A case of JOAG in a patient with Rett syndrome

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ARTICLE INFO

Keywords:
Rett syndrome
Juvenile open angle glaucoma

ABSTRACT

Purpose: In this report, we describe a case of juvenile open angle glaucoma in a patient with Rett syndrome.

Observations: A 39- year-old white woman with a notable history of Rett syndrome was referred to our center with a ten-year diagnosis of juvenile open angle glaucoma. Initial exam was notable for complete cupping of the optic nerve. Upon follow up visits, intraocular pressures were elevated and remained refractory to multiple therapies, including SLT and pressure-lowering drops. Medical management was continued due to the risk of surgery and limited visual potential. Because it was declared that patient did not have substantial feedback to visual stimuli and did not exhibit any signs of pain, conservative management with drops was continued.

Conclusion and importance: This is the first report of a patient with concurrent Rett syndrome and juvenile open angle glaucoma, thus expanding on the literature of an ocular manifestation occurring presumably coincidentally with this disorder.

1. Introduction

Rett Syndrome is a neurodevelopmental disorder mainly affecting females and characterized by normal early development until 6–18 months of age, when patients begin developing a rapid decline in mental and physical ability. 1,2 Most cases are thought to be caused by pathogenic variants in the X-linked methyl CpG binding protein 2 (MECP2) gene. 3 Affected individuals develop characteristic repetitive hand stereotypies, loss of spoken language, and gait problems. 1,2 Additional clinical features that have been reported include: seizures, movement abnormalities, growth features, gastrointestinal issues, and autonomic dysfunction. 2

Current knowledge of ocular manifestations of Rett syndrome are limited. One study performed ocular examinations of 11 Rett syndrome patients and found that the study group had substantial refractive errors but good function of the afferent visual pathways. 4 Another study found that the visual function of 42 Rett patients demonstrated arrested development and abnormal visual processing that further worsened with advancing age. 5

A more recent study observed seven individuals with Rett syndrome. Five of these patients had significant strabismic or refractive abnormalities. None of these patients had abnormalities of ocular structures. However, all patients also had poor visual tracking function. 6

Townend et al. also studied the oculomotor function of 18 girls with Rett syndrome, and their work suggests that this function remains intact in Rett syndrome patients. 7

In the studies above that observed ocular structures in patients with Rett syndrome, all noted normal optic nerves. 4–6 Though these few studies have examined ocular findings in Rett syndrome, to our knowledge there is nothing in the literature describing glaucoma in anyone with the disorder. Here we report a case of juvenile open-angle glaucoma (JOAG) in a woman with Rett Syndrome.

2. Case

A 39-year-old white woman with a notable history of Rett syndrome and glaucoma (diagnosed 10 years ago) presented to our center by a referring provider for glaucoma evaluation, sedated exam, and possible surgical management.

She had a notable family history of primary angle closure and ocular hypertension in her mother, who was diagnosed at 61 years of age and had laser peripheral iridotomies and cataract extraction completed on both eyes (Fig. 1). The patient’s caretakers endorsed minimal history of trauma to her eyes, but some self-induced trauma could not be ruled out. At the time of presentation to our clinic, the patient’s disease had been managed by an outside provider with brimonidine-timolol, latanoprost, and dorzolamide.

Brimonidine-timolol had been started at the time of diagnosis. According to the patient’s mother, vision problems were noted around 9 years after initial diagnosis, which is when advanced glaucoma was
diagnosed. At that time, latanoprost and dorzolamide were added to her regimen.

At presentation to our center, IOPs were 16 mmHg and 19 mmHg. Maximum recorded IOPs were 32 mmHg and 36 mmHg per the referring provider. Visual acuity was unable to be obtained but patient winced to light. Central corneal thickness was 606 μm and 580 μm. Anterior segment exam showed a deep and quiet anterior segment and trace nuclear sclerotic cataract, OU. Fundus exam showed complete cupping of the optic nerve, OU. Gonioscopy was difficult to obtain, but the post-dilation view showed scleral spur with occasional thin ciliary body band, lightly pigmented, OU.

At this visit, brimonidine-timolol and latanoprost were continued but dorzolamide was switched to brinzolamide as the patient was not tolerating the medication.

Selective laser trabeculoplasty was completed one week later, with 122 and 120 spots in OD and OS respectively. Post-procedure IOP was 16 mmHg OU, and we established an IOP goal in the low teens.

Three months later, IOP was elevated to 23 mmHg, and mom noted that the patient was having a difficult time seeing and did not recognize her easily anymore. Netarsudil was started at that time to maximize medical options prior to discussing surgery due to her intellectual disability and a history of eye rubbing.

After netarsudil failed to lower the IOP to an acceptable number, acetazolamide 67.5 mg QID was started. At the two-week IOP check, pressures were still high at 22 mmHg and 26 mmHg, and dose of acetazolamide was increased to 500 mg q12 hr. The next IOP check finally revealed pressure at an acceptable range and this dose was continued.

The patient was unable to return to our clinic for around 18 months. On return, her pressures were elevated at 24 mmHg and 27 mmHg on brimonidine-timolol BID, brinzolamide TID, latanoprost, and acetazolamide 250 mg QID. At this point it was noted that the patient had not had substantial feedback to visual stimuli for at least 3 years.

Cyclophotocoagulation (CPC) was completed in both eyes, and atropine, prednisolone, and dorzolamide-timolol were the only drops she remained on afterward. However, at the 6-week post-procedure visit, IOP remained high into the low 30s mmHg. Latanoprost was started. Atropine and prednisolone were stopped, and a ketorolac taper was started. As pressures remained high, acetazolamide was restarted as well. This regimen lowered IOPs for the next few visits, so acetazolamide was eventually stopped.

IOP was found to be elevated once again at a subsequent visit, but at this point there was no objective data showing that the patient had any vision remaining. Patient also did not show any evidence of pain. Palliative eye care versus surgery was considered, but due to little visual potential and risk of surgery, we continued management of the patient on dorzolamide-timolol and latanoprost.

3. Discussion

Rett syndrome is a progressive neurodevelopmental disorder mostly affecting females. It is one of the most common causes of mental retardation in girls and is characterized by a rapid decline in mental and physical ability at 6–18 months of age. Affected individuals display characteristic repetitive hand stereotypies, gait problems, and loss of spoken language skills.\textsuperscript{1,2}

Few studies have investigated ocular findings in patients with this syndrome, and those reports which have studied eye abnormalities found that refractive errors and gaze tracking were the main areas of concern.\textsuperscript{3,4} JOAG has not been studied as a finding in Rett Syndrome, nor has there been any literature describing any type of glaucoma in patients with this condition.

Juvenile open angle glaucoma is a rare form of open angle glaucoma that is diagnosed in individuals less than 40 years old. It is a particularly severe form of glaucoma and causes significant visual impairment in affected individuals.\textsuperscript{5} It is characterized by high intraocular pressures which damage the optic nerve and cause deep cupping.\textsuperscript{6} Our patient was diagnosed in her late twenties and presented to us late in the course of this disease, with almost complete vision loss and total cupping. She also presented with very high IOPs, as is characteristic of JOAG patients. Many times, this disease is insidious and asymptomatic, which makes regular eye exams crucial for early detection,\textsuperscript{10} not only in children, but as is in our case, developmentally delayed adults as well. However, this may pose an issue as regular glaucoma testing, such as fundus exams, visual field testing, and OCTs, are difficult to obtain in developmentally delayed patients.

Though developmentally delayed patients who are found to have JOAG may be caught early, treatment options are limited. Usually in this disease, medical management alone is insufficient, and many patients

![Pedigree of the family. Round symbols indicate female; square symbols, male; fully filled symbols, juvenile open angle glaucoma; unfilled symbols, unaffected; arrow, proband.](image-url)
require surgical therapy for adequate IOP control. This will prove a challenge in the mentally impaired, as eye rubbing must be avoided. Surgery was considered in our patient as well, but ultimately deferred due to concerns of eye rubbing and lack of visual potential.

JOAG can cause significant visual disability and requires careful monitoring and management to preserve vision. This is of particular concern in Rett syndrome. Because these patients lose verbal language, their means of communication has been noted to be primarily through eye gaze and eye pointing. Eye gaze technology has even been used to supplement communication in these patients. With severely progressed glaucoma leading to blindness, communication is even further limited, and patients may become more isolated. For this reason, regular eye exams are crucial in preserving vision, and caretakers must be cognizant of changes in visual habits and signs of pain from elevated IOPs.

Both JOAG and Rett syndrome have complex genetic considerations. JOAG is known to be associated with a positive family history of glaucoma, but it can be familial or non-familial. Previously it was thought to only be an autosomal dominant disease, but autosomal recessive and sporadic occurrences have been noted. The gene encoding myocilin, MYOC, as well as CYP1B1 and LTBP2 have been associated with high pressure JOAG. More specifically, MYOC variants are associated with both familial and sporadic forms of JOAG and adult-onset primary open angle glaucoma (POAG). The CYP1B1 gene is implicated in primary congenital glaucoma, JOAG, and adult onset POAG. Finally, LTBP2 variants have been associated with the autosomal recessive form of JOAG. In our patient’s case, though no genetic analysis for glaucoma was done, no one else in the family had JOAG or POAG and her mother had a history of bilaterally narrow angles. From this we assume our patient had a sporadic occurrence of JOAG.

Most cases of Rett syndrome are caused by sporadic, pathogenic variants in the X-linked MECP2 gene. In addition, there have been some rare cases of a familial MECP2 variant inherited in a maternal pattern. Genetic testing for our patient was done at the Greenwood Genetic Center and resulted in a normal multiple ligation dependent probe amplification (MLPA) analysis for the MECP2 gene, so she did not have a variant of this gene. However, interestingly, 3–5% of individuals with the clinical features of Rett syndrome do not have a MECP2 variant. Our patient fits into this group, as she was diagnosed at age 8 based on clinical signs.

Since visual function is normally preserved in patients with Rett Syndrome, Jain et al. investigated the genetic cause of this and studied ocular MECP2 expression from the eyes of two Rett syndrome patients. They found no significant differences in MECP2 level or distribution in the Rett syndrome eyes compared to the control eyes. Therefore, patients with Rett Syndrome may have intact vision due to the limited expression of MECP2 in visual pathway neurons. Though our patient did not have a pathologic variant of MECP2, this is interesting to consider if other individuals with Rett syndrome are found to concurrently have changes in MECP2 expression in their eyes.

There have been preliminary studies investigating the relationship of MECP2 and glaucoma. One study found that human retinal samples of patients with glaucoma showed decreased MECP2 when compared to non-glaucomatous eyes. However, much research is yet to be done, and there has not yet been any investigation into any genetic linkage of glaucoma and Rett Syndrome. In the case for our patient, the concurrent diagnoses of Rett and JOAG are assumed to be coincidental, and this is the first report of this occurrence.

4. Conclusion

Rett Syndrome is a neurodevelopmental disorder associated with pathogenic variants in the MECP2 gene and is one of the most common causes of mental retardation in females. The characteristics of this disease have been well documented over the years, which includes stereotypical hand wringing, motor disability and loss of verbal language. Few studies have investigated ocular function in patients with Rett, but none have reported a case of glaucoma concurrent with Rett Syndrome.

We report a novel finding of JOAG coexisting with Rett syndrome in a patient. This case demonstrates the importance of thorough eye exams for patients with Rett syndrome and other developmental disorders, especially when vision and eye movement are the primary means of communication. Because communication can be difficult with patients with significant mental impairment, it is important for caretakers to be cognizant of features that may indicate declining visual function or pain due to elevated IOPs.

Patient consent

Verbal consent by patient’s mother (legal guardian) has been obtained. This report does not contain any personal identifying information.

Funding

No funding or grant support.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

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