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The genetics associated with Primary Congenital Glaucoma

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Abstract

Glaucoma is a progressive optic neuropathy; increased intraocular pressure (IOP) is a modifiable risk factor for primary congenital glaucoma (PCG). Increase IOP causes retinal and optic nerve compression and leads to gradual and irreversible loss of eyesight if left untreated. It is the second most leading cause of blindness. PCG mainly affects children up to the age of three years, and symptoms include epiphora, photalgia, swollen eyes, opaque corneas, blepharospasm, rupture in the retina and ocular nerve damage due to IOP. Early detection, management, and treatment are the keys to preventing vision loss from glaucoma. Many mutations have been discovered in Cytochrome P450 1B1 (*CYP1B1)* gene to be responsible for causing PCG, and there are still a lot of mutations to be discovered. In this review, we will discuss the genetic aspects of PCG and the most frequent mutations responsible for PCG in Pakistani children. PCG can be handled by decreasing IOP either by medication or by surgery. Genetic counselling plays a significant role in the establishment of proper management of PCG.

Introduction

Glaucoma (pronounced: glawko'me) [1], which is originated from Greek word 'glaukos' (denoting blue-greenish blink) [2] is an accumulation of various diseases associated with optic nerve damage [3] in which huge waste of retinal ganglion cells (RGC) occurs [4,5] and carbon copy shape of visual field and vision is dissipated [6].The main clinical mark of glaucoma is the raise in aqueous humor build up in the anterior chamber [7]. The inheritance is mainly autosomal recessive, while a dominant transmission way has also been illustrated [8]. Glaucoma has casual symptoms and consists of rupture in retina, light susceptibility, eye scrub, and irritation. Increased intraocular pressure causes enlarge, cloudy, and opaque cornea (Fig.1), swollen eyes (Fig.2) and ocular nerve damage [4,9]. Glaucoma is the most critical cause of bilateral blindness around the world. The approximated occurrence of glaucoma is 64.3 million, of whom 8.4 million people are bilaterally blind [10]. This frequency is expected to increase with a shocking rate to 76 million in 2020 and 111.8 million in 2040 [11].

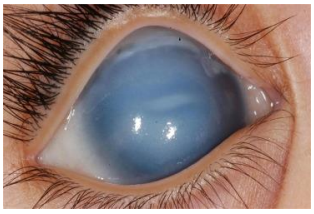

Figure 1: Enlarge and cloudy cornea [12].

Figure 2: Swollen eye [13].

Methods

Literature search and selection criteria:

Different search engines such as PubMed, Google Web, Science Direct, Google Scholar and Research gate were used to retrieve the data for review write up. Glaucoma, *CYP1B1*, PCG, IOP were used as keywords for searching the related data. In this study, 70 peer-reviewed research articles were selected. Manuscripts with other types of glaucoma were excluded to write up this review.

Discussion

Types of Glaucoma:

Commonly, glaucoma has following three subtypes according to the age of infancy, cause of disease, and structure of the anterior chamber, primary open-angle glaucoma (POAG), primary angle-closure glaucoma (PACG) and primary congenital glaucoma (PCG) [14]. The Major form of glaucoma is POAG, holding for 80% of glaucomatous diseases, while PCG is accepted as another critical form of glaucoma in infants, regardless of its low occurrence [14,15].

Primary congenital glaucoma:

Primary congenital glaucoma happens before the age of three years without visible structural error of eye[16]. It is developed by increased intraocular pressure (IOP) [17]. Aqueous fluid produced in the ciliary body is filled in the frontal part of the eye and leaves the optic across trabecular meshwork which is a porous tissue present in the point from where cornea penetrates the iris. Deformity in shape or form of the iridocorneal angle may limit the drain of aqueous humour and ultimately increase IOP,it is a firm cause for the development of glaucoma[18] and constitutes up to 18% of childhood blindness[19,20].At birth, 50% of patients reveal symptoms, and at the age of 1 year 80% of patients are confirmed with PCG; of these, 65% of patients are male and 70% of patients having symptoms of bilateral blindness [21].

Genetics of PCG:

In the early 1990s, the genetic heterogeneity studies for PCG were begun. In 1995 the first locus for PCG on 2p21 chromosomal location was mapped [22]. Loci of five chromosomes, GLC3A (chromosome 2p21), GLC3B (chromosome 1p36.2-p36.1), GLC3C (chromosome 14q24.3), GLC3D (chromosome 14q24.2-q24.3), and GLC3E (chromosome 9p21.2) are directly related with the disease [23]. However, in the development of PCG, only three genes are involved: Cytochrome P450 1B1 (*CYP1B1*) which islocated in the GLC3A locus; Latent Transforming growth factor-beta binding protein 2 *(LTBP2)* situated in the GLC3D; and Tunica interna endothelial cell kinase (*TEK)* is located in the GLC3E. In this disease role of protein encoded by three genes is still uncertain [23-25]. *CYP1B1* or *LTBP2* cause PCG in an autosomal recessive manner. Heterozygous pathogenic variants in *TEK* cause PCG in an autosomal dominant manner [17].

In autosomal recessive inheritance at insemination, each sibling of a diseased parent has a 25% possibility of being affected, 50% possibility of being a non-symptomatic carrier, and 25% possibility of being healthy. Heterozygotes (carriers) show no symptoms; carrier testing of family members is viable if the pathogenic form in the family is recognised [17]. In autosomal dominant inheritance, there is 50% probability in offspring of TEK-related PCG individual to inherit pathogenic form. Early diagnosis of at-risk pregnancy is feasible if mutant variants of PCG are detected in a family [17].

Epidemiology:

In 1842, glaucoma was first reported by Benedict when he discovered glaucoma in two sisters [26]. PCG is more frequent in the Middle East, including Saudi Arabia [27]. PCG is ten times more common in some ethnic groups, where consanguineous relationships, especially cousin-marriages are common [28,29].The incidence of PCG is high in Slovakia and Saudi Arabia, where 1 in 1,250 and 1 in 2500 individuals are affected, respectively [30].PCG

has a variable prevalence in disparate and ethnic groups. The prevalence of PCG in Western countries, like Britain, Ireland and the USA is 1 per 10 to 20,000 live births [3,31-34]. PCG has the lowest incidence in eastern and northern province of Saudi Arabia,11.1% and 9% respectively[35]. The Middle East has 64.8% and the Maghreb has 54.4% of *CYP1B1* mutations. The percentage of these mutations in Europe, Asia and in the United States is 34.7%, 21.3%, and 14.9% respectively. Founder mutations have been discovered in different geographical areas. For example, the most frequently reported variants, p.Arg390His, p.Gly61Glu, p.Val320Leu, p.E387Lys and p.Gly61Glu were observed in Pakistan, Iran/Saudi Arabia, Morocco, Vietnam/South Korea, Europe, and in Lebanon. These discovered variants in seven different countries were quite similar to mutations in *Morocco*. These indications tell us about geographical distribution as well as genetic differences of PCG mainly involve with *CYP1B1* gene variation. In the hereditary screening of patients with PCG, the first step should examine for founder and typical mutations [36]. PCG appears within a few months of life if the family has a high prevalence of PCG. In India, Asia and Saudi Arab, the signified age for having PCG, is from 3 to 4 months and for Western countries it is up to11 months [35,37].

Cytochrome P450 1B1 (*CYP1B1*):

CYP1B1 belongs to the family of cytochrome P450. This oxidase enzyme is bound in the membrane and during development play extensive functions in metabolism of hormones and involve in different metabolic activity [38]. In liver cytochromes are most expressed and in colon,lung,eye and kidney *CYP1B1* is more proliferate [39]. The mechanism of PCG caused by a mutation in *CYP1B1* needs to be further explored. Trabecular meshwork and ciliary body with *CYP1B1* mutations have high intraocular pressure in the eye [24,40]. Current observation suggests that for the growth and functioning of the trabecular meshwork, *CYP1B1* might be necessary[41,42] and that may be a mutation in *CYP1B1* gene change function of trabecular meshwork and impair the regulation of intraocular pressure, optic nerve destruction, and eventually PCG [16].

CYP1B1 gene was sequestered and mapped on chromosomal position 2p21-22 by Tang *et al* [43]. There are three exons in *CYP1B1* gene of human (start with exon II ORF) and two introns and is 8.5 Kb in length. There are 371, 1,044 and 3,707 base pairs respectively in all three exon lengths. In contrast, the length of two introns in base pair is 390 and 3032. These two introns start with sequence of GT and end with sequence of AG.Pyrimidine is abundant in the upstream region of introns, in 2nd exon, coding part of *CYP1B1* gene is initiated from 5' end and finish in terminal exon. Five hundred forty-three amino acids are translation outcome of *CYP1B1* gene (relate to 1,629 bases). Carboxyl terminal part of *CYP1B1* gene is most preserve, recommended a vital function of this part. For normal functioning of cytochrome P450 enzyme, carboxyl-terminal has conserved core-like structures in heme binding part. By using DNA probes against three exons of *CYP1B1* gene in southern analysis it is confirmed that it is a single-copy gene. TATA box is missing in the promoter part of the *CYP1B1* gene and consist of nine TCDD reactive enhancer regions and placed in 2.5 kb upstream [44].

CYP1B1 is a component of cytochrome P450, which is mono-oxygenase protein and belongs to superfamily of enzyme and triggers many reactions involving metabolism of drugs, and formation of steroids, cholesterol and lipids. *CYP1B1* binds to endoplasmic reticulum and involved in metabolism of procarcinogens (PAHs compounds) [17]. In the Human Gene Mutation database around 240 pathogenic variants of *CYP1B1* are listed [11] along with missense and nonsense variants, small deletions/insertions/duplications, and exon and whole-gene deletions [17]. Many studies have carried out by using computer simulation and in laboratory to identify the effect of mutation in *CYP1B1* on composition as well as working of protein. Jansson *et al.* in laboratory conducted the impact of *CYP1B1* mutation on the reliability and working of protein. He investigates the effect of two missense variations (p.Ala469Thr and p.Gly61Glu) on enzymatic role and reliability of *CYP1B1*. He discovered the variant protein p.Gly61Glu had missed 60% reliability, although p.Ala469Thr preserves almost 80% reliability over wild type. Enzymatic technique was used to know the impact of variant on protein working. When contrast to wild type protein, the result establish low metabolic function (50% - 70%) for whole substrates [17]. In 542 PCG patients,147 different mutations are detected in *CYP1B1* gene around the world [45]. These contain insertions, deletions, nonsense, missense, frameshift and also truncating mutations and variation in noncoding part of exon I. The most critical phenotype is related to the frameshift mutations [46]. Genetic mutation of *CYP1B1* in Pakistani population is shown in table 1.

Position	Complementary DNA	Change in Amino Acid	Type of variants	Regions	Ref.
Exon 3	c.1325delC	p.Pro442Glufs*15	Frame shift	Pakistan	[11]
Exon 2	c.868dupC	p.Arg290Profs*37	Frame shift	Pakistan	[47]
Exon 2	c.1209Ins TCATGCCACC	p.Thr404Serfs*30	Frame shift	Pakistan	[48]
Exon 3	c.1169G>A	p.Arg390His	Missense	Pakistan	[24]
Exon 3	c.1310C>T	p.Pro437Leu	Missense	Pakistan	[24]
Exon 2	c.542T>A	p.Leu181Gln	Missense	Pakistan	[11]
Exon 3	c.1436 A>G	p.Gln479Arg	Missense	Pakistan	[11]
Exon 3	c.1168C>T	p.Arg390Cys	Missense	Pakistan	[49]
Exon 3	G1515Ra	Arg390rHis	Synonymous	Pakistan	[24]
Exon 3	c.1325delC	Pro442Glnfs*15	Frame shift	Pakistan	[50]
Exon 3	c.1169 G>A	p.Arg390His	Missense	Pakistan	[51]
Exon 3	c.1294G>C	p.Leu432Val	Missense	Pakistan	[51]
Exon 3	c.1347T>C	p.Asp449Asp	Synonymous	Pakistan	[51]
Exon 3	c.1358A>G	p.Asp453Ser	Missense	Pakistan	[51]
Exon 3	c.1476C>T	p.Arg368His	Missense	Pakistan	[52]
Exon 3	c.1058C>T	p.Glu229Lys	Missense	Pakistan	[53]
Exon 2	c.716C>G	p.Ala115Pro	Missense	Pakistan	[54]

Table 1: Genetic mutation of CYP1B1 in Pakistan

Latent transforming growth factor-beta binding protein 2 (*LTBP2*):

LTBP2 mutations are infrequent in PCG diseases. In Pakistan and Iran, most of the cases that were reported having cousin marriages in the family [55,56]. *LTBP2* form protein outside the cell with the role being considered in cell attachment [57,58] and elastin microfibril assembly [59-61]. *LTBP2* is mainly present in

those tissues which are rich in fibres like arteries and lungs [53]. *LTBP2* is majorly found in eye tissues, and those are involved majorly in maintenance of intraocular pressure and biology of glaucoma, as well as trabecular meshwork and ciliarybody.In addition, *LTBP2* is mandatory for growth of frontal chamber as well as ciliaryzonules [55,62]. As a result of Variation in *LTBP2* hereditary diseases of orbital structure develop, which raised intraocular pressure and cause PCG [16]. *LTBP2* transcript NM_000428.2 comprises 36 exons [17]. The transformed protein NP_000419.1, constituting 1821 amino acids, from the group of latent transforming growth factor (TGF)-beta binding proteins (LTBP).This protein is extracellular ground substance with multidimensional shape, which is the biggest constituent of the LTBP group. It has so far been recommended that the protein may have varying tasks, as a part of the TGF-beta silent compound, as a composed part of microfibrils, and as an intermediate of cell [17].

In the Human Gene Mutation database,around 26 pathogenic variants of *LTBP2* are listed [11]. Pathogenic mutations may damage shape of protein as well as upset functions of protein, also change in both fibrillin 1 and fibulin 5 binding [17].

Tunica interna endothelial cell kinase (*TEK*):

TEK mediate the process of blood vessel formation, mainly present in endothelium as well as in lymphatic endothelia [63,64]. It Plays vital function in glaucoma; this is probably said *TEK* variants lead to change in the growth of orbital shape which is compulsory for aqueous drainage tract as well as maintenance of intraocular pressure and leading to congenital glaucoma [16].*TEK* has different copies of mutation; the largest from them is NM_000459.4 that is 4.7kb long and contains 23 exons [17]. *TEK* form tyrosine-protein kinase which plays role in cell-surface receptor, the angiopoietin-1 receptor. It is present totally in endothelial cells [17]. In the Human Gene Mutation database, 10 disease-causing mutations are recorded, plus missense, nonsense, and dividing mutations, little removal & addition lead to frameshift mutations [17].Pathogenic mutation in *TEK* outcome in venous deformity in nonocular tissues, whereas dysfunction mutation upset anterior chamber vascular development and result in primary congenital glaucoma [17].

Diagnosis:

The structural and clinical changes due to glaucoma are permanent.Therefore; PCG should be detected timely to save visual loss. Early diagnosis can be made by observing optic nerve structure through imaging devices and assess function of optic nerve by using perimetry [65].

Glaucoma can be symmetrical or asymmetrical, unilateral or bilateral. The condition can be observed at birth or after a few months of birth. In situations where PCG is suspicious, emergency eye examination is required under general anaesthesia or sedation to measure coronary diameter and IOP [66,67]. In PCG, diameter of cornea increases abnormally, which is up to 10mm at birth. The visibility of cornea is changed due to corneal oedema, which intensifies rapidly[67]. In usually, intraocular pressure in a child often is about 12.02 mm Hg.Increased in IOP from 21 mm Hg (mercury) in eyes as checked by I-care tonometry™, applanation tonometry, and pneumotonometry on different occasion is evaluated as abnormal. The recognition of PCG is depended on hospital checkup which involves raised IOP in children typically earlier than one year of age, expansion of the globe, increased corneal diameter, dull corneas, breaks in Descemet's membrane (Haab'striae) (Fig.3), buphthalmos (Fig.4) and anomalously deep anterior chamber. The detection of PCG is not difficult when a child has heavy hallmarks. If clinical hallmarks are not revealed then it is tough to diagnose PCG, mainly if PCG is bilateral. However, early detection is vital to initiate rapid care and secure final effective results. The situation is primarily identified at initial months after birth[66,67].Molecular testing proceeded towardunigene checking, use of a multigene panel, as well as complete genomic checking can help in diagnosis [17].

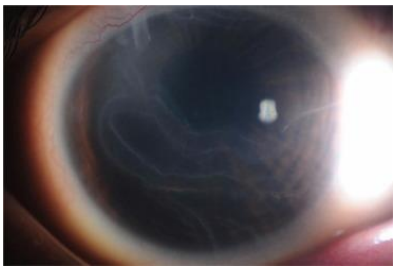

Figure 3: Haab's striae showing breaks in Descemet layer [12].

Figure 4: Left eye buphthalmos [12].

Treatment and Management:

Undiagnosed and untreated glaucoma can be a source of irreversible blindness. Medications, laser therapy and surgical incision are treatment options for glaucoma patients. There are certain risks and advantages of all types of treatment. Therefore, treatment should be carefully selected to minimise the adverse effects while maximising benefits of treatment. Usual first-line treatment of glaucoma routinely starts with the use of topical selective or non-selective β-blockers or topical compounds like latanoprost, travoprost, and bimatoprost. Topical carbon anhydrase inhibitors and α-agonists are considered second-line treatment options. Third-line drugs of choice include Para sympathomimetic agents, most frequently pilocarpine. If medications fail than other methods, laser trabeculoplasty and Incisional surgery can be used to lower IOP [68].

The main surgical options for PCG are angle surgery and drainage surgery.Surgery is best option [69]. If the eye can improve optic visualisation, then it is necessary to stop more optical collapse. In contrast, if delay

identification occurs than a high amount of permanent destruction had previously happened and in these cases, treatment is intended to maintain present optic state and help to stop upcoming collapse [12]. Due to remarkable anatomical abnormality of frontal drainage angle there are some limitations in treatment of PCG by decreasing IOP. In PCG patients reduction in IOP is less than 10% effective [70].

If surgery is unsuccessful than medicine is given to normalise intraocular pressure and routine treatment is accomplished for refractive errors and amblyopia [17]. Cyclodestruction and glaucoma drainage devices can help to maintain intraocular pressure. Glaucoma drainage devices usage data has release 28%-49% decrease in mean intraocular pressure and behind one year of surgical operation achievement rate is 63%-97% [71-73].

Before surgery, discontinuation of medications such as Phospholine Iodide (echothiophate) is essential, mainly if Succinylcholine is used to prevent cessation of breathing. It can help to avoid from secondary complications Alpha-2 agonists should not be taken because of risk for cessation of breathing and decrease in heart rate. Lifetime follow up is essential to control intraocular pressure to protect residual eyesight and stop more loss of vision. Monitoring depends upon control of IOP and extremity of disease. When IOP is control and the child is visually re-establish than every three months follow up is usually done to maintain the IOP at normal level and it dependson the age of individual and extremity of optic nerve harm. Visual field testing, as well as optic nerve photography are included in follow-up tests. Sedation and anaesthesia are essential for the proper ophthalmic observation in newborns and uncooperative youngsters. This procedure is difficult for the patient, the family and the treating consultant [17]. Proper testing of newborn babies in early life may diagnose PCG in their childhood and they can be treated earlier and avoid from routinely checkup under anaesthesia. If the pathogenic variants have been detected than only genetic testing is suitable in sibling of a diseased person. In an affected family member, if the PCG related pathogenic variants have not been recognised, then member screening includes IOP evaluations under anaesthesia [17].

Conclusion:

Primary congenital glaucoma is one of the significant vexing eye alarming problems, which can cause permanent loss of vision if left untreated. PCG represents a common disorder where genetic screening can be very beneficial for ethnic and prenatal diagnoses of at-risk individuals. It has high prevalence in population where consanguinity is common. Factors that can increase the burden of disease are limited resources, delayed presentation, consanguineous relationships, and limited follow-up. This review article started to explore genetic aspects of PCG, especially *CYP1B1*, *LTBP2*, *TEK* and diagnosis and management of PCG to gain a deeper understanding of PCG. Early and precise diagnosis of PCG is essential for predictive testing and early intervention to minimise the effects of visual impairment and eventually blindness. Risk of PCG can be reduced by avoiding consanguinity. Efforts to improve and expand PCG awareness programs must continue in the developing world, and give comprehensive treatment to PCG patients.

Conflict of Interest Statement

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors' Contribution

RH and QQ collected all the relevant manuscripts, AI and UN prepared the initial draft of the manuscript. MUK and RR finalized the manuscript, whereas MUK and AAB technically reviewed the manuscript. All authors read and approved the final manuscript.

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