DIAGNOSTIC REVIEW

New techniques in the detection of juvenile open-angle glaucoma

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INTRODUCTION

Recent advances in molecular biology techniques and imaging instruments have opened up the possibility that genetic-based screening and imaging might become faster, less expensive, and more available.¹ One condition where these new technologies could have an application is juvenile-onset open-angle glaucoma (JOAG). Current practices for detecting cases of juvenile-onset glaucoma involve measurements of intraocular pressure (IOP) and optic nerve assessment by cup-to-disc ratio (CDR). These practices are far from perfect, and results vary from one ophthalmologist to the next. Furthermore, because the levels of IOP and the CDR at which pathology is likely to be seen have not been well defined there is a degree of uncertainty in determining whether or not a diagnosis of glaucoma can be made.² There are problems in the guidelines for current screening for JOAG and the solution to these problems could lie in new technologies such as genetic screening and imaging that could potentially complement each other in helping to better screen for this disorder in the future.

BACKGROUND

Glaucoma is a disease of the eye characterized by increased IOP and progressive degeneration of the optic nerve leading to permanent visual loss. JOAG has a prevalence of 1% in the population and presents in affected individuals between the ages of 3 and 40. Its pathophysiology can be traced to defects in genes, like myocilin, that code for structural components of the eye.³ JOAG is inherited as an autosomal dominant trait and could be detected early in development using imaging of the retina and optic disc at high resolution. The disease is currently detected by measures of IOP. When the increased pressure is noted it can be reduced with medications or laser surgical procedures,⁴ though these techniques prevent progression but do not reverse damage. While screening for glaucoma is done in adults in order to detect increases in pressure and allow initiation of treatment prior to optic nerve damage, it is uncommon to employ such practices in children. Still, while it is uncommon for the disorder to present at such a young age, in cases of JOAG optic nerve damage can develop at a very early age and is irreversible.⁵ As such, genetic screening and imaging in this younger group of individuals could be useful tools for identifying JOAG early before damage occurs.

CURRENT PRACTICE

Currently there are no screening programs for JOAG. The diagnosis is made on an individual basis by combining information from IOP testing and fundoscopic evaluation of the CDR with additional

supporting signs such as visual field loss, presence of myopia, and blurry vision due to corneal edema or thickening.⁵ The diagnosis can be made earlier in children who have a parent, sibling, or more elderly family member affected by the disease. This diagnosis requires clinician judgement, and the interpretation of what is significant is subjective and may differ from one ophthalmologist to the next. However, an earlier diagnosis results in a more favorable outcome because measures to prevent further optic nerve damage are taken earlier.⁶ Criteria for diagnosis were developed from just one demographics study of congenital, infantile, and juvenile glaucoma. Given the lack of research currently being used to establish existing diagnostic criteria, and that intraocular pressure gives us no indication of the extent of optic nerve damage, there needs to be a more reliable method that can be used to both diagnose JOAG and assess optic nerve pathology.

The present treatment for JOAG is trabeculectomy, which usually results in considerable benefit. However, the treatment may result in harm if it is done before the onset of symptoms. Some complications that can arise with premature surgery include hyphema, subconjunctival hemorrhage, vitreous loss, and tearing of the sclera.⁷ If the disease is detected early and IOP is monitored closely and kept in the normal range, optic nerve damage can be prevented. Early treatment is important because a great deal of optic nerve damage has occurred by the time the disorder can be clinically identified.⁸ This risk gives incentive for identifying individuals with potential pathology and following them clinically.

NEW TECHNIQUES IN SCREENING

An emerging tool that may aid in diagnosis of this disorder is genetic testing because JOAG exhibits genetic inheritance. Some genetic variants exhibit more expressivity than others, and genetic testing will allow difficult cases to be more easily recognized and treated. Three main gene variants are implicated, all encoding proteins of the trabecular meshwork of the eye. Mutation of the myocilin (MYOC) gene is the most important of the 3 because it is implicated in cases where subjects have an earlier onset of disease, high intraocular pressure, and a strong family history.⁹ Between 6 and 83% of JOAG cases are associated with MYOC mutations.¹⁰ A strong family history provides an important clue about whether or not screening for the disorder is appropriate. Genetic testing in such families would result in a better prognosis because affected individuals could be identified prior to disease onset.

Another test to aid in screening for JOAG is confocal scanning laser ophthalmoscopy (CLSO). CLSO is a method of examining the

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eye that uses microscopy to image the retina with a high degree of spatial sensitivity. It is helpful for screening for glaucoma and macular degeneration. It is currently being combined with adaptive optics technology to provide images of the retina with a higher resolution. Imaging modalities such as CSLO show promise for improving the detection of the optic disc and retinal nerve fiber layer changes that can be used as clinical indicators of developing glaucoma. Using this technology in combination with clinical judgement and other methods in high-risk individuals could aid in the screening and diagnosis of glaucoma.⁶

LIMITATIONS

Genetic testing may have an application in JOAG though currently there are limitations to its utility. Genetic testing for JOAG is done by gene sequencing for mutations on chromosome 1. It takes approximately 12 weeks to receive results and costs \$200 per test.⁸ The cost of screening can be high, but there is considerable benefit for doing so in individuals with a previous family history. Some possible goals for the future could include reduction in the cost of genetic screening and characterization of the genetic determinants of this illness.

Further research into developing CLSO is also required before it can be widely applied. CLSO is currently limited because measurements may be affected by blood vessels seen in the image of the eye, along with anatomic variation or other pathologic processes. The resolution of the images this technology produces also prevents useful quantitative measurements of changes that are occurring in the retina and optic disc.⁶ Finally, an improved understanding of how levels of IOP and CDR are associated with pathology needs to be better studied.

CONCLUSIONS

Optimal management of JOAG is still hindered by our inability to make an early diagnosis in many individuals that present with the disease before irreversible damage has been done. Genetic screening and CLSO are two methods that show a great deal of promise in advancing the management of this condition; however, neither is currently useful. Goals for the future should include further research and development of these techniques, along with better-defined clinical values of IOP and CDR that are significant. Genetic-based testing and CLSO may hold significant promise in the future for an improved management of JOAG. Specifically, genetic testing may allow for the identification of individuals at a high risk for JOAG, who could then be monitored with CLSO to avoid irreversible vision loss.

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