IOL implantation will probably represent one of his most important accomplishments as the history of our specialty is written over time. In his monograph, [6] he documents his first implantation in a child, a lens placed into the eye of an 8-year-old with traumatic cataract, June of 1957 (Figure 3 C). The second IOL was implanted in a 4-year-old child in April of 1959 (Figure 3 D). By the time of the 1964 monograph, he had implanted a total of 20 lenses, with up to 5 years follow-up [6]. The youngest patient to receive an implant from Choyce prior to 1964 was a 2-year-old. Twelve of the 20 had “moderate” visual recovery; 8 had less than satisfactory results. However, the clinical details regarding these cases is now much less important than the fact that he did it! The results were not stellar, as would be expected in this early era with these early IOL designs. For both children and adults, he developed a series of IOLs with coloured haptics that functioned as artificial irides (Figures 4,5) [6,15]. He could create a “brown iris” utilizing iron (ferrous) compounds admixed with the PMMA polymer haptic, a green iris with indocyanine green, and a blue iris utilizing cobalt blue. This is the direct forerunner of modern artificial iris diaphragms, until today, for various indications, e.g. aniridia[15,22-26]. Choyce was one of the first to do systemic measurements of intraocular components that would be useful, and indeed, should be required for implantation of IOLs[6]. He did measurements of corneal transverse diameters in 230 consecutive eyes, providing information that is still useful today as we study new phakic IOLs. He did measurements on eyes of all ages, including infants and children, in order to best size IOLs for paediatric implantation. He was one of the first to establish quantitatively that all anterior segment and indeed, eye growth was most rapid in the first 24 months of life, i.e. that 90% of eye growth was completed by age 2.6 We were somewhat humbled to note that this was performed almost 4 decades prior to a similar, widely quoted study we did in our laboratory[27].

C. Kerato-Refractive and IOL Surgery

It is also not at all well known that Choyce had a very strong interest and understanding of the field of refractive surgery. He was no doubt one of the first to have worked with both refractive modalities: keratorefractive-and IOL surgery. He
stated that as early as 1948 he was doing research on use of artificial corneal inlays. The earliest written documentation regarding this was in 1952 (on file at Rayner, Ltd., Brighton-Hove, UK). This remained a favourite topic of his throughout his life and he developed many versions of corneal inlays using various biomaterials[28-30]. He also did early work with Ridley on keratoprostheses[31-32]. Both of these techniques are still being researched with limited but ever-improving success, but improvements are to be expected.

Another important foray was the use of phakic refractive IOLs, where he followed the example of pioneers such as Ignacio Barraquer of Spain and Benedetto Strampelli of Italy. Animal studies and governmental Food and Drug administration (FDA) oversight were not required at that time. Evaluation of results was, therefore, not reliable. However, he and others reported some good results in his clinical trials in patients with up to 40 diopters of myopia[6]. Again, what was most important was not details of each clinical outcome, but rather, the fact that he did it and contributed useful information, helpful for future generations. This pioneering work was clearly the forerunner of one of today’s “hottest topics.”

Other pioneering attempts at refractive IOL surgery clearly documented in his monograph included experiments with toric IOLs and the use of stenoptic apertures within the lens optic in order to create a vision-improving pinhole effect in otherwise hopeless cases. Choyce suggested that it may be possible to employ an IOL to achieve temporary and/or complete visual axis occlusion in patients with severe, disabling diplopia, but he did not perform this procedure.

To our knowledge, Choyce was one of the first, if not the first, to apply an IOL in the then newly-emerging field of low vision therapy, using an IOL as a component of a mini-telescopic system. Prior attempts had been made with negative power contact lenses on the surface of the eye, creating a Galilean telescope when combined with a lower power positive lens in front of the eye. His was the first attempt using an IOL as the negative component of the Galilean system (Figure 6 A). He correctly reasoned that this might be an appropriate treatment for patients with unilateral macular degeneration (Figure 6 B). This is the forerunner of present attempts at perfecting a full, complete telescopic lens within the eye that is now being seriously researched, with both positive and negative components of the telescope residing within the IOL itself. This has been successfully applied to a series of patients with macular degeneration in small clinical studies[33-35].

Peter Choyce, in co-operation with contemporary ocular pathologists was one of the first to apply clinico-pathological correlation techniques to IOLs (Figure 7) [36,37]. If such correlative work had been carried out on a consistent basis over the decades following these original examinations, it is likely that improvements of IOLs would have been accelerated.

D. Foundation of the Intra-Ocular Implant Club (IIIC)

Implantation of the artificial lens following cataract surgery was widely criticized by the ophthalmic establishment in UK, North America and several other countries. Because of this opposition and criticism, Ridley and Choyce founded the Intra Ocular Implant Club in 1966. An intangible legacy of Peter Choyce that cannot be fully documented or verified in writings was his non-stop and vocal avocation of IOLs in general. From the very beginning he was Ridley’s number one advocate. This was also evident when Peter, together with Sir Ridley and John Worst, shared their experience on early IOL implantation including foundation of Intra-Ocular Implant Club during a recent Apple Corps Re-union meeting. This meeting was held in the recent American Society of Cataract and Refractive Surgery meetings in Seattle, Washington in 1999. Ridley himself declared in a series of personal papers (“jottings”) he had written: “I had no support in Ophthalmology until D.P. Choyce became a consultant.” Luck would have it that Choyce’s personality was very different from Ridley’s. Sir Harold was essentially non-confrontational and had difficulty debating and thereby defending his clinical presentations. He travelled the world and spoke about the IOL as a clinician-scientist but was not a strong vocal advocate in terms of the “politics” and “political skills” required to fend away criticism. Peter Choyce, on the other hand, had no hesitation in functioning as a defender and would not refrain from arguing with and/or offending anyone he deemed a foe to his beliefs. However his skill as a debater, and advocacy for what he believed helped keep the cataract-IOL procedure in the public eye as it passed through it’s darkest days prior to it’s maturation and a acceptance. At numerous meetings he encountered and answered criticisms that helped steer IOLs through the decades of the 1970s. An excellent example of this is written in Choyce’s own words as follows:[11].

“An important meeting was held in Paris on Saturday, June 1, 1974, following the conclusion of the XXInd international Congress of Ophthalmology. The scientific program of the Congress had contained not one paper on the subject of lens implantation, although dozens of abstracts (including three of my own) had been submitted. Our satellite meeting, held in the ballroom of the Meridien Hotel adjoining the Palais des Congress, was attended by 44 IIIC (The International Intraocular Implant Club (IIIC) and was co-founded by Sir Harold Ridley and Peter Choyce in Oxford, U.K. in 1966) members and twice as many non-members. The interest in lens implantation shown that day demonstrated that we were winning the battle for the mind of the profession and that all our struggles had been worthwhile.”

One of us (DJA) personally attended this 1974 Paris meeting as a junior faculty member an “academic” presenting work on argon laser photocoagulation of the retina. There were no IOL-related presentations on the main program. The hustle and bustle and the general enthusiasm generated Choyce’s
“satellite” meeting is still remembered today by surgeons who were in attendance.

**Concluding Remarks**

Peter would have greatly appreciated this brief chronicle covering substantive issues regarding his professional career. Some might feel that some of the opinions expressed here are exaggerated, but they are objective, based almost entirely on extensive research into his earliest writings. Choyce did not shy away from confrontations and he had an effusive personality, thus evolving some personal conflicts. We have been careful to avoid personal issues and jealousies and focus on documentation. As events and developments in the field of anterior segment surgery have evolved and unfolded, much of his work has already become more and more accepted and applied; this should continue. Hopefully, Peter will not be just remembered as an inventor of “bad AC IOLs” – as is unfortunately now the feeling of many ophthalmologists. It is sad fact to note from his presentations and writings including Letters to Editor written towards the end of his life, that he felt the need – and with full justification to mention and defend his prior art and largely neglected work. However, as this history is written, we predict that Peter’s contributions will be even more recognized and thus even further enhance his legacy as a major figure of the 20th Century ophthalmology who contributed much to society.

**Figure 2.** Contemporaries of David Peter Choyce, who were also pioneers of anterior segment surgery and intraocular lens (IOL) implantation.

A. Sir Harold Ridley of England. B. Svyatoslav Fyodorov of Russia.


**Figure 3.** The first paediatric implantation done by David Peter Choyce (1957). A and B. Implantation of Mark I design in 8-year-old case of traumatic cataract.

C. Postoperative photograph showing an iris capture of the anterior chamber lens in this particular case, but the patient did well.

D. The second paediatric implantation done, (also 1957). The lens shown here is also historical since this is the first “exchange implant” put in as the patient’s refraction changed after growth. Choyce also did some phakic IOL for refractive purpose in both children and adults.

**Figure 4.** It represents Prof. Choyce pioneering colouring of lenses to create an artificial iris, a process that is still done today with modifications of posterior chamber lenses.

Figure 4A shows cobalt blue, Figure 4B shows indocyanine green. The coloured opaque portions were made by thermally fusion the transparent IOL haptic portion to the coloured material doing the moulding process. This exact same principle is used today.

**Figure 5A and 5B shows a patient with a coloured lens of this type, matching his iris (right eye).**

**Figure 6.** Represents the first use of a Galilean telescopic system with an IOL to treat low vision, especially macular degeneration. Figure 6 A is Choyce’s diagram showing a biconcave anterior chamber IOL in place and Figure 6 B is the fundus of his first patient, with macular degeneration.
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Emerging Trends: Role of Functional Magnetic Resonance Imaging In Ophthalmology

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The rapid advancement of technology has transformed neuroscience research, with the introduction of novel imaging methods, some of them non-invasive. The techniques when integrated can yield information on locations, dynamics, fluctuations, magnitudes, and neuronal activity and structural changes. Here, we tried to explicate about rapidly evolving field of neuroimaging i.e. functional magnetic resonance imaging (fMRI), which is based on blood oxygenation level dependent (BOLD) contrast4.

FMRI is use of MRI to measure the change(s) in blood flow and oxygenation in brain linked to neuronal activity. The correlation between fMRI and neuronal activity is due to a tight functional coupling between neuronal activity and hemodynamic or metabolic response[1-3]. The principle of the fMRI technique is based on blood oxygenation level dependent (BOLD) contrast4 (figure 1). It is known that changes in blood flow and blood oxygenation in the brain (collectively known as hemodynamics) are closely linked to neural activity[4]. When nerve cells are active they consume oxygen carried by hemoglobin in red blood cells from local capillaries. The local response to this oxygen utilization is an increase in blood flow to regions of increased neural activity, occurring after a delay of approximately 1 to 5 seconds. This hemodynamic response rises to a peak over 4 to 5 seconds, before falling back to baseline (and typically undershooting slightly). These leads to local changes in the relative concentration of oxyhemoglobin and deoxyhemoglobin and changes in local cerebral blood volume in addition to this change in local cerebral blood flow. Magnetic susceptibility is different in these, i.e., hemoglobin is diamagnetic when oxygenated but paramagnetic when deoxygenated. Hence, the magnetic resonance (MR) signal of blood is therefore slightly different depending on the level of oxygenation (figure:1). These differential signals can be detected using an appropriate MR pulse sequence (echo planar imaging) to detect blood-oxygen-level dependent (BOLD) contrast. Higher BOLD signal intensities arise from decreases in the concentration of deoxygenated hemoglobin since the blood magnetic susceptibility now more closely matches the tissue magnetic susceptibility. By collecting data in an MRI scanner with parameters sensitive to changes in magnetic susceptibility, one can assess changes in BOLD contrast. These changes can be either positive or negative depending upon the relative changes in both regional cerebral blood flow (rCBF) and oxygen consumption. Increases in CBF that outstrip changes in oxygen consumption will lead to increased BOLD signal, conversely decreases in CBF that outstrip changes in oxygen consumption will cause decreased BOLD signal intensity.
**Advantage**

FMRI does not require any external contrast material and hemoglobin act as an endogenous contrast for it. BOLD is considered superior to available other contrast techniques - because the techniques are more technically challenging or, more often, the effect size produced using the specific contrast sensitivity is considerably less than BOLD contrast. Perfusion imaging has perhaps come the closest to BOLD in terms of utility and functional contrast. While it generally has less brain coverage, lower temporal resolution, and lower functional contrast to noise than BOLD, it does have the advantages of higher specificity, baseline information, and less baseline drift. The latter advantage is significant when probing very slow brain activation timing[5]

**Contraindications**
- Claustrophobia
- Subjects showing excessive movement artifacts on fMRI.
- Magnetic (iron) prosthesis.

**VISUAL PARADIGM**

1 LCD Projector: A back-projection system consisting of an LCD projector (VPL-X1000, Sony Co, Japan) fitted with a custom lens (Buhl Optical, Pittsburgh, PA) was employed to deliver the visual stimuli within the bore of the MRI scanner. The stimuli were projected from the control room onto a screen mounted on the head coil and visible to the subject through a set of mirrors. Peripheral vision was constrained with the use of MR-compatible goggles. The subjects were provided an occluder to facilitate monocular stimulation. The occluder prevented direct, central visual stimulation on the occluded eye but allowed some peripheral light scatter. Subjects requiring refractive correction wore contact lenses. The visual stimuli were generated on a personal computer with the aid of the Pixx software package (Concordia University Vision Laboratory, Canada).

**Visual stimuli consist of**
- Sinusoidal grating
- Checkerboard pattern
- Largest dot displacement in a random-dot kinematogram (RDK): for studying motion perception deficit in various diseases [6].

2 Nordic NeuroLab’s (figure:3) new Visual System is a flexible and convenient solution for presenting visual stimuli in the MR. With sharp images and brilliant colors, the Visual System allows you to easily present high quality graphics or text to the patient. The Visual System connects to all standard PC graphics cards or video sources, and has separate channels for each eye. This enables effortless presentation of true 3D stimuli.

The Visual System is designed with both the patient and operator in mind. The patent pending design fits most head coils and is easily mounted. The adjustable arm allows fast positioning of the micro-displays into the preferred angle of view. The built diopter correction and fine-tuning of pupil distance are easily regulated.

The Visual System features a unique optical setup to enlarge images generated by small OLED displays, and projects images to the patient’s eyes without use of fibre cables and risk of dead or grey pixels. The optical system is also prepared for eye tracking, either from one or both eyes. Scientific studies show that presentation of fMRI tasks with visual routes is more reliable with direct input through video goggles than with the conventional use of projection screens. In addition, the discomfort of being in the confined space of an MR-scanner is minimized for the patient due to the placement of the screen close to the eyes.

**CURRENT RESEARCHES USING fMRI:**

1. **Optic neuritis:**
   fMRI identified impaired visual brain function in acute unilateral ON even in cases which showed extinguished response on the VER. fMRI has the advantage over VEP of quantifying a graded response even in the acute ON phase. This might therefore be a suitable technique for monitoring the clinical course of ON (i.e., the degree of functional deficit as reflected in visual cortical function). Along this line, the question arises whether fMRI also reflects time dependent changes in visual cortical reactivity related to clinical evolution. Functional aspects of the repair mechanisms in ON and MS have been investigated using functional magnetic resonance imaging (fMRI), based on the blood oxygenation level dependent (BOLD) contrast (Ogawa et al., 1990). These studies have focused on cortical changes following ON [8-11].
Amblyopia:
The pathogenesis of amblyopia is indeed a subject of much intrigue as there is no ocular pathology. Using fMRI, scientists have elicited that the amblyopic eye has fewer activated voxels, however the magnitude of activation in these voxels is same for each eye irrespective of the presence of amblyopia.

b. Use of levodopa in amblyopic subjects causes recovery of visual acuity in the affected eye, however there is an increased interocular difference in the level of activation between the two eyes.
c. The effect of asymmetries occur in the level of activation in different amblyopic subjects, however these are not sensitive for severity of amblyopia and between strabismic and anisometropic amblyopia.

Conclusion
FMRI rapidly evolving as a investing tool in various neurological conditions not only for understanding the pathophysiology of disease but also to treat underlying cause.

Reference
Incidence of Ocular Complications of Orbital Regional Anaesthesia

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Complications following orbital regional anesthesia are rare, but can occur following both needle and blunt cannula (sub tenon) techniques. Each technique has its own risk/benefit profile and ophthalmologist must be prepared to deal with these rare but serious complications. These complications can range from minor effects to sight threatening complications.

**Method** An observational study of practice of local anesthesia (LA) in the dept. of ophthalmology Govt. Medical college J&K was conducted over one year. Doctors administering LA and surgeon operating were asked to report the complications while administering LA and while operating as per the set proforma.

**Results** Maximum number of complications reported were minor complications while as only 4 major complications were reported i.e retrobulbar haemorrhage which occurred with peribulbar anesthesia only.

**Conclusion** Sharp needle peribulbar block is associated with major complications which could threaten vision, while as subtenon and topical anesthesia results in only minor complications and thus are safer.

**Introduction**
Regional anaesthesia is clinically used to produce temporary loss of sensations, Analgesia and/or function, usually akinesia in a restricted area of the body. Patient comfort, safety, and low complication rates are the essentials of regional anaesthesia. Local anesthesia is the commonest type of anesthesia used for intraocular surgery[1,2]. While LA is generally considered to be relatively safe, serious complications following orbital regional anesthesia can occur with both needle and blunt cannula techniques[3,4,5]. These complications may range from minor to sight threatening complications and even death.

**Material & Methods**
Regional anesthesia provided to the patients was administered by trained personnel which included Registrars, postgraduate students and operating surgeons themselves. Before going for anesthesia an informed consent was obtained from the patient and procedure of LA was explained to the patient. No sedation was given to any patient. LA was provided under complete aseptic precautions.

**Orbital regional anesthesia techniques used were:**

**Peribulbar Block**
Peribulbar anesthesia was given using 5ml plastic syringe with 24G, 0.55x25mm long needle. 7-10ml of local anesthetic solution was used which included 2% lignocaine with 1:2 lac adrenaline with 15 IU of hyaluronidase per ml. This was followed by intermittent digital pressure for 5-10 minutes.

**Subtenon’s Block**
Small amount of lignocaine jelly 2% was put in the conjunctival sac over quadrant to be used for the block (inferior quadrant) 5 minutes before entering the theatre. Once the patient was positioned on the table and drapped a small nick was made in the conjunctiva and tenon’s capsule after holding them with a toothed forceps 5-10mm from the lumbus in the inferonasal quadrant using a blunt Westcott scissor and making a thin channel to the posterior subtenon space. This was followed by insertion of a blunt, metallic, curved, subtenon cannula mounted on a 5ml syringe containing mixture of 2% lignocaine and hyaluronidase, 3-5ml of the anesthetic solution was injected into the subtenon’s space[6].

**Topical Anesthesia**
4% xylocaine was used for topical anaesthesia. 2-3 drops of 4% xylocaine were instilled in the eye at an interval of 5 minutes before entering the theatre. One drop was instilled once the patient was in the theatre. One drop again was instilled once drapes were put. Superior rectus bridle suture was not used.

**Topical with Intracameral Preservative free Xylocaine**
After putting the topical anesthesia 0.3-0.5ml of 1% preservative free xylocaine was injected in the anterior chamber via a side port[7].
All these patients were monitored closely for any ocular complications resulting from regional anesthesia techniques while giving anesthesia and during intraoperative period.
Complications were divided into two groups:
1. Minor Orbital Complications which included those complications which were not sight threatening.
2. Major Orbital Complications included those complications which were sight threatening.

Operative procedure, type of local anesthesia and complications of local anesthesia were coded as per the proforma.

Statistical Analysis
Data was expressed as mean +/- SD and percentage. MS Excel and statistical package for social sciences (SPSS) 11.5 software was used for statistical analysis.

Results
853 LAs were administered, maximum number of patients were in age group of 50-69 years, male & female were almost equal (table 1).

Cataract extraction was the commonest diagnosis followed by POAG (table 2).

POAG = Primary open angle glaucoma
Table 2 shows that cataract was present in 780 (91.4%) patients, Glaucoma in 42 (4.9%) patients. 31 (3.7%) patients had other surgical problems which included 8 patients with aphakia, 8 patients with decentered IOL, 5 patients had hyphema, 2 patients had foreign body in anterior chamber, 2 patients had squint, 2 patients had corneal sutures, 2 had capsular opacification and 2 patients had iris prolapse. Peribulbar anesthesia was the commonest local anesthesia used in our study, reason being that peribulbar is still the most widely used local anesthesia technique in this part of the world and too in our departments, although trend is reverse in west[1]. Subtenon’s anesthesia was the second preferred local anesthesia technique while topical was the least preferred technique because it needs a highly cooperative patient.

Table 3 shows peribulbar anesthesia was given to 705 (82.5%) patients, subtenon’s anesthesia to 96 (11.3%) patients and topical anesthesia was given to 52 (6.1%) patients. Plain topical anesthesia was given to 44 (5.2%) patients and topical with intra-cameral xylocaine anesthesia was given to 8 (1%) patients.

Phacoemulsification was the commonest operative procedure done on our study patients since it is the commonest cataract extraction procedure done worldwide and too in our departments.

Table 4 Shows patients who received peribulbar anaesthesia 348 (49.4%) underwent phacoemulsification, 202 (28.7%) underwent SICS, 105 (14.9%) patients underwent ECCE, 33 (4.7%) patients underwent trabeculectomy and 17 (2.4%) had other minor surgical procedures. Patients who received subtenon’s anesthesia 56 (58.3%) underwent phacoemulsification, 35 (36.5%) underwent SICS, 2 (2.1%) underwent trabeculectomy, 3 (3.1%) had minor surgical procedures. Patients who received topical anesthesia plain 24 (54.5%) patients underwent phacoemulsification, 2 (4.5%) patients underwent SICS and 6 (13.6%) patients underwent trabeculectomy and 12 (27.3%) patients had other minor surgical procedures. Patients who received topical with intracameral xylocaine 2 (25%) patients underwent phacoemulsification and 6 (75%) patients underwent SICS.

Minor orbital complications were the most common complications in our study, while as major complication occurred only with peribulbar anaesthesia (table 5).

Among the minor complications conjunctival chemosis was the commonest complication 35.9% incidence with peribulbar and 57.8% incidence with subtenon’s anesthesia. This was followed by inadequate akinesia with incidence of 11.6% in peribulbar 94.8% in subtenon and 100% incidence in topical (table 5). Inadequate akinesia makes the surgical procedure difficult unless the surgeon is well experienced.

Inadequate analgesia was seen as next complication with incidence of 3.8% in peribulbar group, 14.6% in subtenon, 22.7% in plain topical and 12.5% in topical with intracameral xylocain (table 5). Inadequate analgesia made the patients apprehensive and surgical procedure difficult. Subconjunctival haemorrhage occurred in 59.4% patients who received subtenon’s anesthesia as compared to 3.5% patients who received peribulbar (table 5). Subconjunctival haemorrhage does not create any surgical problems but is commonly disfiguring for the patient. Similar results were seen by Tasneem Parker et al [8]. Zafirakis P et al [9] and Vielpeau et al [10] in their studies also had the same results with subtenon and topical anesthesia. Akinesia was not seen in any patient with topical anesthesia while 94.8% patients in subtenon’s group had inadequate akinesia [table 5].

All these minor complications were statistically significant (p < 0.001) but they did not produce any sight threatening complications in any of our patients. Maximum minor complications were seen with subtenon’s followed by peribulbar and topical being the least. The Cataract National Database Multicentric Audit [11] also proved that minor complications were 2.3 times more common with subtenon block (p < 0.001) as compared to sharp needle block.

Among the major complication only one complication i.e. retrobulbar haemorrhage was seen in our patients. This complication occurred only with sharp needle peribulbar block. Out of 705 peribulbar blocks retrobulbar haemorrhage was seen in 4 patients (0.56%) (Table 5). These retrobulbar
haemorrhages were minor which resulted in chemosis with subconjunctival haemorrhage and raised intraorbital pressure but they immediately responded to digital pressure. Retrobulbar haemorrhage has an incidence between 0.4% to 1.7% as reported by C M Kumar 2006 [12]. Davis DB 2nd et al[13] reported an incidence of 0.46% retrobulbar haemorrhage in peribulbar block in his multicentre study involving 16,224 patients. Our study also had a similar incidence of retrobulbar haemorrhage (0.46%) [table 5]. None of our patients had globe perforation, optic nerve injury or brain stem anaesthesia neither in peribulbar blocks or blunt subtenon’s block [table 5].

Major complications are sight threatening as well as life threatening their incidence being very low e.g. in national Survey 2002-2003 in UK[2] the incidence was found to be 2.9/10000 in peribulbar blocks while as globe perforation in 1996 National survey [14] from peribulbar anesthesia was 1.4/10000, which is very low. Duker et el[4] in a retrospective study found globe perforation only in 2 eyes out of 20. Complications with orbital regional anaesthesia can occur with any technique, be it sharp needle or blunt cannula or topical anaesthesia but most of the complications in literature are with sharp needle technique and that too minor complications. Peribulbar block involves sharp needle very close to important structures of eye which can cause severe damage to the eye but gives the best surgical conditions with complete akinesia and good analgesia. On the other hand subtenon’s anaesthesia uses blunt cannula which prevents these major complications but at the expense of akinesia which is not achieved immediately. Topical anaesthesia which is mostly used in west and most of the centers in our country now-a-days[1] because of the need for immediate visual rehabilitation demanded by the patients on table without using postoperative eye pads is an excellent technique but needs a highly cooperative patient and well experienced surgeon because surgeon has to work without akinesia, besides this the surgical manipulations inside the eye should be very gentle because the iris is not anaesthetized intracameral preservative free 1% xylocaine has overcome this problem which is injected into the eye to anaesthetize iris and other structures.

**Discussion**

1) Subtenon’s anaesthesia showed maximum complications among the three techniques all of which were minor. Out of which inadequate akinesia was seen in almost all patients followed by subconjunctival haemorrhage and chemosis. Analgesia was good except in 14 (14.6%) patients, but there was no major complication [Table 5].

2) Peribulbar anaesthesia was the only technique where major complication was seen as retrobulbar haemorrhage in 4 patients out of 705 patients. Although minor bleed and that too in few patients but could have caused vision threatening damage to the eye. Minor complications were also seen with peribulbar but less than subtenon’s anaesthesia [Table 5].

3) Patients who received topical anaesthesia were very few but still topical proved to be an excellent local anaesthesia technique with very few complications, off course no akinesia at all, and with intracameral xylocaine analgesia part was also improved.

4) Minor orbital complications although the incidence was high, did not have any vision threatening effect on any of our patients.

5) Major orbital complications with very low incidence did not produce any vision threatening effect in any of our patients but could have proved dangerous and could have caused loss of vision.

**Conclusion**

The properties of an ideal eye block technique includes globe analgesia, akinesia, absence of pain during administration, minimal injectate volume and absence of serious complications[15]. None of the blocking technique proved the above criteria. The sharp needle technique peribulbar block was associated with major complications which could have threatened vision while as subtenon’s block and topical anaesthesia resulting in only minor complications. In present scenario where safety and early visual rehabilitation is demanded by the patient and where the incision size is decreasing day by day. The surgeon should also shift from sharp needle peribulbar technique to subtenon’s and topical anaesthesia because these two techniques are safer.

**Table 1: Age (year) and Gender Distribution of the Patients**

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>4</td>
<td>5</td>
<td>1.2</td>
</tr>
<tr>
<td>40-49</td>
<td>34</td>
<td>16</td>
<td>4.0</td>
</tr>
<tr>
<td>50-59</td>
<td>115</td>
<td>138</td>
<td>34.1</td>
</tr>
<tr>
<td>60-69</td>
<td>301</td>
<td>239</td>
<td>59.0</td>
</tr>
<tr>
<td>≥70</td>
<td>4</td>
<td>7</td>
<td>1.7</td>
</tr>
<tr>
<td>Total</td>
<td>448</td>
<td>405</td>
<td>47.5</td>
</tr>
</tbody>
</table>

**Table 2: Diagnosis in Studied Patients**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>f</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract</td>
<td>780</td>
<td>91.4</td>
</tr>
<tr>
<td>POAG</td>
<td>42</td>
<td>4.9</td>
</tr>
<tr>
<td>Others</td>
<td>31</td>
<td>3.7</td>
</tr>
<tr>
<td>Total</td>
<td>853</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 3: Type of Local Anaesthesia given to Patients**

<table>
<thead>
<tr>
<th>Anaesthesia</th>
<th>f</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peribulbar</td>
<td>705</td>
<td>82.5</td>
</tr>
<tr>
<td>Subtenon</td>
<td>96</td>
<td>11.3</td>
</tr>
<tr>
<td>Topical</td>
<td>44</td>
<td>5.2</td>
</tr>
<tr>
<td>Topical with Intra-cameral Xylocaine</td>
<td>8</td>
<td>1.0</td>
</tr>
<tr>
<td>Total</td>
<td>853</td>
<td>100.0</td>
</tr>
</tbody>
</table>

POAG = Primary open angle glaucoma
**Table 4: Type of local anaesthesia with respect to operative procedure of the patients**

<table>
<thead>
<tr>
<th>Operative procedure</th>
<th>Peribulbar</th>
<th>Subtenon</th>
<th>Topical</th>
<th>Topical with Intra-camer al Xylocaine</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>f</td>
<td>%</td>
<td>f</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Phaco</td>
<td>348</td>
<td>49.4</td>
<td>56</td>
<td>58.3</td>
<td></td>
</tr>
<tr>
<td>SICS</td>
<td>202</td>
<td>28.7</td>
<td>35</td>
<td>36.5</td>
<td></td>
</tr>
<tr>
<td>ECCE</td>
<td>105</td>
<td>14.9</td>
<td>0</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>TRAB</td>
<td>33</td>
<td>4.7</td>
<td>2</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>17</td>
<td>2.4</td>
<td>3</td>
<td>3.1</td>
<td></td>
</tr>
</tbody>
</table>

\( \chi^2 = 119.2, \ p = 0.000 \)

**Table 5: Complications as per Type of Local Anaesthesia**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Peribulbar</th>
<th>Subtenon</th>
<th>Topical</th>
<th>Topical with Intra-camer al Xylocaine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>f</td>
<td>%</td>
<td>f</td>
<td>%</td>
<td>f</td>
</tr>
<tr>
<td>Inadequate Analgesia</td>
<td>27</td>
<td>3.8</td>
<td>14</td>
<td>14.6</td>
<td>10</td>
</tr>
<tr>
<td>Inadequate Akinesia</td>
<td>82</td>
<td>11.6</td>
<td>91</td>
<td>94.8</td>
<td>44</td>
</tr>
<tr>
<td>Subconjunctival Haemorrhage</td>
<td>25</td>
<td>3.5</td>
<td>57</td>
<td>59.4</td>
<td>0</td>
</tr>
<tr>
<td>Conjunctival Cemosis</td>
<td>253</td>
<td>35.9</td>
<td>55</td>
<td>57.8</td>
<td>0</td>
</tr>
<tr>
<td>Retrobulbar Haemorrhage</td>
<td>4</td>
<td>0.56</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Globe perforation</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Optic Nerve Injury</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Brain Stem Anesthesia</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
</tbody>
</table>

**References**

2. Tom EKe, John R Thompson. Serious complications of local anaesthesia for cataract surgery: one year National Survey in United Kingdom. BJO 2007; 91: 470-475
Mutation screening of α-crystallin mutations in congenital cataract patients

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2. Dr. Rajendra Prasad Centre for Ophthalmic Sciences, AIIMS, New Delhi

Purpose: To screen α-crystallin (CRYAA) gene in congenital cataract patients and controls.

Methods: Fifty clinically diagnosed congenital cataract cases below 3 years of age from northern India, presenting at Dr. R. P. Centre for Ophthalmic Sciences (AIIMS, New Delhi, India) were enrolled in this study. Genomic DNA was extracted from peripheral blood, all coding and exon/intron regions were amplified using PCR and direct sequencing was performed to detect any nucleotide variation.

Results: The mean age of the patients was 1.75±0.19 years. The age of onset was recorded as the age at which the disease was first noticed by the child’s parents or first documented by a clinician. All cases were sporadic and 32 were males and 18 were females. None of the cases were product of consanguineous marriage and all patients had bilateral lens opacification. The degree of opacification showed variability among patients as 58% (29/50) of patients had nuclear cataract, 28% (14/50) with lamellar/zonular cataract and 8% (4/50) had anterior polar cataract and 6% (2/50) had total cataract.

Conclusion: This study shows that the pathogenesis of the majority of congenital cataract cases in North India seems not to be accounted for mutations by the coding exons of α-crystallins. It is also possible that currently unidentified genes may be a more significant cause of cataract than previously thought. Based on this study CRYAA has no role in congenital cataract in north Indian population.

INTRODUCTION:

Cataract is an opacification of the lens resulting from alterations in lens cellular architecture or in lens proteins or both. Cataracts are an important and treatable cause of visual impairment in infancy. Congenital cataract is a clinically and genetically heterogeneous lens disease responsible for visual impairment and blindness during childhood [Scott MH et al., 1994; Hejtmancik JF, 1998]. Its prevalence is up to 6 in 10,000 live births, causing about 10% of childhood blindness worldwide [Reddy MA et al., 2004]. It is estimated that globally, 20 million children under the age of 16 years suffer from cataract, and among these, 200,000 (15%) are severely visually impaired or blind [Johnson GJ, 2003; Foster A et al., 1997]. Pediatric cataracts are responsible for 7.4% to 15.3% of childhood blindness in developing countries like India [Bhattacharjee H et al., 2008; Titiyal JS et al., 2003; Dandona L et al., 1998]. The population of India in 2001 was estimated to be 1.03 billion, approximately 420 million of whom are children under 16 years of age (40.9%). Overall, there are probably 280 000-320 000 blind children in India [Census of India 2001]. Cataract is responsible for about 12% of childhood blindness in India [Bhattacharjee H et al., 2008; Santihya ST et al., 2010].

Currently there are over 22 loci which have been associated with mutations in specific genes [Hejtmancik JF, 2008; Shiels A et al., 2010; Graw J, 2010] including encoding ten crystallins genes: alpha A gene [CRYAA], alpha B gene [CRYAB], beta A1 gene [CRYBA1], beta A4 gene [CRYBA4], beta B1 gene [CRYBB1], beta B2 gene [CRYBB2], beta B3 gene [CRYBB3], gamma C gene [CRYGC], gamma D gene [CRYGD], gamma S gene [CRYGS] [Berry V et al., 2001; Xu J et al., 2010; Zhou G et al., 2010; Billingsley G et al., 2006; Riazuddin SA et al., 2005; Sun H et al., 2005], two cytoskeletal protein genes: beaded filament structural protein 1, filensin gene [BFSP1], beaded filament structural protein 2, phakinin gene [BFSP2] [Song S et al., 2009], four membrane protein genes: gap junction protein (alpha 3 gene, GJA3), gap junction protein (alpha 8 gene, GJA8), major intrinsic protein of lens fiber gene (MIP) and lens intrinsic membrane protein 2 gene (LIM2) [Zhou Z et al., 2010; Berry V et al., 2000; Pras E et al., 2002], three growth and transcription factor genes: heat shock transcription factor 4 gene [HSF4], paired-like homeodomain 3 gene [PITX3], Maf-like protein gene [MAF] [Shi X et al., 2009; Wang KJ et al., 2010] and chromatin modifying protein-4B gene (CHMP4B), Ephrin receptor EphA2 (EPHA2), Nance-Horan syndrome gene (NHS) [Wang KJ et al., 2010].

Crystallins are the major cytoplasmic proteins of the lens and their stability and appropriate interactions are critical for lens transparency. Crystallin genes encode more than 95% of the water soluble structural proteins and their encoded proteins account for more than 30% of its mass. In the mature human lens, α-crystallin makes up roughly 40%, β-crystallin 35%, and γ-crystallin 25% of the total crystallin protein [Wistow GJ et al., 1988] and are good candidate genes for screening in congenital cataract patients. α-crystallin is essential for lens
transparency and accounts for nearly 50% of the protein mass in human lens. αA-crystallin/HSPB4 is a member of the small heat shock protein family, which also includes αB-crystallin/ HSPB5 and Hsp27/HSPB1.

The binding of αA and αB-crystallin to misfolded proteins occurs with a high efficiency however, once all the α-crystallin in lens fiber cells has been depleted, the concentration of irreversibly denatured proteins could increase, resulting in cataract. Congenital cataract is the most important treatable cause of pediatric blindness in developing countries like India. To detect relative contribution of mutations in the αA-crystallin genes to congenital cataracts in the north Indian population, a systematic screening of the αA-crystallin gene was performed in 50 cases of congenital cataract patients.

MATERIALS AND METHODS:
Clinical examination and selection of cases:
After receiving ethical approval from the institutional review board (IRB#00006862; All India Institute of Medical Sciences, Delhi, India), 30 clinically diagnosed consecutive congenital cataract cases below 3 years of age from northern India, presenting at the Dr. R. P. Centre for Ophthalmic Sciences (AIIMS, New Delhi, India) were enrolled in this study. These congenital cataract cases had no other ocular or systemic abnormalities. Detailed history was taken from parents regarding high fever, TORCHES [(Toxoplasma gondii (T. gondii), Rubella virus (RV), Cytomegalovirus (CMV), Herpes simplex virus (HSV) and Syphilis (caused by Treponema pallidum)] infection, Tuberculosis, exposure to radiation and drug intake during gestation period. Tests like serum biochemistry for levels of blood glucose, calcium and phosphorous evaluations, RBC transferase and galactokinase levels and urine test for reducing sugars (galactosemia) and for amino acids (Lowe syndrome). Cases with known cause of congenital cataract were excluded from the study. Affected status was determined by a history of cataract extraction or ophthalmologic examination. A total of 30 ethnically and age-matched normal individuals without any history of ocular or systemic disorders were enrolled as controls. They had no metabolic, genetic, or ocular disorder on examination by ophthalmologist and an extensive history was taken regarding family, occupation of parents, any medical problem and drug intake by parents. Informed consent in accordance with the Declaration of Helsinki was obtained from all participants or their parents and controls.

DNA Isolation: Genomic DNA is isolated from peripheral blood samples. 2-3 ml of heparinized blood sample is collected from each case and centrifuged at 3000 rpm at 15-20°C for 15 minutes in a 50ml conning centrifuge tube. Plasma is discarded and the cell pellet is disrupted gently by tapping. To the cell pellet, 3 times the volume of Red Cell Lysis Buffer (RCLB) is added. For the frozen samples, the samples are thawed and 3 volumes of RCLB is added. After mixing gently, the suspension is centrifuged at 3000 rpm at 10-15°C for 15 minutes. The process is repeated until a white pellet is obtained (usually 2-3 times). The cells are then washed with Phosphate Buffer Saline (PBS) and one volume of packed cells is mixed with 10 volumes of proteinase K solution. The suspension was initially incubated at 65°C for 15-20 minutes then incubated overnight at 37°C. The next day, equal volume of solution containing phenol:chloroform:isoamylalcohol (25:24:1) is added to the sample and mixed gently for 10 minutes. After keeping the sample at room temperature for 5 minutes, it is centrifuged at 12,000 g for 15 minutes at 10°C. The upper aqueous phase is transferred to a fresh tube using a wide-open mouth pipette. This procedure is repeated till clear aqueous solution is obtained (2-3 times). Equal volume of chloroform:isoamylalcohol (24:1) are added to the sample and mixed gently for 10 minutes. The sample are kept at room temperature for 5 minutes and centrifuged at 12,000 g at 4°C for 15 minute. The upper aqueous phase is transferred to a fresh tube and the procedure is repeated again. To the aqueous phase, 1/10th the volume of 3M sodium acetate and 2.5 volume of cold ethanol are added and mixed gently to precipitate the DNA. After keeping the sample at -20°C for 2 hours to overnight, it is centrifuged at 12,000 g for 15 minutes at 4°C to pellet the precipitated DNA. The pellet is washed with 70% ice cold ethanol and air dried. The DNA pellet is then dissolved in 100-250ul of autoclaved deionized water depending on the yield of DNA and incubated at 37°C for overnight to dissolve the DNA completely. DNA samples are stored at -20°C till further use.

PCR amplification & sequence analysis:
The exon-intron region of the CRYAA were amplified in congenital cataract patients and controls. PCR amplifications for all primer sets were performed in a 40μl volume containing 1.0μl of 20M stock solution for each primer (Eurofins Genomics India Pvt Ltd, Bangalore, India), 100ng of genomic DNA, 1 unit of Taq polymerase (Banglore Genei, Bengaluru, Karnataka, India), 0.1mM of each deoxynucleotide triphosphate (dNTP), and 4μl of 10X PCR buffer (with 15M MgCl2). Amplified PCR products were purified using a gel/PCR DNA fragments extraction kit (Geneaid Biotech Ltd., Sijih City, Taiwan). Purified PCR products were sent for sequencing to Molecular Cloning Laboratories (South San Francisco, CA). All fragments were sequenced in both forward and reverse directions for confirmation of any nucleotide variation in congenital cataract patients and controls and compared to the Human Genome Reference Sequence (NC_000002.11) provided by the National Center for Biotechnology Information (NCBI), using ClustalW2 (multiple sequence alignment program for DNA; European Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK).

Statistical analysis:
The correlation coefficient between parameters like Degree of opacification, morphology of congenital cataract, visual acuity were calculated by spearman’s test. p-value less than 0.05 is considered as significant. Statistical analyses were performed using graphpad software (CA, USA).

RESULTS:
Clinical findings: A total of 50 congenital cataract patients below 3 years of age were enrolled in this study. The mean age of the patients was 1.75±0.19 years. The age of onset was recorded as the age at which the disease was first noticed by the child’s parents or first documented by a clinician. All cases were sporadic and 32 were males and 18 were females. None
Mutation screening of α-crystallin mutations in congenital cataract patients

Chaperone activity and/or an increased tendency of the mutant from various insults [Santhiya T et al., 2006]. Either loss of maintains the integrity of lens fiber cells and their homeostasis acts as a molecular chaperone and is thereby stabilizing, and striking sequence similarity to small heat-shock proteins. It notype. Of the three crystallins, the αA-crystallin shows a concentration, stability, and supramolecular organization [Graw J, 1999]. There are several genes coding for structural proteins; α-crystallin is essential for lens transparency and accounts for nearly 50% of the protein mass in human lenses. It is a large multimeric complex with an aggregate molecular mass of 500,000–1,200,000 Da [Bloemendal H et al., 2004]. Functional changes and alteration of crystallin molecular properties could cause the breakdown of the lens microstructure and result in changes in the refractive index and increased light scattering.

In a study from south India CRYAA was the gene most commonly (5%) involved with causative mutations in congenital cataract [Devi RR et al., 2008]. Direct sequencing of the amplified fragments of CRYAA in congenital cataract patients and controls identified no nucleotide alterations. Congenital cataract is both clinically and genetically highly heterogeneous. Till date more than 40 loci in human genome have been mapped to be associated with various forms of congenital cataract. αA-crystallin is almost exclusively expressed in the eye lens and serves in mixed complexes with αB-crystallin to maintain lens transparency. The transparency and high refractive index of the lens are achieved by the precise architecture of the fiber cells and the homeostasis of the lens proteins in terms of their concentration, stability, and supramolecular organization [Graw J, 1999]. There are several genes coding for structural proteins; in particular, the crystallins have been demonstrated to be involved in cataractogenesis in human as well as in model organisms like the mouse. Most of these genes are expressed predominantly in the lens, and a mutation in any one of these genes would be a reasonable explanation for the cataract phenotype. Of the three crystallins, the αA-crystallin shows a striking sequence similarity to small heat-shock proteins. It acts as a molecular chaperone and is thereby stabilizing, and maintains the integrity of lens fiber cells and their homeostasis from various insults [Santhiya T et al., 2006]. Either loss of chaperone activity and/or an increased tendency of the mutant α-crystallin to form aggregates by virtue of altered positive charge and gain of sulfhydryl group has been speculated towards molecular pathogenesis [Litt M et al., 1998]. This study shows that the pathogenesis of the majority of congenital cataract cases in North India seems not to be accounted for mutations by the coding exons of α-crystallins. A previous Australian study involving systematic screening for mutation in five crystallin genes (CRYAA, CRYBA1, CRYBB2, CRYGC, and CRYGD) in 38 pedigrees has reported only two mutations (CRYBA1-IVS3+1G>A and CRYGD-P23T). Given that studies on independent populations describe a low frequency of crystallin mutations, perhaps the dominance of crystallins in the literature is not a reflection of the true distribution of cataract genes, but rather it represents the attractiveness of the crystallins as candidate genes for screening studies. However the possibility cannot be excluded that mutations in one of the other reported candidate genes such as membrane intrinsic proteins (MIP and LIM2), intermediate filament protein (BFSP2), transcription factors (MAF, PITX3, and HSF4), and glucosaminyl (N-acetyl) transferase 2, 1-branching enzyme (GCNT2) may be the major cause of hereditary cataract in India. Alternatively, it is possible that currently unidentified genes may be a more significant cause of cataract than previously thought. Based on this study CRYAA has no role in congenital cataract in north Indian population.

![Figure 1](image)

**Figure 1:** a) Nuclear cataract: The eye picture shows opacity of both lenses in one of the patient. b) Zonular/lamellar cataract: The zonular/lamellar cataract in one of the patient. c) Polar Cataract: Anterior polar cataract phenotype shown by one of the patient. d) Total Cataract: total cataract phenotype found in one patient.

**Table 1:** Summary of the different cataract phenotypes detected in congenital cataract patients.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Cataract Phenotype</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nuclear cataract</td>
<td>58% (29/50)</td>
</tr>
<tr>
<td>2</td>
<td>Lamellar/Zonular cataract</td>
<td>28% (14/50)</td>
</tr>
<tr>
<td>3</td>
<td>Anterior polar cataract</td>
<td>8% (4/50)</td>
</tr>
<tr>
<td>4</td>
<td>Total cataract</td>
<td>6% (2/30)</td>
</tr>
</tbody>
</table>
References:


Importance of LVAs in Blind Schools

Abhishek Purohit, Namrata Gaikwad, Ulka Srivastava, Pushpa Varma
1. Mahesh Drishtieen Kalyan Sangh, (Mahesh Blind Welfare Association)
2. Hallen Kellar Blind School, Prakash Nagar; Indore.
3. Deaf Dumb and Blind School, Jeevandeep Colony; Indore
4. Mahesh Drishtieen Kalyan Sangh, Kila Maidan, Indore

Low Vision Aids (LVAs) are optical devices that improve residual vision by magnifying the image of an object formed at retina.

The principle aim of our study was to identify the number of children with useful residual vision in blind schools of Indore and assess their need for LVAs. 152(100%) children (5-25yrs) of 4 blind schools of Indore were enrolled in this cross sectional study, of which 96(63.16%) children with useful residual vision were refracted & analyzed.

A detailed ophthalmic evaluation included complete history and thorough ocular examination was done. Children with VA greater than light perception who had useful residual vision were assessed with hand held fixed focus telescopes for distance while magnifying spectacles, hand held magnifiers and telescopic lenses for near.

After best correction, 89(58.55%) children were found to be blind (3/60 to PL+) and 7(4.60%) had severe visual impairment (6/60 to 3/60). For distance, 8(5.26%) children showed an improvement in visual acuity with spectacles and 10(6.57%) improved with fixed focus hand held telescope.

For near vision, 13(8.55%) children improved with magnifying spectacles in half eye frame, 4(2.63%) with telescopic magnifiers and another 13(8.55%) accepted magnifying hand held lenses.

Importance of LVAs in Blind Schools

Thus, our study emphasizes on the need for ophthalmic evaluation, refraction & assessment for LVAs & spectacles in children with useful residual vision in blind schools and periodic review thereafter.

Introduction

Visual impairment during childhood whether total or partial has a great impact on development, education, future work opportunities and quality of life.

Low Vision Aids can be defined as optical or non-optical appliances and devices designed to assist the partially sighted patient.

In order to identify and assess children with low vision through our work, we aimed at identifying number of children with useful residual vision in blind schools of Indore and assessed their need for spectacles and magnifiers as low vision devices.

Materials & Methods

This was a cross sectional study conducted in the Upgraded Department of Ophthalmology, Mahatma Gandhi Memorial Medical College(MGMMC) & Maharaja Yashwantrao Hospital(MYH), Indore from the month of July 2009 to June 2010.

Data collection:

152(100%) children (in the age group of 5-25 yrs) of 4 blind schools of Indore were enrolled in this study, of which 96(63.16%) children with useful residual vision were refracted and analyzed. “WHO guidelines of Prevention of Importance of LVAs in Blind Schools

Blindness (PBL) eye examination record for children with blindness and low vision” were used for evaluation.

A complete history with thorough ocular examination including anterior segment examination by torch and slit lamp biomicroscope, fundus examination by direct and indirect ophthalmoscope and Intra ocular pressure (IOP) measurement were performed to determine the causes of visual impairment. Distant visual acuity was assessed with directional Snellen’s E chart and categorized into WHO categories of blindness.

Near vision was assessed by the Keeler “A” series word – chart.

Children with visual acuity less than 6/18 to perception of light in the better eye, underwent test for assessment of useful residual vision.

Refraction was performed under cycloplegia in children with useful residual vision. Post mydriatic assessment for spectacles was performed after one week.

Children with visual acuity greater than light perception and who had useful residual vision were assessed with spectacles and hand held fixed focus telescopes for distance while we used magnifying spectacles, hand held magnifiers and telescopic lenses for near.

Importance of LVAs in Blind Schools

Results

In this prospective cross-sectional clinical study conducted in the Upgraded Department of Ophthalmology from July 2009 to June 2010, 152(100%) children (5-25yrs) of four blind schools of Indore were enrolled of which 96(63.16%) children with useful residual vision were refracted and analyzed. After best correction, 89(58.55%) children were found to
blind [3/60 to (Perception of light)] PL + ve] and 7 (4.60%) had severe visual impairment (6/60 to 3/60). Out of these 96 (63.16%) children 8 (5.26%) showed an improvement in distant visual acuity with spectacles while 10 (6.57%) had improvement in vision for distance with fixed focus hand held telescope.

For near vision 13 (8.55%) children improved by magnifying spectacles in half eye frame. Amongst these 13 (8.55%), 10 (6.57%) children improved with spectacles of +5 (Diopeter) D sphere with +5 D prisms, and 3 (1.97%) children with that of 10 D sphere. In all of them visual acuity improved by 2 lines on Keeler’s A series chart. Another 13 (8.55%) children accepted magnifying hand held lenses for near and 4 (2.63%) improved with telescopic magnifiers for near.

Remaining 48 (31.57%) children did not show any visual improvement.

Importance of LV As in Blind Schools

Discussion

Low vision patients can utilize their residual vision and possibly relearn to use lost functional vision which often restores the ability to perform daily task like reading & working. In this study the Snellen’s distance visual acuity chart was used instead of log MAR visual acuity, which has been found to exaggerate the visual loss.

In our study the commonest cause of visual impairment was microphthalmos with iridofundal coloboma with nystagmus (46, 30.26%).

According to anatomical sites of major causative pathology, a study conducted in Nepal showed corneal scarring/physical (35.79%), retinal disorders (20%), abnormalities of whole globe (13%), disorders of lens (12.63%) and lesions of uvea (1.4%) as common causes of low vision. (1). Our study is not in accordance to the above study. It shows involvement of retina (34.22.36%), uvea (31.20.39%), optic nerve (15.9.86%), lens (14.9.21%) and cornea (12.7.89%) leading to low vision. A study of the need for low vision services in blind school children in East Africa showed that 63.9% children had functional low vision. (2). Our study shows 96 (63.15%) children from blind schools having useful residual vision, which is nearly similar to the above study.

Importance of LVAs in Blind Schools

A study done for children in blind schools in north India showed that 35.5% children were prescribed spectacles and 22.6% were prescribed magnifiers for near vision. Other study conducted in 291 blind school children in Andhra Pradesh where 31.6% children with functional low vision improved with spectacles and 14% with low vision aids. (3).

In our study 48 (31.57%) children improved with refraction and low vision aids, amongst them 8 (5.26%) were prescribed spectacles and 40 (26.31%) children improved with low vision aids. It is to some extent similar to the above studies.

In our study maximum children accepted magnifying spectacles for near which are economical, easily available and cosmetically acceptable.

Remaining 48 (31.57%) children did not show any visual improvement.

Thus, our study reflects that rather than labelling these children as “Blind” we should emphasise on effective use of LVAs along with proper support, training, follow-up and maintenance guidelines in blind schools, so that many children can be re-educated as “Sighted”.

Limitation

Small sample size was the principle limitation of our study.

Table : Type of LVAs accepted by the children of useful residual vision (total 96)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Type of optical device</th>
<th>Number of students</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Fixed focus hand held telescope for distance</td>
<td>10</td>
<td>6.57%</td>
</tr>
<tr>
<td>2.</td>
<td>Magnifying spectacles in half eye frame for near</td>
<td>13</td>
<td>8.55%</td>
</tr>
<tr>
<td>3.</td>
<td>Telescopic magnifiers for near</td>
<td>04</td>
<td>2.63%</td>
</tr>
<tr>
<td>4.</td>
<td>Magnifying hand held lenses for near</td>
<td>13</td>
<td>8.55%</td>
</tr>
</tbody>
</table>

Bar chart- Type of LVAs accepted by the children of useful residual vision (total 96)

References

Introduction:
Glaucoma is the one of the most common cause of blindness worldwide. Primary congenital glaucoma (PCG; OMIM 231300) a severe form of glaucoma manifests at birth/early childhood with symptoms like presence of buphthalmos, elevated intra-ocular pressure (IOP), photophobia (hypersensitivity to light) and blepharospasm. In India its prevalence is 1 in 3300 (in Andhra Pradesh). It accounts for 4.2% of all childhood blindness. The underlying genetic mechanism is still unknown as the disease shows marked genetic heterogeneity. Genetic heterogeneity is the hallmark of PCG and three chromosomal loci on 2p21 (GLC3A; OMIM 231300), 1p36 (GLC3B; OMIM 600975), and 14q24.3 (GLC3C; Stoilov, et al. IOVS 2002;43:ARVO E-Abstract 3015) have been mapped by linkage analysis, of which only the GLC3A locus harboring the human Cytochrome P450 gene (CYP1B1; OMIM 601771) has been characterized. CYP1B1 exhibits a high degree of allelic heterogeneity and more than 79 different mutations causal to PCG have been identified. Mutations in the cytochrome P450 (CYP1B1) gene are the most prevalent cause of congenital glaucoma in different populations. This study aimed to correlate disease phenotype with genotype (CYP1B1 mutation status).

Material and Methods:
After ethical approval of the Institutional Review Board (IRB00006862; All India Institute of Medical Sciences, New Delhi, India) primary congenital glaucoma cases (n=75) presenting at the Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India, were enrolled for this study. Of these patients, 23 were female and 52 were male cases. Mean age of onset of disease ranged from birth to 3 years. Seventy five ethnically

Purpose: Mutations in cytochrome P4501B1 (CYP1B1) gene are a predominant cause of congenital glaucoma (PCG). We have planned this study to identify CYP1B1 gene mutations in PCG patients.

Methods: After ethical clearance a total of seventy five unrelated PCG patients and 75 healthy controls were enrolled in the study. CYP1B1 gene was screened for mutations by polymerase chain reaction and DNA sequencing.

Results: A total of 32/75 (42.66%; 13 with homozygous mutations, 8 with compound heterozygous and 11 with heterozygous mutations) patients were positive for heterozygous/homozygous CYP1B1 mutations (Table 1). Furthermore, six already reported single nucleotide polymorphisms were also identified in the less conserved region of CYP1B1 both in controls and patients in addition to pathogenic CYP1B1 mutations. A total of 21 sequence changes in CYP1B1 gene were identified in this study. We observed higher mean IOP and corneal diameter in mutation positive cases as compared to mutation negative cases. This is in accordance with the idea of associating the severe phenotype with defective CYP1B1 allele. Mutation positive cases had poor prognosis as they may require multiple surgeries and have poor visual outcome as compared to mutation negative cases (usually underwent surgery once and had good visual outcome).

Conclusion: The information derived from this study has both basic and clinical relevance. Thus mutation analysis is an essential pre-requisite in diagnosis workup in PCG and in future can be used as diagnostic/prognostic marker for detection and charting the path for analysis of the disease progression. This may help in adopting most appropriate therapy (medical and surgical) and also providing comprehensive genetic counseling to at risk families.
matched normal individuals without any ocular/systemic disorders were enrolled as controls.
Peripheral blood samples were collected from patients and controls by venipuncture after informed consent. Blood samples for DNA were collected in EDTA vacutainer and stored in -80C until further use.

**Mutation Screening and Sequence analysis:**
Genomic DNA was isolated from the peripheral blood by Phenol chloroform method. The entire coding region including exon-intron boundaries of CYP1B1 gene from the peripheral blood and controls was amplified and screened for mutations by using three sets of overlapping primers (Table 1).5,9 The primers used were set I (1F-1R, 786 bp) 10, set II (2F-2R, 787 bp)11, and set III (3F-3R, 885 bp)11. Conditions for sets I and II were as reported earlier11 while conditions for set III were initial denaturation at 94°C for 3 min followed by 30 cycles each at 94°C for 30 s, 60°C for 30 s, and 72°C for 1 min. Amplified PCR products were purified using gel/PCR DNA fragments extraction kit (Geneaid Biotech Ltd., Sijhih City, Taiwan. Cat no DF100). Purified PCR product were sent for sequencing at MCLAB (Molecular Cloning Laboratories) South San Francisco, CA 94080, U.S.A. (http://www.melab.com/product.php?productid=19071). DNA sequences were analyzed against CYP1B1 reference sequence ENSG00000138061 (available at http://may2009.archive.ensembl.org/Homo_sapiens/Gene/Summary?g=ENSG00000138061) using ClustalW2 (multiple sequence alignment program for DNA available at http://www.ebi.ac.uk/Tools/clustalw2/index.html).

**Statistical Analysis:**
The correlation of mutation status (patients) with age of onset, buphthalmos, IOP, corneal edema, Haab’s striae of eye was analyzed using one way ANalysis Of Variance (ANOVA), a statistical tool and an appropriate Post-Hoc tool (Bonferroni correction). p-value <0.05 was taken as significant. Correlation between different clinical parameters was analyzed using Pearson Correlation.

**Results:**
PCR-DNA sequencing revealed that 32/75 (42.66%; 13 with homozygous mutations, 8 with compound heterozygous and 11 with heterozygous mutations) patients were positive for heterozygous/homozygous CYP1B1 mutations (Table 1). Furthermore, six already reported single nucleotide polymorphisms8 were also identified in the less conserved region of CYP1B1 both in controls and patients in addition to pathogenic CYP1B1 mutations. These polymorphisms were rs2617266, p.R48G (rs10012), p.A119S (rs1056827), p.L432V (rs1056836), p.D449D (rs1056837) and p.N453S (rs1800440) were also revealed by DNA sequencing. A total of 21 nucleotide variations (SNPs + other mutations) were identified (Table 2).

Clinical phenotypes of the cases with pathogenic CYP1B1 mutations were more severe as compared to mutation negative cases (Table 1). Normal range of IOP in a newborn is between 10-20 mmHg with a corneal diameter <12 mm. A significant correlation (p = 0.003) was observed between mean IOP (29.05± 5.9 mmHg) of cases with pathogenic CYP1B1 mutations as compared to mean IOP (23.90 ± 5.7 mmHg) in mutation negative cases. A significant correlation (p = 0.003) was also observed between mean corneal diameter (13.91±1.2 mm) in patients with CYP1B1 mutations as compared to (12.83±1.1 mm) (Range = 10.7-16.0 mm) in mutation negative cases.

**Discussion:**
We have screened CYP1B1 gene in our patients (n=75). Most common phenotypic feature at the time of presentation in our study was presence of buphthalmos in atleast in one eye. Buphthalmos was followed by photophobia (48%; 36/75) and corneal edema (46.66%; 35/75). In this study majority of patients had parents heterozygous for CYP1B1 mutations but in few cases parents were negative for CYP1B1 mutations. CYP1B1 codes for a 543 amino acid long protein and which expresses in the ocular tissues in anterior chamber of eye, and in non-ocular tissues like kidney and liver (Sutter et al., 1994). It also metabolizes vitamin A in two steps to all-trans-retinal and all-trans-retinoic acid the latter is a potent morphogen and regulates in-utero development of tissue growth and differentiation12-14. Any mutation in this gene can thus cause ocular development defect and result in trabecular dysgenesis which is the main characteristic feature of PCG. Membrane-bound cytochromes such as CYP1B1 have molecular structure containing a transmembrane domain located at the amino terminal end of molecule. This is followed by a proline-rich “hinge” region, which permits flexibility between the membrane-spanning domain and cytoplasmic portion of the protein molecule15. The carboxy-terminal ends are highly conserved among different members of cytochrome P450 super family. They contain a set of conserved core structures (CCS) responsible for the heme-binding region of these molecules. Heme-binding region is essential for the normal function of every P450 molecule.

Mutations in CYP1B1 interfere with the integrity of the CYP1B1 molecule as well as its ability to adopt normal conformation and to bind heme for example - induced mutations in the hinge region have previously been reported to interfere with the heme-binding properties of the cytochrome P450 molecules13,14. CYP1B1 participates in the normal development and functioning of the eye by metabolizing essential molecules13,14. CYP1B1 participates in the normal development and functioning of the eye by metabolizing essential molecules that are probably used in a signaling pathway13. Thus normal development and differentiation of anterior segment is important for normal ocular function and mutations in CYP1B1 result in malformation of anterior chamber structures which dramatically affect visual function by blocking aqueous outflow.

In our study p.R390H is the most common mutation which was found in 16% of patients. This mutation has been reported in other populations16. Mutations at position 390 emerged as a hot spot for mutation in CYP1B1 gene. Mutations p.R390H, p.R390C and p.R390S have been reported from different populations16. Earlier studies have shown that prognosis of patients with p.R390H mutation is poorer than p.R390C mutation. Patients with p. R390H mutation showed little or no improvement in vision as compared to patients with p.R390C

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**Table 1: CYP1B1 Mutations Identified in Our Study**

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Frequency</th>
<th>Associated Phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>p.R390H</td>
<td>12/75 (16%)</td>
<td>Severe</td>
</tr>
<tr>
<td>p.R390C</td>
<td>1/75 (1.33%)</td>
<td>Warning</td>
</tr>
<tr>
<td>p.R390S</td>
<td>1/75 (1.33%)</td>
<td>Severe</td>
</tr>
<tr>
<td>p.R390H</td>
<td>12/75 (16%)</td>
<td>Severe</td>
</tr>
<tr>
<td>p.R390C</td>
<td>1/75 (1.33%)</td>
<td>Warning</td>
</tr>
<tr>
<td>p.R390S</td>
<td>1/75 (1.33%)</td>
<td>Severe</td>
</tr>
</tbody>
</table>

**Table 2: Clinical Phenotypes**

<table>
<thead>
<tr>
<th>Clinical Phenotype</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buphthalmos</td>
<td>36/75 (48%)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>75/75 (100%)</td>
</tr>
<tr>
<td>Corneal Edema</td>
<td>35/75 (46.66%)</td>
</tr>
</tbody>
</table>
Genotype-phenotype correlation: Clinical implications of CYP1B1 analysis in primary congenital glaucoma

Delhi Journal of Ophthalmology

Genotype and phenotype correlation: Clinical implications of CYP1B1 analysis in primary congenital glaucoma. Patients homozygous for p.R368H mutation had no light perception while one patient heterozygous for p.R368H mutation showed little improvement in vision following surgery.

Five patients were heterozygous for p.E229K mutation in our study. Similar observations of p.E229K mutation were reported by Panicker et al.8 In our study, 12% cases (9/75) showed Ter@223 mutation. This mutation has been reported previously from Southern India [8]. Earlier studies showed a very severe phenotype and poor prognosis with Ter@223 mutation. In this study one patient (PCG017) was homozygous for the mutation and two (PCG 034, 041) were compound heterozygotes for the Ter@223 and R390H mutation and one patient (PCG039) was a compound heterozygote for Ter@223 and R368H mutation. Five patients (PCG019, 021,029,040,044) were heterozygous for Ter@223 mutation. Congenital glaucoma is known to be autosomal recessive disorder and hence it is difficult to explain the disease pathogenesis in these five patients. Variants in Myocilin and forkhead box protein C1 (FOXC1) have been detected in PCG indicating higher complexity in the pathogenesis of this disease17,18. We have already screened these cases for mutations in MYOC. These cases did not harbor any mutations in myocilin gene. It is possible that these cases harbor some mutations at some other unidentified locus/loci.

Twenty seven patients with CYP1B1 mutation had p.L432V polymorphism and it has been reported that CYP1B1 protein with Valine at position 432 generates more free radicals and causes oxidative damage to retinal pigment epithelial cells19. Five patients (PCG 019, 0021,029, 040, 044) heterozygous for Ter@223 mutation also had p.L432V polymorphism which is associated with elevated ROS production19. It is possible that in these cases one truncated CYP1B1 protein is produced which is a functionally null protein and second allele is producing a protein which generates high ROS levels and thus causes oxidative stress induced neural-degeneration. Neural crest cells appear to be a particularly vulnerable cell population and are easily destroyed by compounds such as retinoic acid20. It has also been reported that developing neural crest cells are deficient in glutathione and catalase two important antioxidant enzymes21 that are responsible for scavenging free radicals that damage cells and thus it is possible that developing trabecular meshwork suffers oxidative damage which may be the underlying mechanism for trabecular dysgenesis. Three patients (PCG034, 041 and 039) had Ter@223 (heterozygous) with p.R390H and p.R368H mutations and this combination may produce one non-functional allele and other produces a defective CYP1B1 protein with compromised activity. All patients with Ter@223 (homozygote) and compound heterozygote (Ter@223 with p. R390H/R368H) mutation showed no perception of light even after glaucoma surgery. Little improvement in vision (light perception only) was observed in all five heterozygous cases with ter@223 mutation following glaucoma surgery whereas other patients with homozygous/compound heterozygote CYP1B1 mutations showed no improvement.

An intriguing finding that apparently does not match a typical recessive pattern of inheritance is the presence of heterozygous CYP1B1 mutation in PCG patients in our study. This situation has been previously reported22. Heterozygous p.Y81N mutation has also been described in PCG patients from Germany. Heterozygous p.E229K mutation has been identified in unrelated French and Indian patients23. Few heterozygous CYP1B1 mutations were associated with the milder primary open angle glaucoma (POAG) phenotypes in patients from Spain, France, and India. The presence of heterozygous CYP1B1 mutation in PCG suggests the possibility of other loci yet undetected which may be involved in anterior chamber formation.

Recently the presence of double heterozygote variants, CYP1B1 and FOXC1 have been described in two PCG cases although the role of possible digenic inheritance in disease causation is yet to be established18. Defective variants of modifier genes and/or environmental factors have additive effect with loss-of-function CYP1B1 alleles to produce the disease phenotype. However further work is required to understand this mechanism.

We found no significant differences in onset age and IOP between patients with homozygous CYP1B1 mutations and with compound heterozygous for CYP1B1 mutations. But patients with heterozygous CYP1B1 mutations had good prognosis after surgery as compared to patients with homozygous compound heterozygous for CYP1B1 mutations. In this study males (52/75) were affected more than twice compared to females (23/75). Similar findings were reported in various studies24-28. However, exact reason for this is still unknown.

**Genotype and phenotype correlation:**

Genotype and phenotype correlation based on this study were evident from a comparison of the different mutations associated with varying manifestations and prognosis of the disease. We observed higher mean IOP in mutation positive cases. This is in accordance with the idea of associating the severe phenotype with defective CYP1B1 allele. The percentage of severe phenotypes in at least one eye has been reported to be associated with various mutations ranging from 80 to100% for a frameshift mutation (eg. c.376insA) and truncating mutations5. The percentage of severe phenotypes in at least one eye is 62 to 83% for different mutations such as p.G61E, p.E229K, p.R368H, and p.R390C29. CYP1B1 mutation positive cases had poor prognosis as they may require multiple surgeries and have poor visual outcome as compare to mutation negative cases (usually underwent surgery once and had good visual outcome).

**Conclusion:**

The information derived from this study has both basic and clinical relevance. Thus mutation analysis is an essential prerequisite in diagnosis workup in PCG and in future can be used as diagnostic/prognostic marker for detection and charting the path for analysis of the disease progression. Thus mutation analysis is an essential prerequisite in diagnosis workup in PCG and in future can be used as diagnostic/prognostic marker for detection and charting the path for analysis of the disease progression.
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<td>Ter@223 (h)</td>
<td>Medical and OD 1XTalb/Trab+MMC</td>
</tr>
<tr>
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<td>M</td>
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<td>40</td>
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<td>Hazy media</td>
<td>OU</td>
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<td>5 days</td>
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<td>Ter@223(h)</td>
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<td>1 month</td>
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<td>0.3:1/0.3:1</td>
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<td>Sex</td>
<td>Age at presentation/Sampling</td>
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<td>Buphthalmos</td>
<td>IOP OS</td>
<td>IOP OD</td>
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<td>OU; OD&gt;OS</td>
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<td>Hazy media</td>
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<td>0.7:1/0.7:1</td>
<td>Absent</td>
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<td>Medical and 1X OU Trab/Trab+MMC</td>
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<td>M</td>
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<td>M</td>
<td>8 months</td>
<td>11x11.5/10x11.5</td>
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<td>0.6:1/0.6:1</td>
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<td>0.4:1/0.4:1</td>
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<td>0.7:1/0.7:1</td>
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<td>Absent</td>
<td>0.4:1/0.4:1</td>
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<td>OU; OD&gt;OS</td>
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<td>0.5:1/0.6:1</td>
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<td>45 days</td>
<td>15x15/15x14.5</td>
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<td>18 months</td>
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<td>12.5x13/11x12</td>
<td>OU; OS&gt;OD</td>
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<td>M</td>
<td>8 months</td>
<td>14x14.5/15x15</td>
<td>OU; OS&gt;OD</td>
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<td>R390H (H)</td>
<td>Medical and 1X OU Trab/Trab+MMC</td>
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Table 1: Clinical phenotype and CYP1B1 mutation status of PCG cases

Key: M- male; F- female; H- homozygous; h-heterozygous; X- times; Trab/Trab+MMC- combined trabeculotomy trabeculectomy and mitomycin C treatment; OD-right eye; OS- left eye; OU- both eyes; NA- not available; NT cupping- near total cupping
<table>
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<tr>
<th>S. No.</th>
<th>Genomic location</th>
<th>Nucleotide Change</th>
<th>Codon Change</th>
<th>Type of mutation</th>
<th>Location in protein</th>
<th>Mutation identified</th>
<th>Observational history of mutations in different diseases</th>
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<td>c.71T&gt;G</td>
<td>CTG&gt;CGG</td>
<td>Missense</td>
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<td>p.leu24arg (p.L24R)</td>
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<td>c.142C&gt;G</td>
<td>CGG&gt;GGG</td>
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<td>p.arg48gly (p.R48G)</td>
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<td>GCC&gt;TCC</td>
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<td>TTC&gt;TTA</td>
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<td>GAA&gt;AAA</td>
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<td>p.glu229lys (p.E229K)</td>
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<td>c.835C&gt;G</td>
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<td>390</td>
<td>p.arg390cys (p.R390C)</td>
<td>PCG</td>
</tr>
<tr>
<td>17</td>
<td>g.38151832</td>
<td>c.1169G&gt;A</td>
<td>CGC&gt;CAC</td>
<td>Missense</td>
<td>390</td>
<td>p.arg390his (p.R390H)</td>
<td>PCG, POAG</td>
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<tr>
<td>18</td>
<td>g.38151707</td>
<td>c.1294G&gt;G</td>
<td>CTG&gt;GTG</td>
<td>Missense</td>
<td>432</td>
<td>p.ileu432lys (p.I432V)</td>
<td>PCG, PA</td>
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<tr>
<td>19</td>
<td>g.38151702</td>
<td>c.1299A&gt;A</td>
<td>AAG&gt;AAA</td>
<td>Neutral</td>
<td>433</td>
<td>p.lys433lys (p.K433K)</td>
<td>PCG</td>
</tr>
<tr>
<td>20</td>
<td>g.38151654</td>
<td>c.1347T&gt;C</td>
<td>GAT&gt;GAC</td>
<td>Neutral</td>
<td>449</td>
<td>p.asp449asp (p.D449D)</td>
<td>PCG</td>
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<tr>
<td>21</td>
<td>g.38151643</td>
<td>c.1358G&gt;A</td>
<td>AAC&gt;AGC</td>
<td>Missense</td>
<td>453</td>
<td>p.asp453ser (p.N453S)</td>
<td>PCG</td>
</tr>
</tbody>
</table>

Table 2: Summary of the sequence variants identified in CYP1B1 gene in this study

Footnote: PCG- Primary congenital glaucoma; POAG- Primary open angle glaucoma; PA-Peter's anomaly; FS- frameshift; X- stop codon; NA- not applicable; mutations in bold letters- novel mutations

References:
5. Stoiilov I, Akarsu AN, Sarfarazi M. Identification of three different truncating mutations in cytochrome P4501B1 (CYP1B1) as the principal cause of primary congenital glaucoma (Buphthalmos) in families linked to the GLC3A locus on chromosome 2p21. Hum Mol Genet 1997; 6: 641-47. PMID: 9097971
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