Juvenile open angle glaucoma: current diagnosis and management

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Purpose of review
The aim of this article is to summarize up-to-date research on the diagnosis and management of juvenile open-angle glaucoma (JOAG).

Recent findings
JOAG can be subclassified into four clinical phenotypes, and faster myopic shift is a risk factor for disease progression. Vessel density is associated with structural damage and worsening visual acuity in JOAG and can be monitored with optical coherence tomography angiography. Genetic studies have revealed molecular causes of JOAG including variants in CPAMD8, MYOC, and CYP1B1. Tube shunt surgeries as well as gonioscopy-assisted transluminal trabeculotomy have been shown to be successful in JOAG.

Summary
Although genetic advances may improve future screening, intraocular pressure monitoring and fundoscopic exam remain the current mainstay of diagnosis. Medical treatment alone for JOAG is typically insufficient with patients requiring surgical management. Selective laser trabeculoplasty may delay or decrease the need for surgery. Trabeculectomy has traditionally been shown to be effective in JOAG, but tube shunt surgery and microinvasive glaucoma surgery are effective alternatives.

Keywords
CPAMD8, CYP1B1, gonioscopy-assisted transluminal trabeculotomy, juvenile open angle glaucoma, MYOC, myocilin, selective laser trabeculoplasty, trabeculectomy, tube shunt surgery

INTRODUCTION

Juvenile open-angle glaucoma (JOAG) is a form of open-angle glaucoma diagnosed in individuals greater than 3 years old and less than 40 years of age. It is characterized by more severe elevations in intraocular pressure (IOP) and rapidly progressive visual field loss when compared with adult primary open-angle glaucoma (POAG). Its prevalence varies among populations and is estimated to affect 0.7% of patients referred for glaucoma evaluation among whites [1] and 3.4% of glaucoma referrals in a study from India [2]. Given its low prevalence, there is still much that is unknown about JOAG. The purpose of this review is to summarize new research on the epidemiology, genetics, pathophysiology, and surgical and medical treatment of JOAG from the last 2 years.

METHODS

Pubmed was used to conduct a literature review on JOAG limited to articles published in the last 2 years. The initial search resulted in 49 articles from which 30 final articles were selected. Review articles and articles which grouped JOAG patients in with POAG patients without a subset analysis were excluded.

EPIDEMIOLOGY AND CLINICAL PRESENTATION

Recent retrospective studies conducted by Baig *et al.*, Bouhenni *et al.*, Saavedra *et al.*, and Chan *et al.* have reviewed the epidemiology of JOAG in pediatric populations [3▪,4,5▪,6]. Only patients 18 years of age or less were included, and average age at diagnosis was 12 and 10 years [3▪,5▪]. JOAG has a slightly higher prevalence among males compared with

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KEY POINTS

- Genetic testing in JOAG may improve future screening, diagnosis, and prognostication and provide opportunities for gene-specific therapy, but additional research is needed regarding feasibility.
- Medical treatment of JOAG alone is typically insufficient, with most cases requiring eventual surgical management.
- Tube shunt surgeries and microinvasive glaucoma surgeries may provide effective alternatives to trabeculectomy.

females, and a majority of patients have bilateral involvement [3▪,4,5▪,6]. Myopia was also common among patients with JOAG (42%) [3▪,4]. Average baseline IOP ranged from 13.0 to 31.5 mmHg [3▪,5▪]. Baseline visual acuity was 0.37 ± 0.76 [3▪] (Snellen equivalent 20/47), and 82.4% of JOAG patients had a baseline visual acuity less than 20/50 [5▪]. Baseline cup to disc ratio (CDR) was 0.68 ± 0.24 [3▪] and 0.7 (interquartile range (IQR) 0.2) [5▪].

Birla *et al.* [7▪] conducted a large study of 414 unrelated JOAG patients that classified patients into four common subgroups of clinical JOAG phenotype using cluster analysis. The first subgroup consisted of patients with normal appearing irises and angles who had the lowest mean IOP (36 ± 11 mmHg) compared with other subgroups and the oldest age of onset (28 ± 9.2 years). The second subgroup had the lowest number of patients (18.6%) and was characterized by earliest age of onset (24 ± 9.6 years) with normal iris morphology and a featureless angle. The third subgroup was the largest (23%) and consisted of patients with high IOP (41.3 ± 12.7 mmHg) and either high iris insertion or prominent iris processes with a normal iris pattern. High iris insertion was associated with a higher mean IOP in this subgroup compared with those with only prominent iris processes. The fourth subgroup was heterogenous and consisted of patients with abnormal iris features (prominent iris crypts or absent iris crypts) that were associated with high IOP. These clinical phenotypes provide information on the prognosis of various subgroups within JOAG and may be further substantiated with future genetic studies.

Beyond the presenting clinical phenotype, Gupta *et al.* [8▪] has characterized risk factors for progression in JOAG by conducting a retrospective study in 73 JOAG eyes (37 participants) with at least 5 years of follow up. Approximately 15% of eyes progressed over 7.4 years. Myopes with a spherical equivalent of at least -1.00 D were 18 times more likely to have glaucoma progression compared with subjects with milder or no myopia ($P = 0.03$ 95% confidence interval 1.14, 217.44). Patients whose JOAG progressed over the study also had a faster myopic shift over time. This study suggests that more myopic JOAG patients may require closer follow-up.

PATHOPHYSIOLOGY OF JUVENILE OPEN-ANGLE GLAUCOMA

The structural damage to the optic nerve head and thinning of the retinal nerve fiber layer (RNFL) seen in JOAG has previously been studied. However, Abdelrahman *et al.* [9▪] has recently investigated the association of vascular perfusion and structural damage in patients with JOAG by conducting a cross sectional study using optical coherence tomography angiography (OCT-A) [9▪]. Vascular perfusion was correlated with RNFL thinning in 25 JOAG eyes. The study found a strong positive correlation between vessel density and RNFL thickness. Best corrected visual acuity was also strongly positively correlated with vessel densities, but not with RNFL thickness. In comparison with vessel density studies in POAG, vessel densities in JOAG were much lower, implying that younger patients may have more severely affected vasculature given the large IOP fluctuations and advanced disease seen by the time of diagnosis in JOAG. This study suggests that OCT-A may have diagnostic and prognostic value in patients with JOAG, given the association of vessel density with both structural damage and worsening visual acuity.

GENETICS

Recent JOAG genetics research has focused on genome sequencing and identification of new genetic variants. Siggs *et al.* [10▪▪] investigated variations in CPAMD8 in an Australian cohort of 139 probands with JOAG. Variants in MYOC and CYP1B1 accounted for 3.6 and 1.4% of cases, respectively. Of the remaining probands, biallelic CPAMD8 variants were found in two probands (1.4%). Glaucoma penetrance for CPAMD8 was found to be 63.6% by 25 years of age. Biallelic CPAMD8 variants were frequently associated with iris abnormalities, cataract, or retinal detachment. CPAMD8 variations were the second most common inherited cause of JOAG after MYOC, suggesting that genetic testing for CPAMD8 sequencing should be considered for JOAG diagnosis and prognostication.

Knight *et al.* [11▪▪] conducted an additional large retrospective cohort of 327 individuals (622 eyes) with JOAG from Australia and New Zealand to identify additional genes associated with JOAG. Family

history of glaucoma was common in their cohorts (64–76%). The most common genetic variant found was heterozygous variants in MYOC [24 (9.5%)], followed by biallelic variants in CYP1B1 [9 (3.2%)]. Biallelic variants were also found in CPAMD8 [1 (0.4%)], and heterozygous variants were found in FOXC1 [2 (0.8%)], TBK1 [2 (0.8%)], COL2Z1 [1 (0.4%)], and OPTN [1 (0.4%)]. Approximately 15% of JOAG patients achieved a molecular diagnosis. This study highlights the need for a genetic testing panel in JOAG as future therapy may be gene-specific, similar to inherited retinal diseases. Future international collaborative efforts are needed to identify further genes associated with JOAG as the majority of cases still lack a molecular diagnosis.

Multiple smaller case series and case reports have also investigated the molecular basis of JOAG among various populations. Lang *et al.* [12] reported a case of a Swiss JOAG patient with a FOXC1 duplication. The patient had marked optic atrophy, a normal anterior segment, and dysmorphic facial features that may be associated with Axenfeld-Rieger syndrome. Xiao *et al.* [13] conducted a study on a Chinese JOAG family and found a heterozygous pathogenic OAS3 variant that segregates with disease phenotype. Yang *et al.* [14▪] conducted an additional case report in a Chinese family with JOAG and found heterozygous variants in *OLFM2* and *SIX6* genes which are thought to be pathogenic when coinherited.

Variants in MYOC are known to account for the largest portion of molecularly diagnosed JOAG cases. Gupta *et al.* [15▪▪] sought to investigate whether MYOC variants occur more frequently among familial vs. sporadic cases of JOAG. They screened 92 unrelated patients and 22 families affected with JOAG for variants in MYOC [15▪▪]. Three coding sequence variants, Gly367Arg, Gln337Arg, and Gln48His, were identified as JOAG-causing mutations. The frequency of MYOC mutations in familial cases (27%) was significantly higher than in sporadic JOAG cases (2%, $P = 0.001$). This study suggests that genetic screening for MYOC mutations should be targeted toward cases with familial rather than sporadically occurring JOAG. Criscione *et al.* [16] identified a novel MYOC variant (c.1153G>A) in a Hispanic patient with JOAG. Further genetic testing within her family demonstrated that the variant segregates with JOAG in an autosomal dominant pattern, implying its pathogenicity. Additional research has investigated the pathogenicity of MYOC in JOAG at a cellular level. Yan *et al.* [17▪] determined that the N450Y MYOC variant, a mutant myocilin gene that has been identified in JOAG, is pathogenic and promotes apoptosis of primary human trabecular meshwork cells by the endoplasmic reticulum stress induced apoptosis pathway. Genetic testing may aid in future JOAG screening, prognostication, and therapy. However, fundoscopic examination and IOP monitoring currently remain first line for diagnosis and screening. Further research efforts are needed on the feasibility of genetic testing for high-risk JOAG patients.

MEDICAL AND LASER TREATMENT OF JUVENILE OPEN-ANGLE GLAUCOMA

Antiglaucoma medications play a large role in the treatment of JOAG. In Saavedra *et al.*'s [5▪] cohort study of 36 JOAG eyes, all were treated with at least one glaucoma medication; 66.6% were on one medication, 16.7% were on two medications, and 16.7% were on three medications. Prostaglandin analogues were the most frequently used medications [5▪]. Alpha agonist medications, such as brimonidine, are well known to cause adverse central nervous system (CNS) side effects in young children. In 2020, Cimolai [18] reviewed cases of adverse CNS effects of brimonidine in pediatric patients including somnolence, lethargy, apnea, and hypoventilation. Current FDA drug label guidelines maintain that brimonidine should be used with caution in young children.

Gindina *et al.* [19▪] conducted translational research on JOAG medical therapy investigating the ability of tissue plasminogen activator (tPA) to rescue aqueous humor outflow reduction in JOAG following steroid administration. Using a mouse model of JOAG, outflow of aqueous humor was measured following periocular steroid exposure and treatment with tPA. They found that tPA minimized aqueous humor outflow restriction typically seen following steroid administration by upregulating the expression of matrix metalloproteinases leading to extracellular matrix remodeling at the trabecular meshwork.

Although medical therapy for JOAG is a beneficial starting point, it often acts as an adjunct therapy to eventual surgical management. Treatment with selective laser trabeculoplasty (SLT) may delay or reduce the need for surgery. Gupta *et al.* [20] prospectively studied the efficacy of SLT in lowering IOP in 30 JOAG eyes. SLT significantly lowered IOP and eliminated the need for further medication or surgery in 43% of eyes at 12 months follow-up, suggesting that SLT may be an effective alternative to early surgical management.

SURGICAL TREATMENT OF JUVENILE OPEN-ANGLE GLAUCOMA

JOAG is often refractory to medical treatment alone, eventually requiring surgical interventions. In 2020,

Warjri *et al.* [21▪] studied the frequency with which JOAG patients require surgery and found that out of 17 eyes with JOAG only two eyes (11.76%) were controlled with medication alone, nine (52.94%) required surgery, and six (35.29%) required surgery followed by medications. Similarly, Baig *et al.* conducted a retrospective study on 22 pediatric JOAG eyes in Hong Kong found that 68% of eyes ($n = 15$) underwent surgical or laser treatment with 60% undergoing trabeculectomy with antimetabolites, 7% undergoing goniotomy, 7% undergoing nonpenetrating deep sclerectomy, 13% undergoing SLT, and 13% undergoing argon laser trabeculoplasty [3▪]. In 2021, Chan *et al.* [6] reported on 10 pediatric eyes with JOAG in Hong Kong of which 60% underwent glaucoma laser treatment or surgery including SLT and EX-PRESS device. On the contrary, Saavedra *et al.*'s [5▪] retrospective study of 36 pediatric eyes with JOAG in Latin America found that no eyes with JOAG required surgery. These patients were controlled with antiglaucoma medications, and IOP and CDR remained stable over the course of the study (IOP 13.0 mmHg (IQR 6.8) vs. 12.0 mmHg (IQR 2.3) and [CDR 0.7 (IQR 0.2) vs. 0.8 (IQR 0.2)]. However, this study was limited to patients less than 16 years of age with an average follow-up time of 1.3 years and may not have captured patients who eventually required surgical management.

Trabeculectomies have been well studied in JOAG and have traditionally been successful in obtaining IOP control [22]. However, a cohort study by Le *et al.* in 2021 suggests that tube shunt surgeries may be preferable to trabeculectomy in JOAG patients, given the propensity for fibrosis in younger patients and the risks associated with antimetabolites used to reduce fibrosis. In this study, 32 eyes from 25 JOAG patients underwent tube shunt surgery (Ahmed and Baerveldt implants), and surgical success was reported in 90.7% of cases at 1 year [23▪]. IOP decreased 9.8 ± 9.10 mmHg and antiglaucoma medications decreased 0.38 ± 1.06 over the course of the study. This study highlights that tube shunt surgeries are often successful in JOAG patients with favorable visual outcomes, although many patients require continuation of antiglaucoma drops.

Recent research on the surgical treatment of JOAG has focused on microinvasive glaucoma surgery (MIGS). Wang *et al.* [24▪▪] conducted a retrospective review of 59 JOAG eyes and found that gonioscopy-assisted transluminal trabeculotomy (GATT) was successful in JOAG patients, including patients with prior glaucoma surgery and severe JOAG. Overall IOP decreased from 26.5 ± 9.0 mmHg mmHg on 3.7 ± 0.9 medications to 14.1 ± 2.3 mmHg on 0.4 ± 0.8 medications at 18 months postoperatively ($P < 0.001$). Success, defined by no reoperation and significant IOP reduction, was reported in 81.2% at 18 months. Salimi *et al.* [25▪▪] studied 56 eyes that underwent GATT and found that younger age at diagnosis of glaucoma (18–39 years) was predictive of surgical success, suggesting that the JOAG disease process may be more localized to the trabecular meshwork making GATT an effective procedure in JOAG.

Previous MIGS research has demonstrated that 360 degree catheter trabeculotomy is preferable to standard trabeculotomy in JOAG [26,27]. Rojas and Bohnsack [28▪▪] assessed whether complete canalization was achieved in 16 JOAG patients undergoing 360 degree trabeculotomy. Postoperative IOP and medications were significantly lower compared with preoperative baseline (26.6 ± 7.8 vs. 13.8 ± 2.8 mmHg, $P < 0.001$) and (3.1 ± 0.5 vs. 1.1 ± 1.2, $P = 0.004$), respectively. Three-hundred sixty-degree canalization was achieved in 11 of 16 JOAG eyes (69%). In 3 eyes (19%), 270–360 degree catheterization was achieved, and in two eyes (13%) less than 180 degree standard trabeculotomy was achieved after conversion from catheterization to Harms trabeculotomy. Complete canalization was achieved significantly more often in JOAG (69%) compared with primary congenital glaucoma (21% $P = 0.007$). At final follow-up (3.9 ± 1.8 years), success of obtaining IOP control with 360 degree catheter trabeculotomy was 100%, 270–360 degree trabeculotomy was 67%, and less than 180 degree standard trabeculotomy was 50% in JOAG patients. This study demonstrated that canalization of Schlemm's canal using illuminated microcatheter is successful in most JOAG cases.

Recent case reports have reported on the success of less commonly used MIGS procedures in JOAG patients. Khouri *et al.* [29] reported success using the Kahook Dual Blade in a 14-year-old male with JOAG and Klug and Solá-Del Valle [30] reported successful bilateral XEN Gel Stent implants in a 48-year-old female with JOAG.

POSTOPERATIVE COMPLICATIONS

Prevalence and type of postoperative complications in JOAG patients varies by procedure. Wang *et al.* [24▪▪] studied GATT in 59 eyes and found that microhyphema occurred in 49%, and macrohyphema occurred in 51%; the majority of which resolved by 2 weeks postoperatively. Approximately 48% of eyes experienced an IOP spike, and 30% demonstrated some degree of ciliochoroidal detachment [24▪▪]. Additionally, Aktas *et al.* [31] reported a case of acute myopic shift following an uneventful prolene GATT surgery. The myopic shift was thought to

be secondary to supraciliary effusion, and it resolved within 1 week of follow-up. Ishida *et al.* [32] reported on two patients with JOAG that developed persistent hypotony after microhook ab interno trabeculotomy. The hypotony secondary to development of ciliochoroidal detachment was due to either creation of a cyclodialysis cleft or increased uveoscleral outflow. Le *et al.* [23▪] investigated postoperative complications following tube shunt surgery in 25 JOAG patients and found an overall complication rate of 9.3%, including erosion of conjunctiva requiring implant revision ($n = 1$), tube occlusion with vitreous ($n = 1$), and hypotony maculopathy ($n = 1$).

JUVENILE OPEN-ANGLE GLAUCOMA WITH OTHER DISEASE

Recent case reports have documented new instances of JOAG present with other diseases. AbdelRahman *et al.* [33] reported on the first case of Waardenburg Syndrome associated with JOAG in a 20-year-old Egyptian man. Khamar *et al.* [34] documented a case of JOAG associated with hypertriglyceridemia, suggesting vascular dysfunction caused by hypertriglyceridemia may be associated with glaucoma pathogenesis. Swampillai and Booth [35] reported a case of papilledema after trabeculectomy in a patient with JOAG and suggested lower IOP associated with intracranial hypertension may have a protective effect against glaucomatous optic neuropathy. Glaucoma providers should be mindful of these associations when working up new patients and consider multidisciplinary care when appropriate.

CONCLUSION

JOAG is characterized by early disease onset and rapid progression. Recent genetic JOAG research has identified additional pathogenic genes which may allow for earlier diagnosis and screening. However, additional research is needed regarding the feasibility of genetic screening for JOAG, and IOP measurements, fundoscopic exam and clinical testing continue to be the current mainstay of diagnosis. While topical medications are beneficial, surgical management is typically required for adequate disease control. Trabeculectomy is known to be effective in JOAG. However, recent research supports the use of glaucoma drainage devices and MIGS in JOAG as well.

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Conflicts of interest

There are no conflicts of interest.

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