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Secondary developmental glaucoma

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Abstract:

The basic pathophysiology of all childhood glaucoma results from impaired outflow through the trabecular meshwork. Anterior Segment Dysgeneses (ASD) are a group of nonacquired anomalies associated with secondary developmental glaucoma, characterized by impaired development of the structures of the anterior segment. Many genes impact the development of the anterior segment. The cause of the development of the abnormalities is thought to be multifactorial. Molecular research has helped our understanding of the molecular basis of ASD and the developmental mechanisms underlying these conditions. Identifying the genetic changes underlying ASD has gradually led to the recognition that some of these conditions may be parts of a disease spectrum rather than isolated anomalies. The characterization of the underlying genetic abnormalities responsible for glaucoma is the first step toward developing diagnostic and screening tests, which could identify individuals at risk for disease before irreversible optic nerve damage occurs. It is also crucial for genetic counseling and risk stratification of later pregnancies. It also aids prenatal testing by various methods allowing for effective genetic counseling. This review summarizes various ocular and systemic conditions that result in secondary developmental glaucoma and provide an overview of the phenotypes, the diagnosis and principles of management of the various disorders.

Keywords:

Anterior Segment Dysgeneses, Secondary non acquired childhood glaucoma

Introduction

Childhood glaucoma is a treatable cause of blindness, provided it is recognized and treated in time.[1,2] WHO has estimated that it is responsible for Blind Years second only to cataracts.[3] However, childhood glaucoma *per se* is an umbrella term which comprises a wide variety of diseases, including those that occur at birth, those that are developmental but manifests later and those that are due to acquired causes. It is imperative to know precisely what condition one is dealing with since the treatment and prognosis depend primarily on the underlying disease.

Developmental glaucomas comprise primary congenital glaucoma (PCG) and anterior segment dysgeneses (ASD). PCG is referred to as trabecular dysgenesis alone. In contrast, anterior segment dysgeneses (ASD) are a group of nonacquired ocular anomalies associated with glaucoma, characterized by developmental abnormalities of the tissues of the anterior segment.[4]

Anterior Segment Dysgenesis

Anterior segment dysgeneses (ASD) are a group of nonacquired ocular anomalies associated with glaucoma, characterized by developmental abnormalities of the structures of the anterior segment.[5] The cause is multifactorial, and many genes are involved in the development of the anterior segment of the eye. Over the last decade, molecular and developmental genetic research has transformed our understanding of the molecular basis of ASD and the developmental mechanisms underlying these conditions.[6-9]

The abnormalities characterizing ASDs are complex and affect multiple structures, making their clinical classification and description difficult. Arrested development

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of the trabecular meshwork and Schlemm canal causes the aqueous to accumulate inside the eye, raise the intraocular pressure (IOP), and cause glaucoma. Typically, ASDs include combinations of iris and corneal abnormalities, such as iris hypoplasia, ectopic pupils (corectopia), iris holes (polycoria), and corneal opacity. These result in phenotypes such as axenfeld rieger anomaly (ARA), peter's anomaly, and Aniridia. Identification of the genetic changes underlying ASD has gradually led to the recognition that some of these conditions may be parts of a disease spectrum. The nonacquired conditions Axenfeld-Rieger syndrome (ARS), aniridia, and glaucoma associated with anterior segment dysgenesis are caused by mutations in PITX2, PAX6, and FOXC1, respectively.[8-10]

This article looks at the diagnosis and clinical characteristics of the most commonly occurring secondary developmental glaucomas comprising the broad group of anterior segment dysgenesis (ASD). The authors confirm that parental consents were taken to use recognizable photographs of their children for academic purposes.

Nomenclature

Historically, childhood glaucoma had no uniform classification system. Various authors used the terms congenital glaucoma and developmental glaucoma interchangeably. Some of the earlier classifications proposed by multiple authors include the following:

- Hoskins *et al*.[11] classified the disease as per anatomic defects like isolated trabeculodysgenesis or associated dysgenesis of the iris and cornea
- Shaffer and Weiss[12] coined isolated congenital glaucoma, associated with congenital anomalies or acquired glaucoma
- Yeung and Walton[13] added other disorders in the classification by Schaffer and Weiss.

For all such heterogeneous and rare diseases, common terminology and easy-to-use classification help develop standards of care, encourage collaboration and develop new strategies for more effective management. The Childhood Glaucoma Research Network (CGRN) is a group of clinicians and scientists that has managed to connect doctors around the globe to take advantage of each member's unique expertise in caring for childhood glaucoma. The CGRN proposed a standardized nomenclature and classification system, refined and finalized by a consensus statement at the IXth World Glaucoma Association (WGA) in Vancouver in 2013,[14] which the American Academy of Ophthalmology has also adopted.[15]

Table 1 shows the diagnostic criteria for glaucoma and suspects from the WGA consensus. Table 2 presents the major components of the International Classification for Childhood Glaucoma from the same group.

Diagnosis

The signs and symptoms must be recognized in time for early detection of any clinical disease. Unlike glaucoma in adults, which is notoriously difficult to detect since there are usually no symptoms, glaucoma in children usually presents with symptoms and signs that can be detected by primary care providers, parents, and nonmedical care providers, who are traditionally the first contacts of these children. The CGRN and WGA consensus has defined criteria for diagnosing glaucoma in children. Childhood glaucoma is a high-IOP disease, resulting in secondary damage in a young expandable eye, which can stretch under the effects of raised IOP. This results in the classical features of PCG: buphthalmos, photophobia, and tearing. The stretched descemet membrane often gives way, resulting in tears known as haab striae, accompanied by corneal oedema and opacification due to aqueous influx into the corneal stroma. The globe enlargement is evident as axial length elongation and limbal stretching. Gonioscopy reveals the high iris insertion typical of trabecular dysgenesis. However, it is essential to remember that many children in the developing world present with corneal oedema and

Table 1: Definitions of glaucoma and glaucoma suspect* as per childhood glaucoma research network guidelines[7]

Glaucoma	Glaucoma suspect
IOP related damage to the eye at least 2 of the following criteria are present	No definite IOP related damage to the eye at least 1 of the following criteria are present
IOP >21 mmHg investigator discretion is required for children who are examined under anesthesia due to variable effects of anesthesia on IOP measurement	IOP >21 mmHg on 2 separate occasions
Optic disc changes	Suspicious optic disc appearance for glaucoma, i.e., increased cup-disc ratio for size of optic disc
Optic disc cupping or progressive increase in cup-disc ratio	Suspicious visual field for glaucoma
Cup-disc asymmetry of ≥0.2 or focal rim thinning	Increased corneal diameter or axial length in setting of normal IOP
Corneal findings: Haab striae or diameter ≥11 mm in newborn, >12 mm in child <1 year, or >13 mm any age	
Progressive myopia, myopic shift, or an increase in axial length out of keeping with normal growth	
Reproducible visual field defect consistent with glaucomatous optic neuropathy	

IOP=Intraocular pressure, WGA=World Glaucoma Association

Table 2: Childhood glaucoma classification[7]

Primary childhood glaucoma (isolated angle anomalies)	Secondary childhood glaucoma			
	Associated with nonacquired (usually congenital) ocular anomalies	Associated with nonacquired systemic disease or syndrome	Associated with acquired condition	Glaucoma following cataract surgery
PCG Neonatal-onset glaucoma (0–1 month of age) Infantile glaucoma (1–24 months of age) Late-onset or late recognized (after 2 years) JOAG	Glaucoma associated with ocular anomalies in addition to angle dysgenesis Axenfeld rieger anomaly/ syndrome Peters anomaly Ectropion uveae Congenital iris hypoplasia Aniridia PFV Microphthalmos Microcornea Ectopia lentis	Glaucoma and associated nonacquired systemic features Phacomatoses (NF, SW syndrome) Chromosomal disorder (e.g., trisomy 21) Homocystinuria Metabolic disorder (e.g., lowe syndrome) Connective tissue (e.g., marfan, stickler) RSTS NF Congenital rubella syndrome	This group includes secondary glaucoma due to various acquired causes other than cataract surgery Uveitis Trauma Steroid Induced Tumours Retinopathy of prematurity Prior ocular surgery other than cataract	Glaucoma after cataract surgery has been given a separate place considering the high frequency of glaucoma following cataract surgery in children

PCG=Primary congenital glaucoma, IOP=Intraocular pressure, PFV=Persistent fetal vasculature, NF=Neurofibromatosis, SW=Sturge-weber, WGA=World Glaucoma Association, RSTS=Rubenstein-taybi syndrome

opacification/scarring.[16-18] Conversely, many children may have had symptoms for a considerable period before presentation to an ophthalmologist simply because the disease was not thought of, hence delaying diagnosis.

Age of Onset

- The age of diagnosis depends upon the national criteria for pediatric patients
- USA: <18 years
- UK, Europe, Asia: <16 years.

Structural Abnormalities in the Angle

The common denominator in all developmental glaucoma is the underdevelopment of the Trabecular meshwork. The underlying trabecular dysgenesis is common to all these disorders and causes the aqueous to dam inside the eye, thuPara 2s raising the IOP. Recognizing an abnormal angle is an essential factor leading to the diagnosis.

The dysgenetic anterior chamber angle resembles immature trabecular meshwork with thick sub canalicular tissue.[19] One report of the trabecular tissue obtained during surgery described the thickening of trabecular beams, increased collagen fibrils in the trabecular matrix, and a thick and constant layer of amorphous material underlying the endothelium of the Schlemm canal.[20] The resultant impaired outflow may be one of the primary causes of increased IOP in developmental glaucoma. Though not widely used or available, recent evidence[21] suggests that hand held anterior segment optical coherence technology may be helpful in the angle assessment in the management of PCG.

Examination Under Anesthesia

Once developmental glaucoma is suspected, a detailed examination under anaesthesia is required to accurately diagnose the phenotype and meticulously record baseline parameters for comparison during follow-up. The standard components of EUA are given below, with a suggested proforma adopted by the Indian Pediatric Glaucoma Society.

A comprehensive sequence of examination should comprise the following components:

- IOP assessment (without speculum) as soon as possible under the mask before intubation to minimize the effects of anaesthesia on recorded IOP
- Operating microscopic examination (corneal diameter, clarity, details of the anterior chamber, iris, pupil, lens clarity, gonioscopy)
- Central corneal thickness and axial length
- Fundus examination and optic nerve head photo if possible, with attention to cupping and rim changes if visibility allows
- Ultrasound biomicroscopy (UBM) in hazy corneas-an asset to evaluate the anterior chamber.

Nonacquired Ocular Anomalies

Nonacquired ocular anomalies meet the definition of childhood glaucoma associated with ocular abnormalities and trabecular dysgenesis and comprise the disorders classified as anterior segment dysgeneses. Table 3 lists the conditions which fulfil this definition. We shall describe the common conditions usually encountered in the clinic.

Aniridia

The most well-known anterior segment abnormality affecting the iris is aniridia or absence of the iris. Aniridia is a panocular disorder affecting the cornea, anterior chamber, iris, lens, retina, macula, and optic nerve.[22] There is complete or incomplete iris absence [Figure 1].

Table 3: Childhood glaucoma entities classified as per (childhood glaucoma research network)*

Primary childhood glaucoma
PCG
Isolated angle anomalies (± mild congenital iris anomalies)
Meets glaucoma definition (usually with ocular enlargement)
Subcategories based on age of onset
Neonatal or newborn onset (0–1 month)
Infantile onset (>1–24 months)
Juvenile onset or late-recognized (>2 years)
Spontaneously arrested cases with normal IOP but typical signs may be classified as PCG
JOAG
No ocular enlargement
No congenital ocular anomalies or syndromes
Open angle (normal appearance)
Meets glaucoma definition
Secondary childhood glaucoma
Glaucoma associated with nonacquired ocular anomalies
Includes conditions of predominantly ocular anomalies present at birth which may or may not be associated with systemic signs and meets glaucoma definition
Includes
Axenfeld rieger spectrum (syndrome if systemic associations)
Peters anomaly spectrum (syndrome if systemic associations)
Ectropion uveae; congenital iris hypoplasia
Aniridia
PFV (if glaucoma present before cataract surgery)
Oculodermal melanocytosis (nevus of Ota)
Posterior polymorphous dystrophy
Microphthalmos
Ectopia lentis
Ectopia lentis et pupillae
Megalocornea with zonular weakness
Glaucoma associated with nonacquired systemic disease or syndrome
Includes conditions predominantly of systemic disease present at birth which may be associated with ocular signs and meets the definition of glaucoma
Glaucoma associated with acquired condition
Glaucoma following congenital cataract surgery
Meets glaucoma definition after cataract surgery performed
Excludes acquired cataract or cataract in the setting of a syndrome with a known glaucoma relationship, such as lowe syndrome, congenital rubella syndrome, aniridia

*Beck A, Chang TC, Freedman S. Section 1: Definition, classification, differential diagnosis. In: Weinreb RN, Grajewski A, Papadopoulos M, Grigg J, Freedman S, editors. WGA Consensus Series-9: Childhood Glaucoma. Amsterdam, The Netherlands: Kugler Publications; 2013. p. 3-10. PCG=Primary congenital glaucoma, JOAG=Juvenile open angle glaucoma, PFV=Persistent fetal vasculature, IOP=Intraocular pressure, WGA=World Glaucoma Association

Four phenotypes of aniridia have been identified based on associated ocular and systemic anomalies:[23]

1. Aniridia with iris changes and normal visual acuity
2. Aniridia with foveal hypoplasia, nystagmus, corneal pannus, glaucoma, and reduced vision
3. Aniridia associated with Wilm's tumor (the aniridia – Wilm's tumor syndrome) or other genitourinary anomalies
4. Aniridia that is associated with mental retardation.

Glaucoma is reported later in childhood at 6% to 75%.[24,25] Children with aniridia develop glaucoma in late childhood or early adulthood due to progressive anatomical changes in the anterior chamber angle.[26] Grant and Walton[6] found that progressive angle structure changes may occur during the first two decades of life in patients who will develop glaucoma. These changes include attachment of the rudimentary iris anteriorly, thereby covering the filtration area of the trabecular meshwork. Most of the filtration area is covered by the iris remnant in patients with glaucoma.

Axenfeld and Rieger Anomaly

ARS, first described in 1883, is a rare genetic disease associated with ocular anterior segment dysgenesis and a high prevalence of early-onset glaucoma. Due to the variability of ARS presentation, it was initially categorized as multiple distinct pathologies (Axenfeld anomaly, Rieger anomaly, Rieger Syndrome) (AXENFELD 1920; RIEGER 1935)[7] Due to dysregulation of aqueous humour flow through the abnormal angle, approximately 50% of patients with anterior segment dysgenesis (ASD) develop glaucoma.[8,9] It may manifest during infancy,

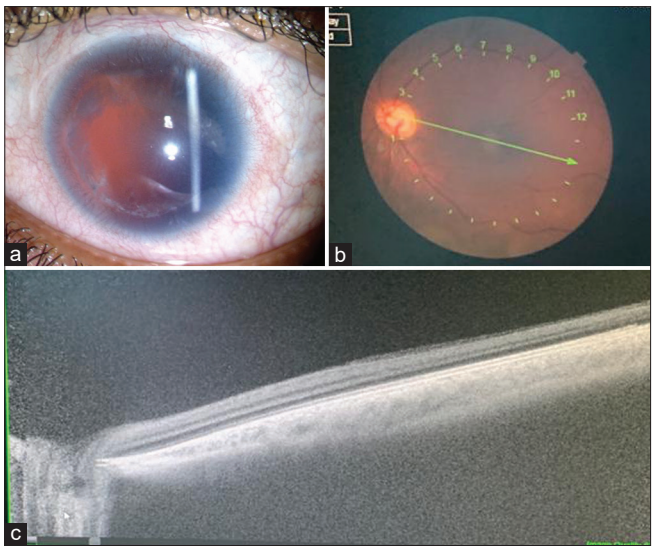

Figure 1: (a) Clinical photograph of a child with aniridia showing limbal stem cell deficiency and corneal pannus, and absence of iris. (b) Fundus picture of the same patient showing loss of foveal reflex. (c) OCT scan throught the fovel center showing a lack of foveal controur indicating foveal hypoplasia

although it commonly appears in childhood or young adulthood. Congenital glaucoma has also been reported with ARS in conjunction with corneal oedema or buphthalmos.[22,27]

Ocular defects in ARS are typically bilateral. Axenfeld anomaly is characterized by posterior embryotoxon [Schwalbe's line is visible by external examination, Figure 2a] and peripheral iris-corneal attachments obstructing or distorting angle structures, causing glaucoma. Peripheral anterior synechiae (bridging of tissue between the iris and anterior angle [Figure 2b]), is the most common feature.[22,27] Posterior embryotoxon may occur in 15% of the normal population itself. The additional feature of peripheral iris attachments indicates the presence of an Axenfeld anomaly. The cornea is otherwise normal in the typical case of ARS, though occasional patients may have a variable size or shape of the cornea.

Rieger anomaly has additional iris abnormalities, including corectopia (ectopic pupils), loss of iris stroma, and polycoria (multiple pupils). There is considerable overlap in the clinical features of Axenfeld and Rieger anomalies, and they are usually referred to together as the ARA.[23,28]

ARA association with systemic abnormalities is termed ARS. The systemic anomalies most commonly associated with the ARS are the teeth and facial bone developmental defects.[29] The dental abnormalities comprise a reduction in crown size [microdontia, Figure 2c], a decreased number of teeth (hypodontia), and a focal absence of teeth (oligodontia or anodontia).[30,31] Facial anomalies include maxillary hypoplasia with flattening of the mid-face, a receding upper lip, and a prominent lower lip, which is significantly associated with dental hypoplasia. Hypertelorism, telecanthus, and a broad flat nose are additional features of the condition.[32] Other features described are redundant periumbilical skin [Figure 2d], oculocutaneous albinism, heart defects, middle ear deafness, mental deficiency, hypospadias, and a variety of neurologic and dermatologic disorders.[33]

Peters Anomaly

Von Hippel in 1897 and Peters in 1906 described patients with buphthalmos with bilateral corneal opacities and iridocorneal adhesions. The hallmark of peters anomaly (PA) is a defect in the Descemet membrane and corneal endothelium with thinning and opacification of the corresponding area of the corneal stroma [Figure 3]. It is usually associated with iridocorneal and/or lenticulocorneal adhesions and a central corneal opacity.[34]

Nearly half of the patients with PA develop glaucoma, which is frequently present at birth. Though the disorder is thought of as occurring in three groups, each may have more than one phenotypic presentation.[35,36]

- Not associated with keratolenticular contact or cataract,
- Associated with keratolenticular contact or cataract,
- Associated with ARS.

The combination of abnormalities in PA causes significant visual impairment due to interruption of the visual axis, often in combination with cataracts.[37]

Peters Plus Syndrome

The clinical features of Peters plus syndrome include the anomaly with short stature, cleft lip/palate,

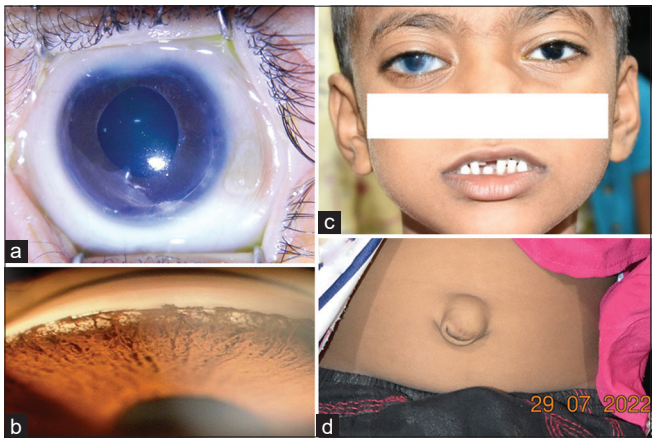

Figure 2: (a) Clinical photograph of a patient with Axeneld Reiger Syndrome showing prominent Schhwalbe's line visible as a posterior embryotoxon. (b) Gonioscopy picture showing the characteristic irido corneal strands and prominent iris processes. (c) Young girl with ARS showing microdontia. (d) Same girl as above showing redundant umbilical skin

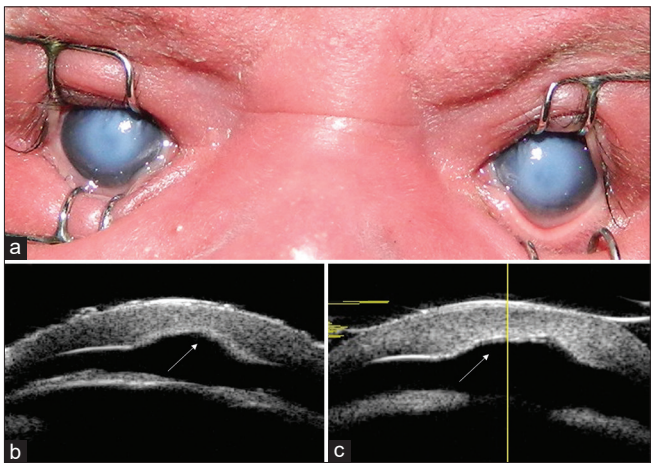

Figure 3: (a) Clinical photograph of both eyes of a baby with Peters anomaly showing the corneal opacity with central clear area. (b and c) Ultrasound Biomicroscopy scans of both eyes showing a thick cornea and a marked Descemet's and posterior corneal defect (white arrows)

brachydactyly, facial dysmorphism, and intellectual disability.[38] Rarely, patients can also have congenital cardiac defects (atrial and ventricular septal defects, aortic and pulmonary stenosis), structural brain abnormalities, hearing loss, and genitourinary abnormalities.

Congenital Primary Aphakia

Congenital primary aphakia (CPA) is a rare anterior segment dysgenesis resulting from aborted lens development during the 4th week of gestation due to failed lens placode induction from the surface ectoderm.[39,40] The presence of the lens is crucial for other developing anterior segment structures. Abnormal lenticular development has a detrimental effect on forming the other anterior segment structures.[41] Disrupted lens development results in a variety of ocular disorders that include glaucoma, microcornea, microphthalmia, PA, and primary aphakia.[42]

CPA has often been labelled the nonspecific term "sclerocornea."[43] The implication of accurately recognizing this entity lies in avoiding incisional surgery, which almost always results in phthisis bulbi.[41] Eyes with cloudy corneas and a silvery-blue hue should be suspected to have CPA [Figure 4a]. UBM demonstrates the absence of the lens and no precise details of the iris or angle visible [Figure 4b].[42,43]

Nonacquired Systemic Anomalies

Nonacquired systemic anomalies include systemic disease conditions present at birth, which may be associated with ocular signs and meet glaucoma's definition. The CGRN has identified the following diseases to qualify for nonacquired systemic anomalies [Table 2].

Some of these conditions are described below:

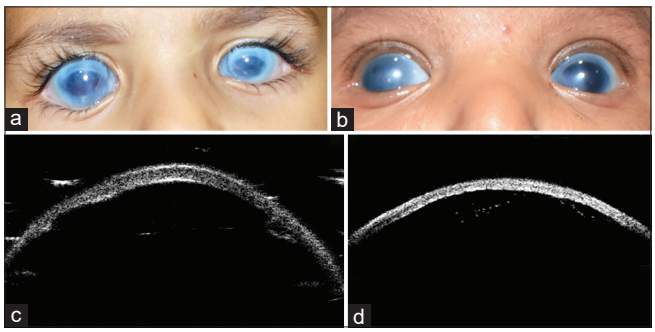

Figure 4: (a and b) Clinical photographs of two children with Congenital Primary aphakia with glaucoma. Note the buphthalmos and silvery hue characteristic of the condition. (c and d) Ultrasound Biomicroscopy scans of children with CPA showing absence of lens, thin hypoplastic cornea and absence of other anterior segment structures

Sturge-weber syndrome (encephalofacial angiomatosis, encephalotrigeminal angiomatosis)

Sturge-weber syndrome (SWS) is a flat facial capillary malformation that follows the distribution of the fifth cranial nerve. Glaucoma is seen in nearly 50% of patients and is more likely to appear in infancy than later.[44] If glaucoma occurs in infancy, the mechanism is an isolated trabeculodysgenesis angle anomaly with or without abnormalities in the canal of Schlemm and juxtacanalicular tissue. As the child ages, the elevated IOP is due to an elevation of episcleral venous pressure. The most typical postoperative complications are hypotony and choroidal detachment due to rapid expansion of the choroidal hemangioma with fluid effusion into the suprachoroidal and subretinal spaces.[45] Medical therapy involves peri-operative oral propranolol[45] and antiglaucoma medications. Oral propranolol is an effective method to minimize the development of sight-threatening choroidal effusion after glaucoma surgery in SWS.[46]

Phacomatosis pigmentovascularis

Phacomatosis pigmentovascularis (PPV) is characterized by the co-existence of vascular and pigmentary birthmarks.[47] Signs and symptoms include port-wine birthmark, dermal melanocytosis, patches of hyperpigmentation, and café au lait spots.[48] About half of the people with PPV have systemic involvement, such as neurologic, ocular, or muscular abnormalities.[49] Several subtypes of PPV have been identified, which are generally distinguished based on the specific type(s) of skin features present. Ocular melanosis (also called ocular melanocytosis) commonly occurs along with nevus of Ota. Complications of nevus of Ota include glaucoma and melanoma. Other eye conditions reported in PPV include iris hamartomas and iris nodules.[50]

Neurofibromatosis

Neurofibromatosis 1 (NF1), also known as the von Recklinghausen's disease, is a rare dermatosis with an autosomal dominant inheritance, characterized by myriad symptoms and signs that mirror the involvement of skin, eye, peripheral nervous system, and skeletal system.[51] The National Institute of Health Consensus Development Conference proposed the term NF1 and formulated the current diagnostic criteria 1987.[52] NF1 is the form with the most characteristic ocular manifestations. Lisch nodules of the iris are among the well-known diagnostic criteria for the disease. Glaucoma and associated globe enlargement have been described in many patients with NF1. Optic nerve glioma may cause strabismus and proptosis, and palpebral neurofibroma may reach a considerable size and occasionally show a malignant transformation.[53] NF type 1 patient with or without orbital facial involvement. In patients with orbito-facial signs, glaucoma was present in 23% of patients.[54]

Rubinstein taybi syndrome

Rubinstein Taybi syndrome (RTS) is a rare autosomal dominant genetic disorder with a reported prevalence of 1:125,000 live births. The diagnosis of RSTS is essentially clinical, with typical characteristics such as a beaked nose, broad thumbs, and hallux valgus. Ocular features reported commonly include lacrimal duct obstruction, corneal abnormalities, congenital glaucoma, congenital cataract, and the iris and optic nerve head coloboma.[55] Congenital glaucoma is an infrequently reported condition in RSTS. A review of ocular findings in 614 patients with RTS said glaucoma in 32 cases and corneal opacities in 25 cases.[56] In a series of 24 patients with ocular features in RSTS, only one had bilateral congenital glaucoma.[57]

Management

The management of congenital glaucoma starts with counselling the parents, which should include a discussion of what glaucoma is, the need for surgery and possibility of multiple surgeries. They need to be explained the need for life-long follow-up and the combination of problems to be tackled like IOP control, amblyopia management, refractive correction and the possibility of the requirement of keratoplasty in nonclearing corneal opacity.

Examination under anaesthesia is the first step to gauge the severity of the disease and the extent of glaucomatous damage. The parameters evaluated include corneal oedema, IOP, and cup-disc ratio.

The treatment of developmental glaucoma is surgical. Medical management is temporary until the child can be posted for general anaesthesia.[58] The surgical options include goniotomy, trabeculotomy, and trabeculectomy with antifibrotic agents.[59] A trabeculectomy-trabeculectomy combined surgery has resulted in more favourable outcomes, and many surgeons prefer that approach.[60] The surgical success is varied. Mandal *et al*. reported an IOP drop of 41.1% in PCG patients, with IOP <21 mmHg maintained at 94.4% and 63.1% at the 1st and 6th year postsurgery respectively.[16] In refractory cases not responding to surgery, repeat surgery is needed. Glaucoma drainage devices, both valved and nonvalved, have been reported to be successful after the failure of conventional surgery.[61]

Conclusions

With the varied phenotype and overlapping features among various forms of anterior segment dysgeneses, it sometimes becomes challenging to reach an exact diagnosis by clinical evaluation and investigation alone. A screening test of the most common genes implicated in the diseases we encounter would be the first step in unravelling the mystery of diagnosing these problematic conditions. Because information from genetic testing allows the determination of the mode of inheritance, it can also be used to inform genetic counselling and risk assessment for family members. This approach would result in a more holistic and informed management of these complex diseases.

Declaration of patient consent

The authors certify that they have obtained all appropriate consent forms from the legal guardians of the patients. In the form, the guardians have given the consents for the images and other clinical information of the patients to be reported in the journal. The guardians understand that the names and initials of the patients will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Nil.

Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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