1. Classification of Childhood Glaucoma

Cenk Zeki Fikret

The prognosis for this devastating disease has been improved because to the development of new diagnostic instruments, IOP-lowering drugs, and improved surgical methods, which have also maintained the vision of affected youngsters. To avoid permanent vision loss, childhood glaucoma is a diverse range of illnesses that each call for close observation and comprehension. A uniform classification system that is simple to use, clear, and applicable globally benefits the standard of care, collaboration, and dissemination of new breakthroughs. It was frequently unclear what was meant by the terms "developmental," "congenital," or "infantile" when used to describe childhood glaucoma in the past.

Because it may not always manifest right away after birth, primary congenital glaucoma is also known as developing glaucoma. The primary congenital glaucomas have been categorised into the following groups based on the age of onset:

1. True congenital glaucoma – Also called infantile glaucoma. In this case, the infant either has enlargement of the eyes from birth or within the first month of life. IOP is thought to increase during intrauterine life itself. These patients make up about 25% of all cases.

2. Infantile glaucoma – Patients who present between the ages of one and 36 months fall under this category. It affects about 65 percent of people with primary congenital glaucoma.

3. Juvenile glaucoma – Patients who exhibit indications of elevated intraocular pressure after the age of three but before adulthood are included in this category. Approximately 10% of instances involve this.

Badawi AH, Al-Muhaylib AA, Al Owaifeer AM et al. Primary congenital glaucoma: An updated review. Saudi J Ophthalmol. 2019;33(4):382-388.

Hoskin classification is a different classification scheme that has been developed based on the dysgenesis field.

1. Trabeculodysgenesis – The formation of the trabecular meshwork has a flaw.

2. Iridotrabeculodysgenesis – Includes stromal hypoplasia or hyperplasia, abnormal iris vessels, and structural flaws such coloboma or aniridia.

3. Corneotrabeculodysgenesis – Congenital glaucoma complex cases like Axenfield, Rieger, or Peters abnormality are included in this.

According to Hoskin's categorization, types 2 and 3 are referred to as secondary congenital glaucoma, while type 1 is referred to as main, primary congenital glaucoma.

Between 40% and 100% incomplete penetrance. Primary congenital glaucoma has been associated with five gene loci. These include the following: GLC3A, GLC3B, C, D, and E. The CYP1B1 gene has been connected to locus GLC3A.

Autosomal recessively inherited instances are most frequently caused by mutations in this gene. Primary congenital glaucoma has also been closely associated with another gene, latent transforming growth factor-beta (LTBP2), which is located near GLC3C.

Hoskins HD, Shaffer RN, Hetherington J. Anatomical classification of the developmental glaucomas. Arch Ophthalmol. 1984;102(9):1331-6

2. Genetics of Primary Congenital Glaucoma

Cenk Zeki Fikret

PCG is a genetic condition that can be inherited in a familial or sporadic manner. Approximately 10–40% of cases are familial and autosomal recessive with varied penetrance transmitted. The prevalence of PCG varies depending on the population analyzed (e.g., Saudi Arabia, Middle Eastern countries), ranging from 1:2,500 to 1:10,000. It is much more prevalent in populations where consanguinity is common. PCG has been linked to four different genetic loci to date: GLC3A on chromosome 2p21, GLC3B on chromosome 1p36, GLC3C on chromosome 14q24, and GLC3D on chromosome 14q24 as well.

Sarfarazi M, Stoilov I, Schenkman JB. Genetics and biochemistry of primary congenital glaucoma. Ophthalmol Clin North Am. 2003;16:543–554.

Lewis CJ, Hedberg-Buenz A, DeLuca AP, et al. Primary congenital and developmental glaucomas. Hum Mol Genet. 2017;26:R28–R36

Akarsu AN, Turacli ME, Aktan SG, et al. A second locus (GLC3B) for primary congenital glaucoma (Buphthalmos) maps to the 1p36 region. Hum Mol Genet. 1996;5:1199–1203.

Sarfarazi M, Akarsu AN, Hossain A, et al. Assignment of a locus (GLC3A) for primary congenital glaucoma (Buphthalmos) to 2p21 and evidence for genetic heterogeneity. Genomics. 1995;30:171–177.

Stoilov IR, Sarfarazi M. The third genetic locus (GLC3C) for primarycongenital glaucoma (PCG) maps to chromosome 14q24.3. *Invest. Ophthalmol. Vis. Sci. 2002;43:3015.*

In a study involving 17 Turkish families, the first locus associated with PCG was found to be GLC3A. The CYP1B1 gene was later discovered to be located at the GLC3A locus, which was initially identified as being on chromosome 2p21. In 1996, a different locus on chromosome 1p36 was discovered in 8 families, 7 of Turkish

and 1 of Canadian descent, with 37 offspring, 17 of whom had PCG. In this cohort, none of the patients had a genetic connection to the GLC3A locus. Two more loci (GLC3C and GLC3D) on chromosome 14q24 have also been linked to PCG. The LTBP2 gene, which codes for the latent transforming growth factor-beta binding protein 2, has been linked to the GLC3D locus.

Ali M, McKibbin M, Booth A, et al. Null mutations in LTBP2 cause primary congenital glaucoma. Am J Hum Genet. 2009;84:664–671.

A likely candidate for the GLC3B locus at 1p36.2 is the CDT6/ANGPTL7 gene, whose protein product is an angiopoietin-like molecule (angiopoietin-like factor 7) and was discovered to be expressed in significant amounts in the human trabecular meshwork region. However, no specific gene has been linked to the GLC3B locus at 1p36.2.

Tomarev S, Wistow G, Raymond V, et al. Gene expression profile of the human trabecular meshwork: NEIBank sequence tag analysis. Invest Ophthalmol Vis Sci. 2003;44:2588–2596.

Various genetic loci associated with or implicated in the pathogenesis of primary congenital glaucoma

Locus (Year Identified)	Chromosomal Region	Gene Product	Function
GLC3A (1995)	2p21	CYP1B1	Endogenous steroid metabolism
GLC3B (1996)	1p36	CDT6/ANGPTL7*	Extracellular matrix organization and formation
GLC3C (2002)	14q24	Unknown	Unknown
GLC3D (2008)	14q24	LTBP2	Extracellular matrix organization
Undesignated (2016)	9p21	TEK/Tie2	Formation and homeostasis of Schlemm's canal

*Implicated in PCG pathogenesis

Recently, it was discovered that 10 out of 189 families with PCG had mutations in the angiopoietin receptor TEK (Tie2). TEK mutations that cause PCG, in contrast to CYP1B1 mutations, seem to be passed down via an autosomal dominant mode of inheritance with variable expression.

3. Epidemiology of PCG

Cenk Zeki Fikret

The prevalence of PCG varies greatly between various ethnic groups. According to studies from western nations, the incidence might range from 1/10,000 to 30,000 live births. *[https://www.ncbi.nlm.nih.gov/books/NBK574553/#article-140088.r6 6]*

From nations like Saudi Arabia, the incidence has been claimed to be as high as 1/2500. A separate study revealed that glaucoma affected 7% of children enrolled in schools for the blind.

The higher prevalence of consanguineous marriages is associated with the higher occurrence in specific nations and ethnic groupings. The majority of instances (between 65 and 80 percent) are bilateral.

Studies from the United States and Europe have found that there are roughly three times as many men as women.

Slovakia has recorded an extremely high frequency of roughly 1:1250. According to a Japanese study, the ratio of men to women was 6:5 in individuals with the CYP-1BI mutation and 19:2 in those without the same gene mutation.

Alabdulwahhab KM, Ahmad MS. Visual Impairment and Blindness in Saudi Arabia's School for the Blind: A Cross-Sectional Study. Clin Optom (Auckl). 2020;12:169-173.

Yu-Wai-Man C, Arno G, Brookes J, et al. Primary congenital glaucoma including next-generation sequencing-based approaches: clinical utility gene card. Eur J Hum Genet. 2018;26(11):1713-1718.

DeLuise VP, Anderson DR. Primary infantile glaucoma (congenital glaucoma). Surv Ophthalmol. 1983;28(1):1-19.

Ohtake Y, Tanino T, Suzuki Y, et al. Phenotype of cytochrome P4501B1 gene (CYP1B1) mutations in Japanese patients with primary congenital glaucoma. Br J Ophthalmol. 2003;87(3):302-4.

5. History and Physical Examination

Cenk Zeki Fikret

Consanguineous marriage between parents and glaucoma in the family are required tests that must never be omitted. Papadopoulos M, Cable N, Rahi J, Khaw PT., BIG Eye Study Investigators. The British Infantile and Childhood Glaucoma (BIG) Eye Study. Invest Ophthalmol Vis Sci. 2007;48(9):4100-6.

Both unilateral and bilateral involvement can be present in the presentation. Watering, photophobia, and blepharospasm make up the traditional triad for primary congenital glaucoma. Parents may occasionally complain of rapid whitening of the cornea, bluish staining of the eyes, or unusually enlarged eyeballs. Additionally, the youngster can considerably lessen amblyopia, myopia, astigmatism, and anisometropia. the following elements must be covered by the clinical exam,

The Fixation of light – It is essential to analyze the patient's ability to track and fixate on light with each eye individually. Long-standing cases of nystagmus and inadequate fixation may result in exotropia.

Sclera – Due to extreme myopia, scleral thinning, and exposure of underlying uveal tissue, the sclera may exhibit bluish discolouration.

Cornea – Examination of the cornea may reveal symptoms of corneal hypertrophy, also known as buphthalmos. Between 9.5 and 11.5 mm should be the range for the normal corneal size from birth to up to 6 months. The presence of glaucoma should be suspected if the size is greater than 12 mm. Any subsequent child with a corneal diameter of greater than 13 mm also has enlarged corneas. The Descemet's membrane may develop Haab's striae, or tears and breaks, during the slit-lamp examination (horizontal or oblique tears in the Descemet membrane). Corneal edema is a significant additional finding. Typically beginning as epithelial edema, this eventually affects the deeper layers of the cornea and, on rare occasions, results in persistent opacities that significantly impede vision.

Anterior chamber- Typically, the anterior chamber is deep.

Iris - It is crucial to examine the iris for any atrophic patches, hypoplasia, ectropion uvea, irregularities or iridodonesis.

Pupil - Oval, dilated, and ischemic pupils are possible.

Lens - The ophthalmologist should check for lenticular opacities or any lens subluxation brought on by severe zonule straining.

Optic disc- This often exhibits early reversible cupping. In later phases, there may be atrophy or even an increased cup disc ratio.

Intraocular pressure- IOP can be assessed in the outpatient department using a pneumotonmeter because it is typically higher at presentation.

Evaluation;

Any suspicion of congenital glaucoma justifies a thorough examination under anesthesia so that subsequent therapy can be planned.

Beck AD. Diagnosis and management of pediatric glaucoma. Ophthalmol Clin North Am. 2001;14(3):501-512.

An examination under anesthesia should include the following

Cornea – Along with the thorough corneal evaluation described above, the corneal diameter should be measured using calipers. The cornea and anterior segment features can also be assessed using a hand-held slit lamp.

Ophthalmoscopy – A thorough dilated fundus assessment ought to be performed. For future use, the size of the optic disc and cupping should be diagrammatically represented. Any unusual vessels or other important discoveries should be thoroughly noted.

Intraocular pressure (IOP) – IOP can be measured with a pneumotonometer or handheld Perkin's applanation tonometer, as well as with a Schiotz or Perkin's tonometer. It is important to consider how the anesthetic used will affect IOP. These kids typically have IOPs between 30 and 40 mmHg, which causes corneal epithelial edema.

Gonioscopy – With the aid of Koeppe's lens, a gonioscopic examination can be performed; this may indicate trabeculodysgenesis with a flat, scalloped, or concave iris insertion.

Pachymetry – Patients' corneal thickness should be assessed because it can influence intraocular pressure results. Patients who have central corneal edema will have thicker corneas.

8. Immunogenetic Disorders Associated with Glaucoma

Cenk Zeki Fikret

Mendelian immunogenetic illnesses are a subset of monogenic disorders that trigger autoimmunity or autoinflammation and disrupt immunological pathways, ultimately resulting in disease pathology. Aicardi-Goutieres syndrome (AGS) and Singleton-Merten syndrome are two archetypal disorders that have the common trait of having glaucomatous optic neuropathy (SGMRT).

Eight children from five different families with severe early-onset encephalopathy comprised the case series used by Jean Aicardi and Francoise Goutières in 1984 to initially identify AGS.

Aicardi J, Goutieres F. A progressive familial encephalopathy in infancy with calcifications of the basal ganglia and chronic cerebrospinal fluid lymphocytosis. Ann. Neurol. 1984;15:49–54.

Significant allelic heterogeneity exists in AGS, which can be inherited as either an autosomal dominant or recessive disease. Pathogenic mutations in the genes TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, and ADAR, as well as the innate immunity gene IFIH1, are the main causes of AGS.

Crow YJ, Leitch A, Hayward BE, et al. Mutations in genes encoding ribonuclease H2 subunits cause Aicardi-Goutieres syndrome and mimic congenital viral brain infection. Nat. Genet. 2006;38:910–916.

Rice GI, Del Toro Duany Y, Jenkinson EM, et al. Gain-of-function mutations in IFIH1 cause a spectrum of human disease phenotypes associated with upregulated type I interferon signaling. Nat. Genet. 2014;46:503–509. doi: 10.1038/ng.2933.

Rice GI, Park S, Gavazzi F, et al. Genetic and phenotypic spectrum associated with IFIH1 gain-of-function. Hum. Mutat. 2020;41:837–849.

Microcephaly, leukodystrophy, brain atrophy, intracranial calcifications, hepatosplenomegaly, and thrombocytopenia are all characteristics of the condition's most severe version. It is connected to increased levels of type I interferon signaling in the central nervous system and frequently develops to early childhood death and severe neurologic symptoms. Milder forms, however, may appear later and have lupus-like symptoms, such as painful skin lesions and congenital glaucoma. In a sizable investigation on AGS, glaucoma was noted in 6.3 percent (23 patients), with 20.8 percent (10/48 patients) having SAMHD1 pathogenic mutations, however there were no cases of ADAR or IFIH1 pathogenic variations.

Edward B. Singleton and David Merten originally identified the autosomal dominant Singleton-Merten syndrome (SGMRT) in 1973. Gain-of-function mutations in one of the two RIG-I-like receptor proteins (DDX58 or IFIH1) are the root cause of SGMRT.)

Jang MA, Kim EK, Now H, et al. Mutations in DDX58, which encodes RIG-I, cause atypical Singleton-Merten syndrome. Am. J. Hum. Genet. 2015;96:266–274.

Feigenbaum A, Muller C, Yale C, et al. Singleton-Merten syndrome: An autosomal dominant disorder with variable expression. Am. J. Med. Genet. A. 2013;161:360–370.

Rutsch F, MacDougall M, Lu C, et al. A specific IFIH1 gain-of-function mutation causes Singleton-Merten syndrome. Am. J. Hum. Genet. 2015;96:275–282.

As part of the antiviral response, these receptors often identify foreign exogenous double-stranded RNA and trigger innate immune systems and type I interferon signaling. A psoriasiform skin rash, vascular calcifications, skeletal dysplasia, and dental anomalies are some of the systemic characteristics of SGMRT. Although there is a range of expressivity, juvenile open-angle glaucoma is the most noticeable ocular characteristic. Glaucoma, which is present in 17/18 (94 percent) of documented cases and is the most pervasive aspect of SGMRT induced by DDX58 mutations.

Prasov L, Bohnsack BL, El Husny AS, et al. DDX58(RIG-I)-related disease is associated with tissue-specific interferon pathway activation. J. Med. Genet. 2021 doi: 10.1136/jmedgenet-2020-107447.

Ferreira CR, Crow YJ, Gahl WA, et al. DDX58 and Classic Singleton-Merten Syndrome. J. Clin. Immunol. 2019;39:75–80.

The median age of diagnosis is 5 years old (range: 2–18 years), but there is intra- and inter-familial diversity in the start and severity. Glaucoma is present in a lesser percentage of IFIH1-related SGMRT cases (40%), and up to 13.5 percent of carriers of the pathogenic variation can have no symptoms. Additionally, patients with

9. ROP and Glaucoma

Cenk Zeki Fikret

Retinopathy of prematurity (ROP), which affects preterm infants, is the most common cause of juvenile blindness. It results from the inadequate development of retinal blood vessels. Preterm infants that have ROP, a vasoproliferative retinal condition, are born before term. Retrolental fibroplasia was the term first used to describe it in 1942. Concern over a "third epidemic," especially in middle- or low-income nations, is growing as the prevalence of ROP rises due to the viability of newborns born at earlier gestational ages (GA) around the world.

Retinal vascular development begins in the typical human baby at gestational week 16, moving from the center to the periphery of the retina. The normal human fetus has a gestational period of 40 weeks. Preterm infants do not have retinas that are fully grown at birth, including the arteries and neuronal cells. Birth and the subsequent transfer to lung ventilation cause a change in arterial blood oxygen tension that is substantially higher than that of the intrauterine fetus because preterm infants need to be placed in high supplemental oxygen due to their undeveloped cardiopulmonary systems. This "supra-physiologic" tissue oxygenation in the incompletely vascularized preterm newborn retina is thought to start the initial stage of ROP.

ROP is the result of this, which endangers the retina's growth.

Due to improvements in neonatal intensive care, it is now usual for very low birth weight preterm infants to survive longer, which raises the risk of ROP. In fact, ROP has become a significant contributor to preventable childhood blindness in both industrialized and developing nations. According to the most recent estimates from the National Eye Institute, severe ROP necessitates treatment in 1100–1500 infants (5% of infants weighing less than 1.25 kg at birth and less than 31 weeks gestation). These young children should be periodically monitored since they are more likely to develop astigmatism, extreme myopia, and retinal detachment as they age. Unfortunately, according to recent estimates from the National Eye Institute, 400–600 children with ROP still go legally blind despite therapy (40,000 of these infants have

severe ROP, and 2 percent of them were born weighing less than 1.25 kg), which equates to losing 30,000 life years of vision. The long-term handicap and significantly reduced quality of life that ROP patients experience places a heavy load on the global healthcare systems for children, adolescents, and adults. ROP is a significant public health concern and justifies the need for effective care because it is expected to have a substantial societal cost over a long period of time as the population ages.

ROP, a disorder frequently observed in preterm infants that is connected to the improper development of retinal blood vessels, is a significant contributor to blindness in children. Clinically, preterm infants are given a lot of extra oxygen to help them breathe because their cardiopulmonary systems are still developing. While promoting the development of reactive oxygen species (ROS), exposure to high oxygen levels (hyperoxia) during the initial ischemic phase decreases the production and release of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1). Vascular endothelial cells undergo apoptosis, which stops normal vessel formation and prunes the existing immature vasculature, resulting in retinal avascularity.

Although their functions are still unknown, hyperoxia-induced free radicals may also play a role in mediating the retinal response during this period. When the preterm baby has developed sufficient cardiopulmonary capabilities, oxygen supplementation is stopped and the baby is allowed to return to regular room air. Due to the increasing oxygen demand from the growing neuronal components, relative retinal hypoxia now occurs. During this second vaso-proliferative phase, pro-angiogenic substances are released as a retaliatory mechanism. In addition to increasing VEGF, IGF-1, and erythropoietin (Epo) expression, hypoxia also promotes the buildup of hypoxia-inducible factor (HIF).

Currently, neovascularization and increased vessel development are occurring. Further damage to these vulnerable neovascular tufts will result in retinal detachment, intravitreal hemorrhages, and vision loss. Although little is known, variations in oxygen tension also increase the risk of retinal neurons deteriorating. In fact, retinal impairment in newborns and kids with a history of ROP has been documented. ROP's genesis appears to involve multiple factors. The main risk factor for ROP, gestational age, has an inverse relationship with the severity of the condition. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), a multi-center nationwide trial, demonstrated that pre-threshold ROP does not proceed any further when oxygen saturation is between 96 and 99 percent.

However, there isn't a shred of evidence to imply that preterm newborns with early-stage ROP and high oxygen levels are safe for their developing eyes. On the

11. Congenital Ectropion Uvea

Cenk Zeki Fikret

A rare, often unilateral eye defect known as congenital ectropion uvea is defined by the presence of iris pigment epithelium on the anterior surface of the iris at birth.

Dowling JL Jr, Albert DM, Nelson LB, Walton DS. Primary glaucoma associated with iridotrabecular dysgenesis and ectropion uveae. Ophthalmology. 1985;92(7):912-21.

Ritch R, Forbes M, Hetherington J Jr, Harrison R, Podos SM. Congenital ectropion uveae with glaucoma. Ophthalmology. 1984;91(4):326-31.

Although this syndrome is frequently an independent discovery, it can also be linked to systemic diseases and other ocular anomalies, such as Riegers Anomaly, coloboma, and ptosis (e.g. neurofibromatosis type 1, Prader-Willi Syndrome and facial hemihypertrophy).

The age of diagnosis for glaucoma, a typical consequence of congenital ectropion uvea, ranges from early childhood through early adulthood. Elevated intraocular pressures may be caused by a variety of processes. The anterior insertion of the iris at the level of the trabecular meshwork is seen during gonioscopy in younger children with congenital ectropion uvea. In addition, a membrane that extends into the angle from the periphery of the iris is frequently mentioned. According to histologic research, this membrane is made up of strange, abnormal endothelial cells.

Harasymowycz PJ, Papamatheakis DG, Eagle RC Jr, Wilson RP. Congenital ectropion uveae and glaucoma. Arch Ophthalmol. 2006;124(2):271-273.

Additionally, both clinically and histologically, enucleated eyes with end-stage glaucoma exhibit complete angle closure.

Edward DP, Morales J, Bouhenni RA, et al. Congenital ectropion uvea and mechanisms of glaucoma in neurofibromatosis type 1: new insights. Ophthalmology. 2012;119(7):1485-1494.

Congenital ectropion uvea produces angle closure at an unknown stage. This implies that progressive angle closure caused by defective endothelial cell membranes and developmental anomalies of the angle structures may both contribute to glaucoma in congenital ectropion uvea. This trend may be related to angle surgery's overall long-term inefficiency in treating congenital ectropion of the uvea.

The majority of congenital ectropion uvea-related glaucoma cases require surgical therapy. Despite the publication of numerous case series and reports, there is no agreement on the most effective method of treating this particular type of glaucoma. A review of the literature reveals that goniotomy or trabeculotomy angle surgery is not very efficient in maintaining long-term intraocular pressure control.

The most common glaucoma surgeries for congenital ectropion that are successful involve filtering techniques with antifibrotics. *Edward DP, Morales J, Bouhenni RA, et al. Congenital ectropion uvea and mechanisms of glaucoma in neurofibromatosis type 1: new insights. Ophthalmology. 2012;119(7):1485-1494*

AGV plate encapsulation has been documented to result in long-term intraocular pressure management failure in 2 percent to 16 percent of cases with different types of pediatric glaucoma. Early aqueous humor flow, which contains inflammatory cytokines that promote fibrosis inside the episcleral connective tissue, is associated with plate encapsulation.

Iris Hypoplasia

Iris hypoplasia (IH) is an uncommon autosomal dominant condition that causes abnormalities of the umbilicus, eyes, and iris stroma. Mutations in the paired-like homeodomain 2 (PITX2) gene are the root cause of this illness.

Three allelic disorders—iris hypoplasia (IH), iridogoniodysgenesis syndrome (IGDS; OMIM 137600), and Axenfeld-Rieger syndrome—are linked to mutations in the PITX2 (paired-like homeodomain 2) gene (ARS; OMIM 180500). *Alward WL, Semina EV, Kalenak JW, et al. Autosomal dominant iris hypoplasia is caused by a mutation in the Rieger syndrome (RIEG/PITX2) gene. Am J Ophthalmol 1998;125: 98–100.*

In IH, IGDS, and ARS, which are defined by aberrant development of the anterior segment of the eyes and umbilicus anomalies, a variety of dental abnormalities, including tooth agenesis, are also present. *Shields MB, Buckley E, Klintworth GK, Thresher R. Axenfeld-Rieger syndrome. A spectrum of developmental disorders. Surv Ophthalmol 1985;29: 387–409.*