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Association of infantile-onset glaucoma with collagen disorders

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ABSTRACT

Primary infantile-onset glaucoma is a rare, potentially blinding disease that is due to malformation of the trabecular meshwork and aqueous outflow tracts (goniotrabeculodysgenesis). While goniotrabeculodysgenesis is typically an isolated finding, there are reports of primary infantile-onset glaucoma in the setting of collagen disorders, specifically Stickler syndrome and osteogenesis imperfecta.

In Stickler syndrome, defects in type II or type XI collagen are commonly associated with craniofacial anomalies, hearing loss, hypermobile joints, and vitreoretinal abnormalities. Osteogenesis imperfecta is caused by disruption in type I collagen synthesis and is characterized by frequent bone fractures. Both type I and type II collagens are major structural proteins in the trabecular meshwork of the eye and both of these collagen disorders show higher incidences of adult-onset glaucoma. Herein we review the association between primary infantile-onset glaucoma and collagen disorders, which gives insight into the development of the trabecular meshwork and the aqueous outflow tracts of the eye.

Primary infantile-onset glaucoma

Primary infantile-onset glaucoma is a potentially blinding disease that has an incidence of approximately 1 in 10,000 live births[1,2]. This congenital eye disease is more common in males (2:1) and can affect one or both eyes[3]. Light sensitivity (photophobia), tearing (epiphora), and excessive blinking (blepharospasm), which are due to corneal clouding and edema, constitute the classic triad of symptoms[3,4]. Primary infantile-onset glaucoma is characterized by elevated intraocular pressure (IOP) caused by abnormal development of the trabecular meshwork and aqueous outflow tracts in the eye (goniotrabeculodysgenesis)[5,6]. This is in contrast to glaucoma that is secondary to other congenital eye anomalies such as in Axenfeld-Rieger Syndrome, congenital cataracts, microphthalmia, Peters Anomaly, and aniridia[7-11]. Mutations in the *CYP1B1* gene are the most commonly identified genetic cause of primary infantile onset-glaucoma, however, the molecular mechanism by which this gene regulates eye development has yet to be determined[12-14].

Increased IOP has more deleterious effects on eye structure and visual function in infants and young children than in adults. The cornea and sclera are more distensible in children such that increased IOP causes globe enlargement (buphthalmos) and axial lengthening[15]. This correlates with increased refractive error (high myopia) and predisposes these eyes to retinal detachment and lens subluxation[16-18]. Further, increased IOP results in breaks in Descemet's membrane, the less compliant basement membrane of the corneal endothelium (Haabs striae) that cause image distortion and irregular astigmatism[4,19,20]. In addition, prolonged elevated IOP can cause decompensation of the corneal endothelium which may

necessitate corneal transplantation[21]. As in adult-onset glaucoma, elevated IOP in children leads to loss of the retinal nerve fiber layer, which results in the characteristic cupping of the optic nerve[22]. In addition to the damage to ocular structures, vision loss in children can be due to amblyopia. Persistently decreased vision in one or both eyes due to high myopia, Haabs striae, corneal edema, or optic neuropathy during the first decade of life can result in dense amblyopia[23].

Unlike other forms of glaucomas, surgical management is required to control IOPs in primary infantile-onset glaucoma. The mainstay of treatment is angle surgery (goniotomy or trabeculotomy), which involves the incision of the trabecular meshwork to remove resistance of aqueous outflow from the anterior chamber into Schlemm's canal. Both goniotomy and trabeculotomy have high success rates (70-80%) in primary infantile-onset glaucoma, especially in children diagnosed between 2 and 12 months of age[24-26]. Cases refractory to goniotomy or trabeculotomy, may require surgery to create alternative aqueous outflow paths (trabeculectomy or glaucoma drainage device placement) or surgery to decrease aqueous humor production (ciliary body ablation)[23,27-29]. Thus, primary infantile-onset glaucoma is a rare disease that requires early diagnosis and surgical intervention to optimize visual outcomes.

Primary infantile-onset glaucoma and collagen tissue disorders

Although primary infantile-onset glaucoma is typically an isolated finding, goniotrabeculodysgenesis has been associated with genetic defects in collagen synthesis. Collagens are the major structural proteins in the extracellular matrix and types I and II are the most abundant. Different genes encode for specific collagen chains that through a series of enzymatic modifications aggregate into groups of three to form tropocollagen. Polymers of tropocollagen form collagen fibrils and fibers. Mutations in the genes encoding for collagen chains or modifying enzymes required for fiber formation can affect numerous tissues throughout the body[30-32].

Stickler Syndrome is due to mutations in the collagen type 2 alpha 1 (COL2A1, Type I Stickler Syndrome) or the collagen type 11 alpha 1 (COL11A1, Type II Stickler Syndrome) genes, which result in abnormal type II and type XI collagen fibril formation[33,34]. In the eye, type II collagen is in the vitreous humor, sclera, cornea, and trabecular meshwork[35-37]. Type XI collagen, a minor form that consists of collagen type 2 and 11 chains, is predominantly in cartilage but is also in the vitreous[38,39]. While Stickler Syndrome typically follows an autosomal dominant pattern, there are rare cases of autosomal recessive inheritance. People affected with Stickler Syndrome have craniofacial anomalies (Pierre Robin sequence, cleft palate, micrognathia), hearing loss, and hypermobile joints. The most common eye abnormality is non-glaucomatous axial lengthening with associated high myopia and predisposition for retinal detachments[33,34]. The mechanism of the posterior lengthening of the globe is not well understood, but is likely due to abnormal vitreo-retinal interactions due to type II and XI collagen abnormalities.

It is generally accepted that adults with Stickler syndrome have a higher incidence of ocular hypertension (10%) and angle abnormalities (26%), and mutations that may affect *COL2A1* splicing may be more likely to cause adult-onset glaucoma[40,41]. Glaucoma in children is more rare as only 2 cases of infantile-onset glaucoma associated with Stickler syndrome have been reported in the literature[42,43]. There are also a few reported cases from the 1960s of infantile glaucoma in the setting of Pierre Robin sequence, which was prior to recognition of Stickler Syndrome as a specific entity[44,45]. Primary infantile-onset glaucoma in Stickler syndrome is likely underreported, however, it is unclear the prevalence of goniotrabeculodysgenesis in the setting of Stickler Syndrome.

The mechanism behind defective trabecular meshwork development and function in infants with Stickler Syndrome is unknown. In the prenatal eye, type II collagen may play a role in the formation of the anterior segment and trabecular meshwork. Transgenic mice carrying mutations in the *Col2a1* gene show anterior segment alterations including abnormal trabecular meshwork, thickened lens capsule, and shallow anterior chambers[46]. Further, type II collagen, which interacts with hyaluronic acid to mediate aqueous outflow resistance, is decreased in the trabecular meshwork in eyes with adult-onset glaucoma[37,47]. Decreased or absence of type II collagen in the trabecular meshwork may also compromise function in young children. Thus, infantile-onset glaucoma in the setting of Stickler syndrome could be a result of both structural malformations and function of the trabecular meshwork. Further studies are required to discern the mechanism behind this disease.

Osteogenesis imperfecta is a group of connective tissue disorders due to defects in type I collagen, which is the predominant protein in bone. The hallmark of osteogenesis imperfecta is frequent bone fractures that lead to skeletal deformities[48]. Additional findings include progressive hearing loss, abnormal teeth, and cardiopulmonary problems. There are 8 types of osteogenesis imperfecta that are categorized based on severity of the disease. Types I through IV are the most common forms and are due to mutations in genes encoding the collagen type 1 alpha 1 chain (*COL1A1*) or collagen type 1 alpha 2 chain (*COL1A2*)[48-50]. Type I collagen is located throughout the eye including in the sclera, cornea, trabecular meshwork,

lens capsule, uvea, and lamina cribosa[51]. The most common ocular finding in type I and III osteogenesis imperfecta is a bluish hue to the sclera. This was originally thought to be due to decreased scleral thickness, however, electron microscopy demonstrated that the blue color is a result of thinner collagen fibers and altered extracellular matrix composition[52-54]. On the other hand, the central corneas are significantly thinner in children and adults with osteogenesis imperfecta[55]. The alterations in these tissues may account for the few reports of degenerative ocular pathologies such as retinal detachment, posterior staphyloma, and keratoconus in adults with osteogenesis imperfecta[56-62]. In addition, there is an association between osteogenesis imperfecta and primary open angle glaucoma. One case series showed that all members of a particular family affected with osteogenesis imperfecta developed early adult-onset primary open angle glaucoma[63]. Recently, a second case series reported increased intraocular pressures and early onset glaucoma in 2 unrelated patients with osteogenesis imperfecta[64]. The pathophysiology between type I collagen defects and adult primary open angle glaucoma is not clear. It may be related to altered corneal biology, increased distensibilty of the lamina cribrosa, or alterations in trabecular meshwork.

There are few cases of congenital eye anomalies in children with osteogenesis imperfecta. One child had Rieger anomaly who developed secondary glaucoma as a teenager[65]. The other was an infant with anterior megalophthalmos of one eye and primary infantile-onset glaucoma of the other eye. The eye with glaucoma had goniotrabeculodysgenesis and intraocular pressure control was successfully obtained with angle surgery[66]. Interestingly, another patient, who was not clinically affected with osteogenesis imperfecta, was reported to have heterozygous variants in the *COL1A1* gene that caused primary infantile-onset glaucoma[64]. Type I collagen is a major component of the core of the endothelial-covered trabecular beams in the trabecular meshwork[67]. In animal models, decreased structural integrity of the trabecular beams results in collapse of the trabecular meshwork. Interestingly, in mice, mutation of *Cyp1b1,* the gene associated with primary infantile-onset glaucoma in humans, causes fragmentation and disorganization of the collagen fibers in the trabecular meshwork[68]. The question raised is why are there not more cases of infantile-onset glaucoma associated with type I collagen defects and osteogenesis imperfecta. While this may be due to lack of genetic testing for mutations in collagen chains in cases of infantile-onset glaucoma, this could also be due to the specific collagen chains affected, the type of mutation, and effect of other genes involved in trabecular meshwork development. Both collagen type 1 alpha 1 and collagen type 1 alpha 2 chains contribute to type I collagen fibers. However, the ratio between these two chains as well as the incorporation of additional chains into final collagen fibers varies. The development and function of trabecular meshwork may be sensitive to the specific composition of the type I collagen fibers. Further numerous *COL1A1* and *COL1A2* mutations have been identified and there is a wide range of phentoypes as evidenced by the differences between the types of osteogenesis imperfecta. Different mutations have various effects on collagen fibril formation such that there are differences in collagen fiber thickness, integrity, and length between patients with osteogenesis imperfecta[48-50]. The specific structure of the collagen fiber in these patients may more highly affect the formation of the trabecular beams. In addition, the abnormal collagen fibers in the trabecular beams may be influenced by polymorphisms in other genes that regulate trabecular meshwork development and function. Mild alteration in the function of a gene such as *CYP1B1* may not be disease causing, however, in the setting of abnormal type I collagen fibers, development and function of the trabecular meshwork may be compromised. Additional studies that investigate the role of type I collagen in trabecular meshwork development and function are required to better understand the relationship between collagen mutations and primary infantile onset glaucoma.

Conclusions

Primary infantile-onset glaucoma is a congenital disease, which can lead to significant visual impairment and in some cases complete blindness. Early diagnosis and appropriate surgical treatment to obtain intraocular pressure control is critical for good visual outcomes. Primary infantile-onset glaucoma is due to goniotrabeculodysgenesis, which in rare cases can be associated with Stickler Syndrome and osteogenesis imperfecta. Type I and type II collagens are both integral to trabecular meshwork structure and function. The few cases of primary infantile-onset glaucoma associated with collagen diseases suggest that these collagens are important in trabecular meshwork development.

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