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Juvenile-onset open-angle glaucoma – A clinical and genetic update

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Abstract

Juvenile-onset open-angle glaucoma (JOAG) is a subset of primary open-angle glaucoma that is diagnosed before 40 years of age. The disease may be familial or non-familial, with proportions varying among different populations. Myocilin mutations are the most commonly associated. JOAG is characterized by high intraocular pressures (IOP), with many patients needing surgery. The mean age at diagnosis is in the 3rd decade, with a male preponderance. Myopia is a common association. The pathophysiology underlying the disease is immaturity of the conventional outflow pathways, which may or may not be observed on gonioscopy and anterior segment optical coherence tomography. The unique optic nerve head features include large discs with deep, steep cupping associated with high IOP-induced damage. Progression rates among JOAG patients are comparable to adult primary glaucomas, but as the disease affects younger patients, the projected disability from this disease is higher. Early diagnosis, prompt management, and life-long monitoring play an important role in preventing disease progression. Gene-based therapies currently under investigation offer future hope.

Keywords

juvenile onset open angle glaucoma; juvenile open angle glaucoma; early onset glaucoma; juvenile ocular hypertension; juvenile normal tension glaucoma; myocilin; MYOC; CYP1B1; JOAG; juvenile glaucoma

1. Introduction

Juvenile-onset open angle glaucoma (JOAG) has long been a subject of interest in view of its rarity and unique clinical features. It is relatively common in people of South Asian, West Asian, and African descent when compared to European Caucasians.[25] Because of genetic heterogeneity, the genotype and phenotype characteristics are incompletely understood; however, if left unattended the disease is associated with considerable morbidity in the

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most socioeconomically productive subgroup of the population. In one study, the economic burden of eye disorders and vision loss among the United States population less than 40 years of age was estimated to be $27.5 billion per year.[217] Glaucoma in this population drew a 2% share of all medical costs. Being a disease of childhood and young adults, JOAG patients require life-long close monitoring to preserve their socially productive status.

2. Prevalence

The prevalence of JOAG varies in different populations. It was found that JOAG accounted for 3.4% of all the newly diagnosed glaucomas in a tertiary care center in Nigeria,[108] as compared to 3.3% in India,[43] 1.9% in Saudi Arabia,[7] and 0.7% in Caucasians.[61] The prevalence in the United States of America was estimated to be 1 in 50,000.[196]

JOAG is classified under the umbrella terms of both pediatric glaucoma and adult-onset primary open-angle glaucoma (POAG), and hence its proportion in various studies is different. Studies on the profile of childhood glaucomas have shown a prevalence of 15% in South India[168] and 16% in Ohio.[27] These studies set an upper age limit of 16–18 years, producing the higher reported prevalence. A hospital-based study in Egypt has, however, suggested that JOAG contributes to only 1% of childhood glaucomas.[142] A screening program for POAG in West Africa found that 16% of diagnosed patients were between 20 and 40 years of age.[192] Goldwyn and coworkers[61] found that one-fourth of adolescents and young adults between the ages of 10 and 35 years referred for glaucoma had JOAG.

3. Nomenclature and classification

Primary congenital glaucoma (PCG), JOAG, and adult-onset POAG can be considered a continuous disease spectrum. Immaturity of the conventional outflow pathway is the important underlying pathology for JOAG and PCG. At present, the definition of JOAG is limited to POAG occurring within the limits defined by age, although a classification based on genetic mutations could be useful.

3.1. Nomenclature

3.1.1. Juvenile-onset open-angle glaucoma—JOAG is a type of POAG, where the onset of disease is before 40 years of age.[77] Both the upper and lower age limit considered for this diagnosis has been variable, ranging from 5–35 years,[46] 10–30 years,[195] 10–35 years,[124] and 10–40 years;[70, 71] however, 3 years of age is generally taken as the lower limit as the eye is not expected to enlarge in response to high IOP after this age.[8] To address such discrepancy in nomenclature of childhood glaucomas, the Childhood Glaucoma Research Network proposed an International Consensus Classification[193] that stated that the earliest age of onset for JOAG is considered to be 4 years, and the upper limit may extend up to 30 or 40 years, after which it will be classified under adult-onset POAG. The discrepancy in age-based classification, as reflected through recruitment criteria of different studies, remains. The crucial features for diagnosis include an IOP >21 mmHg on at least 2 occasions, with open angles, supported by distinct glaucomatous optic neuropathy with or without corroborative visual field (VF) defects.

3.1.2. Juvenile ocular hypertension (JOHT)—

The term ‘juvenile ocular hypertension’ (JOHT) was first coined in 1948.[93] JOHT is diagnosed when the central corneal thickness (CCT)-corrected IOP is over 22 mmHg on at least 2 different occasions in the absence of glaucomatous optic neuropathy and VF defects in patients younger than 40 years.[77, 124] Up to 43% of fellow eyes of unilateral JOAG can manifest JOHT.[72] It is frequently associated with an IOP greater than 30 mmHg, fluctuating IOPs, and thick corneas.[184] Sun proposed that many patients with high IOP detected in the juvenile age group may normalize during adolescence and need only long-term follow up, labeling it as ‘adolescence IOP fluctuation’ or ‘adolescence ocular hypertension’.[184] Rousseau and Bito[44] performed primate eye studies of IOPs in rhesus monkeys and proposed that JOHT could be a physiological phenomenon critically important for normal development of the globe size. JOHT is important to be identified and monitored, however, as in some families with JOAG, the younger members may present with only high IOP in the initial stages. JOHT may sometimes be incorrectly diagnosed in young children because of difficulty in obtaining IOP measurements. In such cases an examination under sedation will be useful not only to measure IOP, but also to rule out a secondary cause that could contribute to it.

3.1.3. Juvenile normal tension glaucoma (JNTG)—

JNTG is clinically defined as glaucomatous damage occurring at baseline/highest IOPs ≤ 21 mmHg in individuals less than 40 years of age. Adult onset NTG is more prevalent in Asia, estimated to comprise about 52–92% of all open-angle glaucomas;[37] however, only a few series of JNTG have been documented, primarily focusing upon their distinct vascular and perimetric characteristics.[5, 18, 24, 116, 151, 152] Neuroimaging to rule out possible underlying causes is important. Some unique reports of JNTG include a family of autosomal recessive juvenile glaucoma with novel *LTBP2* variants[162] and a 27-year-old patient with chronic low cerebrospinal fluid pressures from a shunt procedure.[224] A new phenotype of familial normal-tension glaucoma with features of anterior segment digenesis was reported in a two-generation pedigree,[19] though the underlying cause was not evaluated.

3.2. Classification

JOAG is clinically heterogeneous, with variations in age at onset, IOP elevation, extent of goniodysgenesis, and inheritance pattern. This range of manifestations is likely related to the underlying genetic heterogeneity. Birla and coworkers[25] studied the phenotypic characteristics of 414 unrelated Indian JOAG patients and performed a cluster analysis to classify them based on the age of onset, highest untreated IOP, gonioscopic findings and iris features (Table 1). The mean age of the study population was 27 ± 9 years and mean highest untreated IOP was 38.67 ± 12.5 mmHg. Of their cases, 64% had abnormal angle features, and 30% had abnormal iris pattern. They found differences not only in the baseline IOP, but also in their apparently normal looking iris and angle morphology. Figure 1 shows the different angle and iris features observed.

From these clusters, the authors classified JOAG into 4 phenotypic groups.

Group 1: Normal angle and iris features: They presented at a later age than all other clusters and had the lower baseline untreated IOP.

Group 2: Featureless angle and normal iris pattern: They had the earliest presentation.

Group 3: Prominent iris processes or high iris insertion, with a normal iris pattern: They presented with high IOPs, and high iris insertion was associated with greater mean IOP than the presence of only prominent iris processes.

Group 4: Prominent iris crypts and high iris insertion resembling subtle forms of Axenfeld- Rieger anomaly: They had the highest baseline untreated IOP, with over half having an IOP ≥ 40 mm Hg.

Whether this classification system could be applied to all high pressure JOAG patients across different populations needs further evaluation.

4. Demographic and Clinical features

4.1. Demography

The mean age at diagnosis has varied among studies from 16 years to the 3rd decade.[7, 48, 112, 142, 168] Males are more commonly affected.[17, 46, 61, 112, 168] JOAG is usually bilateral,[27, 72, 112] but up to 25% of patients have been reported to present with unilateral disease.[72] The proportion of familial JOAG is variable across populations:[30] 28% among Koreans,[112] 30% among Indians,[25] 43% in Americans,[61, 124] and up to 88% among Africans.[48, 108] Smoking has not been found to confer any risk to disease onset or IOP levels in JOAG.[202]

4.2. Intraocular pressure

Mean IOP during diagnosis of JOAG is usually between 30 and 40 mmHg, significantly higher than that of JOHT.[74, 84, 124] Wide diurnal fluctuations of up to 22 mm Hg have been observed. Peak IOPs could be associated with transient corneal edema, resulting in colored halos and blurred vision;[153] however, one third of patients could remain totally asymptomatic.[112]

4.3. Gonioscopy

JOAG eyes may exhibit angle dysgenesis;[199] however, this phenotypic finding may be more common in some ethnic groups than others. Urbak and coworkers[198] suggested that goniodysgenesis in the form of a transparent to yellow/brown/greyish pretrabecular membrane and abnormally exposed greater arterial circle of iris may be present in some patients. In some subjects, distinct iris processes and persistent uveal meshwork were also noted. Gupta and coworkers[80] studied the gonioscopic characteristics of a cohort of JOAG patients and identified 34% of them as possessing a normal looking angle, while the remaining 66% showed developmental anomalies in form of a featureless angle, a high iris insertion, or prominent iris processes. They defined these forms of angle dysgenesis as: (i) prominent iris processes, where multiple iris processes were seen extending onto the trabecular meshwork (TM) in at least 2 quadrants (180 °), (ii) high iris insertion, when the root of iris was inserted over the trabecular meshwork anterior to the ciliary body band. They may present with or without prominent iris processes (iii) a featureless angle, where there was a lack of pigmentation, and TM could not be differentiated from the scleral

spur. Probably, the compact TM/persistent embryonic tissue gave a featureless/ground-glass appearance to the angle. A high iris insertion with or without prominent iris processes was the most common manifestation of angle dysgenesis in their study.[25, 80]

En face gonioscopy, while being an important tool to determine angle dysgenesis, may not be able to elicit the true extent of trabecular dysfunction.[196] On the other hand, prominent iris processes or other features of goniodysgenesis may not necessarily indicate impaired aqueous outflow.[62] In fact, the line between a normal and abnormal angle (dysgenesis) on gonioscopy is a thin one. Further, the prevalence data for gonioscopic anomalies as anatomical variants in nonglauco-matous eyes has not been analyzed.

4.4. Optic disc

In comparison to adult onset POAG, the optic discs of JOAG patients were found to be of normal size in one study,[98] while another showed larger disc size.[73] A relatively low frequency of disc hemorrhages and smaller beta zone parapapillary atrophy has been noted in comparison to adult-onset POAG.[97, 98] Also, the size of disc hemorrhages have been observed to be smaller in JOAG as compared to NTG, contributing to lower detection rates as well.[97]

4.5. Myopia

Myopia is commonly associated with JOAG.[61, 95, 112, 124, 134, 196] JOAG patients have been seen to have longer axial lengths and myopic refractive status when compared to adult POAG patients.[107] About 42–72% of JOAG patients are myopic, compared to 59% of JOHT patients.[27, 124] Lotufo and coworkers found 38.5% of JOAG eyes to have myopia of 6 diopters or more.[124] An association of JOAG with keratoconus has also been described.[60]

5. Rare associations

The rare systemic associations of JOAG have been summarized in Table 2.

6. Differential diagnosis

Other causes of high IOP in the juvenile age group, discussed below, need to be excluded before labeling a patient as JOAG.

6.1. Pigmentary glaucoma

Pigment dispersion syndrome and pigmentary glaucoma can be distinguished by the presence of a Krukenberg spindle, Sampolesi line, excessive angle pigmentation, a very deep anterior chamber, Scheie stripe or Zentmayer ring on the lens capsule and sometimes even concave iris configuration confirmed on UBM. Patients may present with post-exercise coloured halos and/or blurred vision due to transient IOP spike.

6.2. Steroid-induced glaucoma

Steroid-induced glaucoma can be difficult to differentiate unless there is a history of steroid use, either topical or systemic. A history of seasonal/chronic red eye, itching, skin disorders,

systemic diseases like asthma/nephrotic syndrome and over-the-counter medication usage may raise suspicion. Steroid-induced glaucoma is associated with very high IOPs and in many, though not all, cases IOP decreases once steroids are withdrawn, unlike untreated JOAG that progressively worsens.

6.3. Traumatic glaucoma

Traumatic glaucoma is generally unilateral and can be difficult to distinguish, especially if the history is not forthcoming. Signs of blunt trauma such as sphincter tears, iridodialysis, asymmetrically deep and irregular anterior chamber, phacodonesis, and angle recession on gonioscopy help in diagnosis.

6.4. Uveitic glaucoma

A case of uveitis with minimal telltale signs could be misdiagnosed as JOAG unless carefully looked for. Residual keratic precipitates and retrolental cells may provide a clue. Continuous steroid usage in this setting can also lead to a white eye with high IOP.

6.5. Congenital glaucoma

PCG after 3 years of age can be misdiagnosed as a JOAG, unless one carefully looks at the corneal diameters. Both conditions may have angle dysgenesis and myopia.

6.6. Other developmental glaucomas (Axenfeld-Rieger anomaly, congenital ectropion uveae)

Subtle forms of Axenfeld-Rieger anomaly may be difficult to distinguish from JOAG. Posterior embryotoxon is more common in patients with developmental glaucomas. Congenital ectropion uveae in older individuals is generally unilateral and may be misdiagnosed as JOAG unless the other eye is carefully examined. Gonioscopic anomalies in an eye with JOAG would be symmetrical, while those in congenital ectropion uveae would be more pronounced in the affected eye.

6.7. Primary angle-closure glaucoma (PACG)

Without gonioscopy, early onset PACG (or PACG of the young) may be misdiagnosed as JOAG. With gonioscopy, the high iris insertion typically observed in JOAG needs to be distinguished from the broad peripheral anterior synechiae seen in PACG.

6.8. Megalopapilla

Megalopapilla is a congenitally anomalous optic disc with surface area >2.5 mm^2.[115] The physiologically large disc is accompanied by a large cup, raising suspicion of juvenile glaucoma, if the patient presents at a young age; however, the neuroretinal rim, contour of blood vessels, IOP and visual fields are normal.[115, 165]

6.9. Optic disc cupping secondary to prematurity

There is controversy whether low birth weight is associated with larger optic disc cupping or whether large (physiologic) cupped discs are genetic.[58] In a study of over 2000 children, it was shown that low birth weight, short birth length, and small head circumference at

birth were associated with larger cup/disc ratio suggesting that fetal growth restriction could adversely influence optic nerve head parameters.[164] Prematurity-associated periventricular leukomalacia has been shown to result in pseudoglaucomatous cupping characterized by a large horizontal cup and minimal to no displacement of nasal vessels.[64, 123] Associated VF defects can result from thinning of the periventricular optic radiations and/or transsynaptic degeneration of retinal ganglion cells;[64] however, the IOP tends to remain in normal range, raising suspicion of JNTG.

6.10. Chandler syndrome

Chandler syndrome, the predominantly corneal subtype of iridocorneal endothelial (ICE) syndrome, may be confused with JOAG, especially when the corneal changes are subtle. It is commonly unilateral and may progress to involve the iris at later stages. Demonstration of ICE cells on confocal microscopy can clinch the diagnosis.

7. Investigations

7.1. Structural

7.1.1. Anterior Segment

7.1.1.1. Biometry: A biometric study showed that JOAG patients had lower CCT (mean 521 ±20μ), greater axial length (mean 24.63 ±0.83mm), and deeper anterior chamber depth (mean 3.52 ±0.25mm) compared to age-matched normal subjects, likely attributed to myopia;[46] however, the sample size of the study was not large. The endothelial cell counts of JOAG eyes have also been shown to be lesser.[200, 225]

7.1.1.2. Angle imaging: An ultrasound biomicroscopic study showed that JOAG eyes had wider angles as compared to normals,[199] and another showed shorter TM height, suggesting a structural abnormality underlying the reduced outflow facility.[180] The resistance to outflow in JOAG eyes could be at various levels, either pretrabecular, trabecular or at posttrabecular Schlemm canal (SC) and collector channels.[199] Gupta and coworkers[67] studied the angle of JOAG patients using high definition spectral domain anterior segment optical coherence tomography (OCT) and identified abnormal tissue/hyperreflective membrane covering the TM in 40% of them. Also, the SC could not be identified in 40% of the eyes (Fig. 2). Whether the inability to identify SC is a marker of primary dysgenesis or secondary to trabecular resistance and consequent poor aqueous outflow needs to be further explored.

7.1.2. Posterior segment—Studying the optic disc features on scanning laser ophthalmoscopy, Gupta and coworkers[73] showed that JOAG eyes had enlarged cups, with increased cup depth, cup volume, and cup to disc area ratio compared to PCG and POAG. In OCT retinal nerve fibre layer (RNFL) studies, it has been seen that JOAG eyes have thinner RNFL compared to JOHT and normal age-matched controls.[143, 146]

OCT angiography (OCT-A) has revealed a strong positive correlation between RNFL thickness and vascular density (VD) of disc and peripapillary region in JOAG.[1] The superficial vascular plexus VD of perifoveal regions showed a trend to reduce with increase in IOP.[34]

In patients with JNTG, central retinal arteriolar equivalent, a measure of the diameter of retinal arterioles passing around the disc, was found to be significantly less when compared to JOAG.[116] Another study[5] showed narrowed arterioles in preperimetric JNTG eyes as well. This arteriolar narrowing could translate to reduced blood flow to the optic nerve head and result in glaucomatous optic neuropathy despite normal IOPs.[5, 152] A subsequent study, however, aiming to characterize these vascular differences using OCT-A showed contrasting results, with JOAG eyes manifesting greater peripapillary microvascular attenuation than healthy controls or JNTG.[151]

7.2. Functional

Patients with JOAG usually present at moderate-advanced stages, with baseline mean deviation of <−8.5 dB.[68, 72, 75, 112] The pattern of VF defects depends upon the baseline IOP at which the damage occurs. VF defects in JOAG are not very different from those of adult onset POAG; however, Ko and coworkers, and Park and coworkers found JOAG VF defects to be more diffuse and symmetric between the superior and inferior hemifields.[107, 152] The authors attributed this to the longer axial length and myopic refractive status in their patients, which may confound localized glaucomatous VF defects.[107] In contrast, JNTG showed vertically asymmetric VF defects, especially deeper in the superior paracentral area.[152] This was proposed to be caused by localized impaired blood flow to the optic nerve.

7.3. Histopathology

The decisive pathological feature of goniodysgenesis is anomalous persistence of foetal endothelial membrane that covers the TM at the iridocorneal angle and interferes with the aqueous drainage. This membrane usually becomes fenestrated by the end of the third trimester to allow conventional aqueous outflow.[160] An early histological study[191] on juvenile glaucoma eyes showed thick compact tissue at the anterior chamber side of SC, representing an underdeveloped TM. An electron microscopic study[59] of trabeculectomy specimens from JOAG eyes showed large amounts of extracellular material arranged in a fingerprint-like pattern, resembling basement membrane-like material, causing significant thickening of the cribriform trabecular meshwork in all cases. Characteristically, these histopathological changes may be present among JOAG patients even with normal appearing angle on en face gonioscopy,[191] reinforcing the deeper layer dysgenesis that may account for glaucoma.

8. Genetic factors

Recent evidence suggests that JOAG is genetically heterogenous.[76] While it was typically considered as an autosomal dominant disease with variable penetrance and expressivity,[193, 211] autosomal recessive and sporadic occurrence are also common in certain ethnicities.[22, 76, 102]

Initial linkage analysis pointed to chromosome 1q21–31 as the locus of interest for JOAG (GLC1A), which was later refined to 1q23–25.[118, 158, 196, 210–212] Further studies identified the gene encoding Myocilin (*MYOC*) as the JOAG causing gene in the GLC1A locus.[57, 102] Apart from *MYOC, CYP1B1* and less commonly *LTBP2* have been associated

with high-pressure JOAG. Optineurin (*OPTN*) and TANK-binding kinase 1 (*TBK1*) have been associated with JNTG. For JOAG families, genetic testing allows for identification of family members with disease-causing mutations which makes possible early diagnosis and treatment, and also obviating the need for unnecessary regular ophthalmic check-ups when negative.[35, 89, 176]

8.1. Myocilin (MYOC)

Myocilin was the first identified glaucoma-causing gene, and mutations are known to cause JOAG and adult onset POAG.[87, 101] The distribution of *MYOC* mutations contributing to JOAG have varied among different ethnicities, ranging from 5.8% in Chinese cohorts[87] to 12.5% in Taiwanese,[222] 17.4% in Iranian,[22] and 34% in Brazilian cohorts.[186] Such diversity also existed among familial cases, with *MYOC* contributing to 8% of cases among North American JOAG pedigrees,[209] to 27% among Indians,[77] and to 33% in a mixed-ethnicity study.[170] The sample sizes widely differed among these studies, however, and not all *MYOC* mutations were accounted for.

The lifetime risk of developing open-angle glaucoma in *MYOC* mutation carriers is estimated to be 60–100%.[76] The gene was initially cloned as a steroid-response protein from cultured TM cells, named ‘trabecular meshwork-induced glucocorticoid response (TIGR) protein’.[9, 96] Subsequently, the gene was isolated and localized to cilium connecting the inner and outer segments of photoreceptor cells, and therefore named the ‘myocilin’.[209] Myocilin is an extracellular protein widely expressed in normal tissues, with high expression in the trabecular meshwork.[188, 205] *MYOC* mutations cause intracellular protein aggregation resulting in reduced amounts of extracellular protein. Aggregated mutant protein can cause apoptosis.[205] A histochemical study of a JOAG case caused by *MYOC* p.Tyr437His identified abundant accumulated mutant protein within endoplasmic reticulum (ER) of TM cells that caused ER stress and cell loss.[82]

Over 250 *MYOC* mutations have been reported, among which 37.7% are deemed pathogenic.[205] At least 93% of disease-causing mutations are located in the 3rd exon that encodes the olfactomedin-homology domain.[28, 57, 111, 145, 196, 205] The majority of pathogenic *MYOC* mutations are missense alleles (84%); however, the most common *MYOC* mutation (in both JOAG and POAG) is a nonsense mutation (p.Gln368stop) that also causes protein aggregation.[205] *MYOC* mutations can cause both JOAG and adult onset POAG, however, most of the mutations cause JOAG,[88, 133, 196, 205, 214, 222] and usually familial disease.[77, 170, 209] p.Pro370Leu is a frequent and severe JOAG causing *MYOC* mutation.[76] Selected *MYOC* mutations have been summarised in Table 3. Many *MYOC* mutations have only been found in one or few families, such as p.Asn57Asp,[170] p.Cys245Tyr,[54] p.Pro274Arg,[129] p.Ile345Met,[186] p.Thr377Arg,[207] p.Asp384His,[87] p.Glu385Lys,[41] p.Tyr453MetfsTer11,[186] and p.Ile499Ser.[170] Several common *MYOC* polymorphisms have also been identified including, p.Glu340Glu, p.Arg76Lys and p.Gly122Gly.[77, 181] A combination of the p.Asn480Lys mutation and IVS2 730+35 G>A polymorphism has also been proposed to increase the susceptibility to JOAG.[139] A Brazilian study supported a founder effect of *MYOC* p.Cys433Arg variant in JOAG, predicting its age to be of 43–59 generations.[130]

While *MYOC* mutations are commonly associated with autosomal dominant JOAG, *de novo* mutations have also been reported.[111, 175] A study among JOAG patients (both familial and sporadic forms) found that *MYOC* mutations were much more common in familial (27%) as compared to sporadic JOAG cases (2%) and concluded that genetic screening for *MYOC* among the sporadic group may not be entirely fruitful.[77]

8.2. Cytochrome P450 Family 1 Subfamily B Member 1 (CYP1B1)

The *CYP1B1* gene has been implicated in PCG, JOAG and adult onset POAG.[132, 137, 185] The prevalence of *CYP1B1* mutations causing JOAG have also varied across the world, ranging from 2% among Brazilian cases[186] to 11.7% in Indian,[4] 17.4% in Iranian,[22] and nearly 86% among Saudi Arabian cases.[2]

It has been hypothesized that *CYP1B1* and *MYOC* genes may act through a common biochemical pathway, with the former acting as a modifier for the latter's expression.[201] Svidnicki and coworkers[186] performed gene sequencing in Brazilian JOAG patients and identified both *MYOC* and *CYP1B1* variants. The *MYOC* damaging variants were identified in 34%, but *CYP1B1* damaging variants were found only in 2%. While the role of *CYP1B1* in glaucoma is not entirely understood, animal models have shown that *CYP1B1* deficiency leads to abnormalities in the TM.[186] Acharya and coworkers[4] suggested that monoallelic *CYP1B1* mutations may lead to JOAG, while biallelic mutations cause PCG. Digenic inheritance of JOAG was also identified, where both *MYOC* and *CYP1B1* mutations led to JOAG in a family, while only *MYOC* mutation manifested as POAG.[201]

Gupta and coworkers[78] studied the frequency of *CYP1B1* p.Glu229Lys and p.Arg368His mutations among 120 families of sporadic JOAG and found that only 7.5% and 5.8% of them harboured the mutations respectively. Interestingly, Abu-Amero and coworkers[2] identified p.Gly61Glu mutations in 86% of JOAG patients of Saudi Arabian origin. Bashir and coworkers[20] reported a Pakistani family with coexisting recessively inherited JOAG and PCG from the same mutation (Gly61Glu).

Selected *CYP1B1* mutations identified in JOAG cases are summarised in Table 3. The less frequent mutations reported are p.Pro52Leu,[186] p.Trp57Cys,[4] p.Thr404SerfsTer30,[186] p.Ile471Ser,[87] and p.Arg523Thr.[4]

8.3. Latent transforming growth factor-beta-binding protein 2 (LTBP2)

An autosomal recessive form of JOAG associated with two novel variants of *LTBP2* was identified by Saeedi and coworkers,[162] although LTBP2 mutations have been classically associated with Weil-Marchesani syndrome. A case of digenic inheritance of *MYOC* and *LTBP2* in a family with autosomal dominant JOAG is also reported.[173]

8.4. Optineurin (OPTN) and TANK-binding kinase 1 (TBK1)

The evidence for a role of *OPTN* (optic neuropathy–inducing protein) in JOAG has been conflicting. *OPTN* is expressed in trabecular meshwork, nonpigmented ciliary epithelium, retina, and in other nonocular tissues such as brain.[216] The role of *OPTN* as an autophagy receptor has been linked with glaucoma pathogenesis. *OPTN*-mediated autophagy is

promoted by *TBK1*.[83] Both have been associated with familial NTG. Rare mutations and variants of *OPTN* such as p.Leu41Leu, p.His486Arg, p.Arg329Gly and p.Leu494Trp have been identified in some JOAG patients in the Canadian, Chinese, and Korean population,[87, 150, 216] but these variants have uncertain pathogenicity and these results have not been validated in functional studies.[203, 221] Two large families of autosomal dominant *TBK1* associated JNTG have also been reported.[24, 56]

8.5. Others

Other loci for JOAG candidate genes have been proposed at 5q, 9q22, 15q22-q24 and 20p12 by genome-wide scan maps.[149, 204, 213] Mutations in several other genes that have an association with JOAG are:

The *CPAMD8* gene (complement component 3- and pregnancy zone protein-like alpha-2-macroglobulin 360 domain-containing protein 8) was associated with 4 members of 2 families with apparent JOAG, with one of the families also having Stickler syndrome.[171] Most patients with *CPAMD8* variants in this study had cataract, iris hypoplasia and retinal detachments and hence may not be the classical primary JOAG.

Mutations in *LMX1B (*LIM homeobox transcription factor 1-beta) gene have been shown to increase the susceptibility of glaucoma in patients with nail patella syndrome.[140, 194]

Hereditary motor and sensory neuropathy has been associated with congenital and juvenile glaucomas,[14, 104, 197] with some reports suggesting myotubularin-related protein (MTMR) genes to play a role.[16, 148]

22q11.2 microduplication syndrome has also been associated with infantile and juvenile glaucomas, likely attributed to mutations in *CLDN-5* (claudin-5) gene.[39, 45]

Pediatric glaucoma, congenital more often than JOAG, has been diagnosed in many patients with cutis marmorata telangiectatica congenita (CMTC).[47, 144] Generalised CMTC disease and CMTC lesions on the face posed higher risk of glaucoma.[31] Their genetic relations are yet to be known in detail.

Variants of EFEMP1 (epidermal growth factor containing fibulin-like extracellular matrix protein 1) have been associated with severe JOAG in three Philippine families, with 76% of the affected blind in at least one eye.[38]

Fernández-Martínez and coworkers reported heterozygous variants in *RPGRIP1* (retinitis pigmentosa GTPase regulator-interacting protein 1) to be associated with JOAG.[55]

A heterozygous mutation in oligoadenylate synthetase 3 (*OAS3*) gene was reported in a Chinese JOAG family.[218]

The role of glutathione S-transferase (*GSTM1, GSTT1*) polymorphisms in JOAG susceptibility has been studied but significant associations were not detected.[127]

9. Genotype-phenotype

Understanding the relationship between disease-causing mutations and clinical phenotype can help define a surveillance and treatment plan for affected patients; however, for many JOAG-related mutations clear genotype-phenotype correlations are not defined, partly because of variable expressivity and, in some cases, reduced penetrance. Additionally it is possible that environmental factors can also modify disease phenotypes.[220]

Depending on the site and nature of the *MYOC* mutation, most JOAG patients have higher IOP and a more severe disease course compared to adult onset POAG.[190] *MYOC* mutation carriers usually respond less well to medical and laser therapies, warranting early surgical interventions.[57, 84, 90, 138, 220] The penetrance also varies; for example, the penetrance at 30 years of age in pedigrees carrying *MYOC* p.Pro370Leu was up to 100%, while for p.Asn450Tyr, p.Gly367Arg it was 50%, and 25% for p.Gln368stop mutation (unpublished data).[35, 90, 227]

Disease secondary to *MYOC* Pro370Leu mutations exhibit earlier onset and a more aggressive phenotype, with high IOP refractory to medical management.[32, 208, 227, 228] *MYOC* p.Gly246Arg, p.Tyr437His and p.Asn450Tyr also have been shown to manifest early with severe disease.[15, 207] On the other end of the spectrum are p.Gln368stop and p.Cys433Arg mutations associated with milder disease that manifested at a later age with lower IOP.[10, 214, 227] Phenotypic features of other *MYOC* mutations appear to be intermediate between these extremes.[121, 207] Table 4 summarizes the mean age at diagnosis and maximum IOPs recorded for selected JOAG causing *MYOC* mutations.

Phenotypic variability associated with *MYOC* mutations is also population dependent. Yao and coworkers[220] reported a recurrent missense p.Gly367Arg *MYOC* mutation transmitted as autosomal dominant JOAG in 5 generations of a Chinese family. This genotype was characterized by early age at onset, incomplete penetrance, high IOP with rapid deterioration after 30 years of age, and no significant gender disparity. On the other hand, Iliev and coworkers[90] studied the same mutation in a large Swiss pedigree and summarized the phenotype as a late-onset JOAG.

Gupta and coworkers[81] showed that familial JOAG patients presented at least 4 years earlier than those without a family history of glaucoma and had better disease outcomes, likely due to their awareness and early presentation. A negative family history was associated with ten-fold higher likelihood of presenting with a severe glaucomatous VF defect; however, another larger study by the same authors comparing the phenotype of familial versus non-familial patients found no significant differences between age at diagnosis, gender distribution, baseline IOP, goniodysgenesis, and high myopia.[74]

There are limited studies examining the genotype-phenotype correlations of other JOAG contributing genes. JOAG patients with *CYP1B1* mutations are in general younger and manifested a more severe glaucoma when compared to those without them.[177] The phenotype of *TBK1* duplications was characterized by severe, early-onset optic neuropathy with vision loss and a normal IOP.[83]

10. Gene-based therapy

Gene-based therapies have promise to be effective for JOAG caused by *MYOC* mutations. Trimethylamine *N*-oxide (TMAO), a natural osmolyte, facilitated folding and secretion of mutant *MYOC* and rescued cells from apoptosis by alleviating ER stress.[94] Another investigational drug, sodium 4-phenylbutyrate, a molecular chaperone that relieves misfolded protein response in urea cycle disorders, has also been shown to relieve ER stress and lowered IOP in transgenic *MYOC* mouse.[111, 214] Since *MYOC* associated JOAG results in a continuous disease process, it is difficult to administer these drugs over the entire lifetime of the patient. Genome editing using CRISPR/Cas9 system has shown promise by reducing expression of mutant *MYOC* and ER stress, that resulted in lowered IOP and prevented glaucoma development in a mouse model.[92]

11. Management

11.1. Medical

Juvenile glaucoma is often considered difficult to control medically;[6] however, those with not so high IOP and milder disease severity can be controlled on medical therapy. Gupta and coworkers[75] showed that up to 50% of patients could achieve optimal IOP control on medical therapy over 5 years; however, in their series VF worsening was more evident in medically treated rather than surgically treated patients.

While all classes of glaucoma agents can be used in older JOAG patients, alpha agonists are generally avoided in children less than 10 years of age. Latanoprost shows a good ocular hypotensive effect in JOAG eyes as compared to other pediatric glaucomas.[3, 51, 52, 125] Dorzolamide, in association or in fixed combination with timolol, has been shown to improve retinal blood flow in JOAG patients.[40] Miotics though effective, maybe poorly tolerated in JOAG due to ciliary spasm and induced myopia; however, pilocarpine gel forms and Ocusert cause lesser side effects and may be tried in older patients.[189]

Pregnant and nursing JOAG patients pose a therapeutic challenge.[23] Brimonidine is the only drug that is considered possibly safe in pregnancy (FDA category-B); however it is best to avoid it closer to delivery in view of the possible central nervous depression to the newborn. While all other drugs fall into category-C, apraclonidine and pilocarpine can be prescribed in all three trimesters based on the limited data available. Beta-blockers may be used in the first two trimesters, while prostaglandins can be used in third and possibly second trimester as well, with a risk of early labor. Latanoprostene bunod is to be avoided in all trimesters.

The use of oral acetazolamide (FDA category-C) in pregnancy has remained controversial. While animal studies showed teratogenic insults, its usage in pregnant women to treat idiopathic intracranial hypertension did not show a higher incidence of congenital malformations.[53, 85, 114] The dosage varied from 250 mg to 2 g per day and was used in all trimesters.[53, 114]

11.2. Laser trabeculoplasty

Early studies on trabeculoplasty in JOAG eyes using Argon laser showed poor response, and even worsening in a few eyes with pressure spikes reaching up to 35–70 mmHg.[86, 131, 215] Melamed and coworkers[131] proposed trabeculopuncture as a modality to be tried before invasive glaucoma surgeries were planned for JOAG. In this technique, Q-switched YAG laser energy was delivered to create holes in the TM disrupting it, to penetrate into the Schlemm canal, under topical anesthesia. Blood reflux from SC and retro displacement of the iris adjacent to treatment site could be seen. They compared two techniques of trabeculopuncture–the confluent (2 clock hours) versus focal (4 punctures in 4 quadrants),– and concluded that the former treatment was superior, simulating trabeculotomy. The energy levels required for 1-clock hour of trabeculotomy was 156 mJ and for one focal trabeculopuncture was 42 mJ. This treatment is now rarely used.

Selective laser trabeculoplasty (SLT) has gained popularity in treatment of open-angle glaucomas in view of its simplicity, safety, and repeatability. A case report[174] on the use of SLT in a treatment naïve JOAG patient showed 40% IOP drop at one month. Another study[122] compared the outcomes of SLT in JOAG and JOHT against adult onset POAG and found comparable results. Over 70% of the young patients in this study attained success at 12 months, with mean IOP reduction of 30%. High pretreatment IOP was identified as a predictor for SLT success. Gupta and coworkers,[71] in a longitudinal 12-month follow up, evaluated SLT as secondary therapy for medically-uncontrolled JOAG patients and found that 43% of eyes showed >20% reduction in IOP. Absence of angle dysgenesis on gonioscopy was a favorable prognostic factor. Hence, SLT may not be a contraindication in JOAG and could be tried before resorting to surgery. This could also be a viable option in young pregnant women with JOAG.[157]

11.3. Surgical

Many patients of JOAG may require surgical intervention, especially those who are non-compliant or refractory to medical/laser therapy.[84, 196, 210] It has been shown that 40–70% of JOAG require filtering surgeries.[75, 154, 210] Glaucoma surgeries for JOAG can be broadly classified into micro- (or minimally) invasive glaucoma surgery (MIGS) that are performed via an *ab interno* microincision with minimal tissue trauma[163] or invasive surgeries that require external dissection of the conjunctiva and sclera.

11.3.1. Micro-(or minimally)invasive glaucoma surgery

11.3.1.1. Goniotomy: Goniotomy showed 53% complete success and an additional 23.5% qualified success in JOAG eyes at an average 9 years follow-up.[223] Being less invasive with fewer complication rates, it improved the aqueous outflow via the conventional drainage system and spared the conjunctiva for future surgeries if needed. Therefore, it was proposed as the initial procedure of choice in JOAG by some authors,[223] but has not been universally agreed upon due to lack of extensive studies.

Goniotomy with Kahook dual blade has an advantage over conventional incisional goniotomy in that the TM tissue can be excised, and thus prevents fibrosis of the TM

by adhesion of the incised leaflets. Khouri and coworkers showed >30% drop in IOP up to 18-months, using the Kahook dual blade in a 14-year-old JOAG patient.[103]

11.3.1.2. Ab interno trabeculotomy: *Ab interno* trabeculotomy can be performed as microcatheter/suture aided Gonioscopy assisted transluminal trabeculotomy (GATT) or by using a microhook. Grover and coworkers[65] reported 100% clinical success for microcatheter (iTrack, Ellex, Menlo Park, California, USA) aided GATT at mean 20 months in a series of JOAG eyes. Hyphema was the only reported complication, and open trabecular shelves (>180 °) could be seen in all operated eyes at the last follow-up. A subsequent study[206] using the same device showed complete success of only 58% and qualified success of 81% at 18 months in JOAG patients. Another similar device (Trab360™, Sight Sciences, Menlo Park CA, USA) showed 83% success at mean 16 months follow-up, but only six JOAG eyes were studied.[12] *Ab interno* trabeculotomy using prolene suture cannulation is a similar cost-effective alternative that has also been attempted in a few JOAG eyes.[21]

Microhook (Inami & Co. Ltd, Tokyo, Japan) trabeculotomy has been performed in a few JOAG eyes, but a series[91] showed severe hypotony with annular ciliochoroidal detachment in two eyes, attributed to excessive uveoscleral outflow or development of cyclodialysis cleft. The authors proposed that young age and JOAG can be important predictors to risk of ciliochoroidal detachment after microhook ab interno trabeculotomy.

11.3.1.3. Ab interno trabeculectomy: Using a trabectome (NeoMedix Corporation, Tustin, CA) to perform *ab interno* trabeculectomy, a case of JOAG showed IOP and VF stabilization without need for topical glaucoma medications for up to 4.5 years.[147] A subsequent larger case series, however, showed survival rate of 73% at 12 months post-op, with no significant drop in the number of medications.[13]

11.3.1.4. XEN implantation: Usage of the XEN implant has been reported in two JOAG cases; one with intraoperative mitomycin C (MMC) showed better result,[106] while the other in a pregnant woman required several needlings with 5-fluorouracil post-partum to combat early bleb encystment.[226] A few JOAG cases have been included as a part of large-scale XEN studies, but their individual outcomes are unavailable.[167, 169]

11.3.2. Invasive surgeries

11.3.2.1. Ab-externo Trabeculotomy: Trabeculotomy has shown high success rates in JOAG eyes in the long term.[63, 105] With the advent of the illuminated micro catheter, the procedure of trabeculotomy became more predictable and safe. Complete 360-degree Schlemm canal cannulation was possible in 69–100% of JOAG eyes using this technique.[42, 161] Two studies showed encouraging results with 90–100% success at mean 15–43 months follow-up,[42, 161] while another study showed only 53% success at 36 months follow-up, with no significant drop in the number of topical glaucoma medicines.[120] Transient hyphema developed in up to 20% of eyes.[42] Another variation was to combine 180 ° trabeculotomy with sinusotomy (microtrephination of scleral flap over the Schlemm canal); however, it did not show any added benefit in JOAG eyes.[110]

11.3.2.2. Nonpenetrating glaucoma surgeries: To obviate the complications of penetrating surgeries, nonpenetrating surgeries were tried. Viscocanalostomy showed 80% overall success at the end of 3 years, though there were trabeculo-Descemet-membrane micro- and macroperforation in 10%.[179] Nonperforating sclerectomy with intrascleral sodium hyaluronate implant has also been tried in JOAG eyes.[109]

11.3.2.3. Trabeculectomy: The success of trabeculectomy in JOAG has been variable, ranging from 50–90% at 3 years.[154, 195, 219] The complete success rates have been reported to be 80% in 5 years[154] and 52% at 10 years.[172]

Though the results of trabeculectomy may appear encouraging, they also carry a higher risk of complications. Early bleb failure necessitating needling developed in 20% of cases treated with MMC,[49] and younger age at onset has been identified as a risk factor for failure.[154] On the other hand, hypotony also occurred in 20–25% with the usage of MMC in JOAG eyes.[49, 195] A case of hypotony and subsequent maculopathy 14 years after trabeculectomy was reported in a JOAG patient with high myopia. This was hypothesized to be the result of progressive scleral thinning and loss of rigidity with age, leading to biomechanical weakening and collapse of the scleral wall.[99] Chen and coworkers[36] proposed that prophylactic sclerotomy could be combined with standard trabeculectomy in high risk JOAG cases to reduce the chances of massive choroidal effusion or suprachoroidal hemorrhage.

11.3.2.4. Glaucoma drainage devices (GDD): In an attempt to obtain better long-term IOP control and safety profiles, GDD have been tried in JOAG. At 1 year, Ahmed and Baerveldt drainage implants have shown 90.7% success in JOAG eyes, with postoperative complication rates of 9.3%.[113] A long-term study of Molteno implants in juvenile glaucomas showed 83% success at mean 12 years; however, the post-operative complication rate was high in this study, with 53% of cases requiring one or more surgical interventions later.[6]

12. Long-term outcomes and prognosis

There are only a few studies looking at progression rates among JOAG patients. Gupta and coworkers[75] showed that JOAG patients from India exhibited 4.7% structural progression and 7.1% functional progression over 5 years. On the other hand, Kwun and coworkers[112] showed 28% functional progression in Korean patients over a 7-year period. A deterioration of −0.9% per year on the VF index (VFI) was reported among treated JOAG patients.[68] A subsequent study[11] divided functional progression as fast (progression rate <−1 to −2 dB/yr) and catastrophic (progression rate <−2 dB/yr), and identified 3.1% and 1.5% of JOAG eyes to fall within these groups respectively. Though the progression is similar to other primary glaucomas, their younger age portends that a larger proportion could end up with visual impairement.[11] Higher IOP at last hospital visit and long-term IOP fluctuations have been identified as significant risk factors for progression.[68, 112] Another recent study[66] found higher degrees of myopia among JOAG patients to be a significant risk factor for progression. The glaucoma progressors also showed significant progression of myopia in this study.

Among untreated preperimetric JOAG patients from Korea, Bak and coworkers reported 43% overall progression at 5 years, 39% by structural criteria and 5% by functional criteria.[18] Older age at presentation, baseline lamina pore visibility, baseline temporal raphe sign, and greater pattern standard deviation at baseline were identified as risk factors.

Among JOAG patients, reversal of structural and functional parameters has also been observed. With surgical control of IOP, reversal of cupping occurred in up to 17% of JOAG cases.[75, 117, 187] This was proposed to be dependent upon the degree of IOP reduction, age at presentation, compliance of lamina cribrosa and composition of tissues supporting the retinal ganglion cells;[117] however, the changes in RNFL have not been consistent. While a report noted supportive increase in RNFL thickness and reversal of VF defect,[117] another case showed decrease in RNFL, as well as macular ganglion cell complex thickness, over a 3-year period despite a reversal of optic disc cupping after lowering of IOP.[187] It has also been suggested that, though cupping may show reversal after surgical lowering of IOP, this may not reflect a truly healthy rim, but just proliferative glial tissue.[50]

13. Visual disability and quality of life

Visual loss occurring from glaucoma results in substantial decrease in patient utility values and quality of life.[61] The patient's socioeconomic status (SES) also influences the disease outcome, clinical management, and medication expenses.[33] Lower SES and poor health literacy among JOAG patients, who are generally not targeted in glaucoma screening programs, have been associated with severe disease at presentation.[81]

About two-thirds of Nigerian JOAG patients had a visual acuity of 6/18 or worse in their better eye at the time of presentation.[108] Among Indian JOAG patients presenting to a tertiary care facility, 15% were bilaterally blind, and an additional 21% were unilaterally blind by World Health Organization criteria.[70] In Cameroon, the prevalence of bilateral blindness among JOAG patients was 33% at presentation. The affected eye was blind in 50% of patients with unilateral glaucoma. School eye health programs and community-based case detection could aid in early detection, reducing morbidity arising from this disease.[108] Gupta and coworkers[68] showed that the projected risk of bilateral blindness was 10% over a JOAG patient's lifetime even under treatment. This risk could be dependent upon ethnicity. Quality of life of glaucoma patients, as of others, is directly related to the degree of visual acuity loss in the better eye.[79] In a study, Gupta and coworkers[69] found JOAG patients to have a better quality of life compared to adult-onset POAG with the same level of visual disability, primarily because the younger patients had better social support systems and fewer co-morbidities.

14. Conclusion

JOAG is a relatively uncommon subset of the primary glaucomas that has an important impact on the quality of life of young adults who form a productive part of the family and society. The prevalence and inheritance patterns are widely variable in different populations. There may be many genetic causative loci, and only a few have been discovered and understood. Further research on genetic etiology of JOAG will likely identify new and

interesting causative genes that may allow a better classification of the disease. Surgical treatment is needed for many JOAG patients, and although MIGS procedures are being tried, longer term studies are needed to establish their efficacy in this subgroup of patients. Early identification of those at risk and treatment at an early stage remain key to avoid irreversible visual disability.

15. Method of literature search

Literature search was performed in PubMed Medline using the following keywords: juvenile open angle glaucoma, JOAG, juvenile ocular hypertension, juvenile normal tension glaucoma, *MYOC* glaucoma, childhood glaucoma surgery and pediatric glaucoma surgery. Articles published up to December 2020 were reviewed and suitable ones between 1990 and 2020 were mainly included. A few selected articles published before 1990 have been included for historical purposes. Reference lists of included articles were also reviewed to identify additional relevant papers. Articles in English were mainly considered. If non-English articles possessed an English abstract, they were also reviewed. Case reports were included only if they contributed to new information about the disease.

15.1. Limitation

A uniform diagnostic criterion for JOAG was lacking in many of the studies, and sometimes, adolescent secondary glaucomas were included under the umbrella term ‘juvenile glaucoma’. This discrepancy made comparison of data difficult between the studies, and generalized the outcomes in some.

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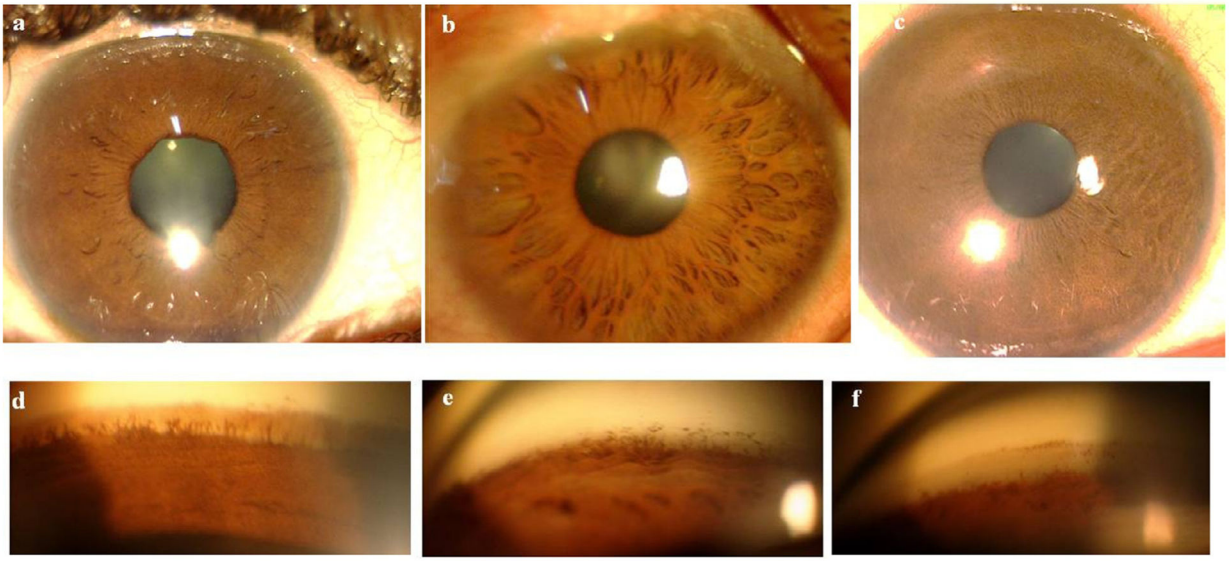

Figure 1 –.

Anterior segment photographs showing a) normal iris crypts, b) prominent crypts of iris, c) lack of iris crypts. Goniophotographs showing d) prominent iris processes, e) high iris insertion, and f) a featureless angle.

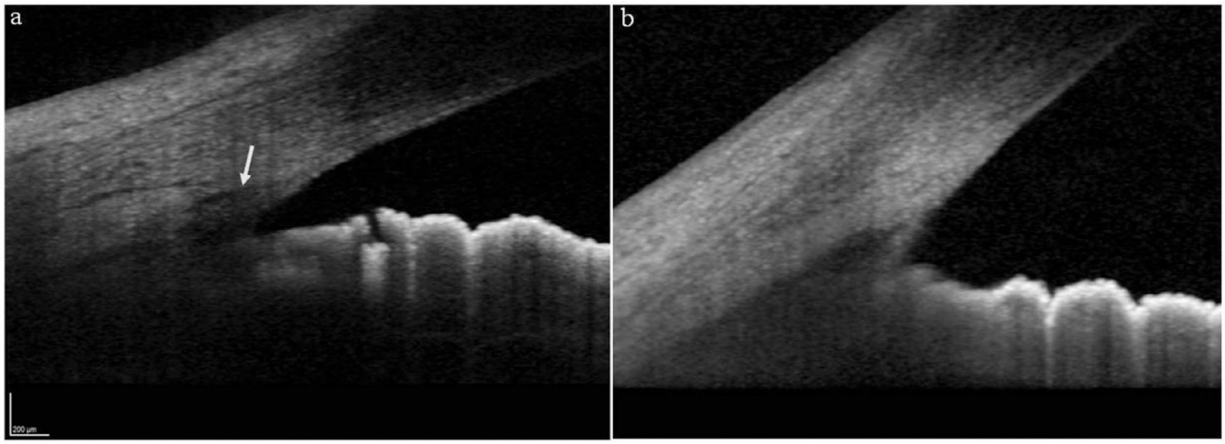

Figure 2 –.

High-definition anterior segment OCT images showing a) normal appearing angle with the white arrow pointing towards the Schlemm's canal, b) an angle of a JOAG patient showing abnormal thickness in the region of trabecular meshwork and without a visible Schlemm's canal.

Table 1 –

Phenotypic classification of JOAG by Birla et al[25]

	Angle			
Iris crypts	**Normal**	**Featureless angle**	**High iris insertion**	**Prominent iris process**
Normal	*Cluster 1*	*Cluster 2*	*Cluster 3*	
	28 ± 9.2 years *	24 ± 9.6 years *	26 ± 7.8 years *	
	36 ± 11 mmHg †	37.8 ± 12.8 mmHg †	41.3 ± 12.7 mmHg †	
Absent Prominent		*Cluster 4*		
		27.4 ± 9.2 years *		

* Mean age at onset

† Mean highest intraocular pressure

Table 2 –

Systemic associations with JOAG

Disease	Systemic features	Ocular features
Hereditary motor and sensory neuropathy[14,16,104,148,197]	Progressive weakness and atrophy of distal limb muscles. Impaired sensation in distal part of limbs. Club foot.	Congenital cataract, JOAG, JOHT, congenital glaucoma, retinitis pigmentosa, optic atrophy.
Nail patella syndrome[119,140,166]	Dysplasia of nails, patella, elbow and iliac horns. Nephropathy. Neurological or vasomotor peripheral limb abnormalities. Epilepsy.	Ptosis, epicanthal folds, hypertelorism, sclerocornea, microcornea, keratoconus, pupillary ectopia, anisocoria, cataracts, JOAG, JOHT, OHT, POAG, NTG.
22q11.2 microduplication syndrome[39,45]	Mental retardation, heart and urogenital malformations, hypotonia, hearing impairment, hypothyroidism, seizures.	Downslanting palpebral fissures, hypertelorism , epicanthal folds, hyperopia, congenital cranial dysinnervation disorders, JOAG, infantile glaucoma, retinal vascular abnormalities.
Cutis marmorata telangiectatica congenita[47,126,141,144]	Generalized red-blue reticular vascular skin pattern, port-wine stain, telangiectasia, ulcers, mental retardation.	Corneal opacity, congenital glaucoma, JOAG, peripheral retinal avascularity, neovascularisation, retinal detachment, granular appearance of macula.

JOAG = Juvenile open angle glaucoma; JOHT = Juvenile ocular hypertension; OHT = ocular hypertension, POAG = Primary open angle glaucoma; NTG = normal tension glaucoma.

Table 3 –

Selected JOAG-causing mutations.

Chromosome	Locus	Gene	Mutations
1q23–25	GLC1A	*MYOC*	p.Gln48His[77,178]
			p.Gly252Arg[26,170]
			p.Gln337Arg[77,182]
			p.Gly367Arg[77,90,135,136,220]
			p.Gln368stop[10,186]
			p.Pro370Leu[35,87,135,136,170,181,186,208,209]
			p.Thr377Met[10,156]
			p.Lys423Glu[29,186]
			p.Val426Phe[121,128]
			p.Cys433Arg[130,155,186]
			p.Tyr437His[10,82,209]
			p.Ile477Asn[10,159]
2p21	GLC3A	*CYP1B1*	p.Gly61Glu[2,20]
			p.Glu229Lys[4,78]
			p.Arg368His[4,78,100,201]
			p.Arg390His[87,183]
14q24	GLC3D	*LTBP2*	p.Pro432Leu[173]
			p.Pro989Arg[162]
			p.Asn1745Lys[162]

Table 4 –

Genotype-phenotype characteristics of commonly associated *MYOC* mutations in JOAG[84, 145]

Amino acid change	Nucleotide change	Weighted Mean age at diagnosis (years)	Weighted Mean Maximum recorded IOP (mmHg)
p.Gly246Arg	NM_000261.1:c.736G>A	21.1 ± 6.2	31.8 ± 6.1
p.Gly252Arg	NM_000261.1:c.754G>A	35 ± 7.3	31.7 ± 6.5
p.Gly364Val	NM_000261.1:c.1091G >T	34	36
p.Gly367Arg	NM_000261.1:c.1099G >A	26.4 ± 6.3	36.3 ± 8.1
p.Gln368Ter	NM_000261.1:c.1102C >T	37.8±5.4	21.1 ± 2.4
p.Pro370Leu	NM_000261.1:c.1109C >T	13.3 ± 2.4	30.9 ± 3
p.Lys423Glu	NM_000261.1:c.1267A>G	28.8 ± 8.1	31.3 ± 3
p.Val426Phe	NM_000261.1:c.1276G >T	18.6 ± 1.4	30.6 ± 0.8
p.Cys433Arg	NM_000261.1:c.1297T>C	22.8 ± 8.9	20±6.3
p.Tyr437His	NM_000261.1:c.1309T>C	21.7 ± 1.2	44.3±1
p.Asn450Tyr	NM_000261.1:c.1348A>T	25.7 ± 4.3	48.3 ± 12.1
p.Ile477Asn	NM_000261.2:C.1430T>A	20.7 ± 1.3	39.6 ± 1.9

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