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Rare Presentation of Attenuated Mucopolysaccharidosis Type IIIA as Isolated Retinitis Pigmentosa

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Abstract

Purpose: To describe a patient presenting in adulthood with isolated retinopathy found to have mucopolysaccharidosis type IIIA. **Methods:** A single case was evaluated. **Results:** A 36-year-old man presented with 5 years of worsening peripheral vision and night vision. The initial examination and testing raised concerns for rod-cone dystrophy. Genetic testing with an Invitae Inherited Retinal Disorders Panel showed 2 variants of *SGSH*, which is associated with mucopolysaccharidosis type IIIA. Laboratory testing showed low heparan-N-sulfatase levels and elevated heparan sulfate levels. These results and a thorough literature review support a diagnosis of mild attenuated non-neuronopathic mucopolysaccharidosis type IIIA. **Conclusions:** This case highlights the necessity for collaboration with genetic counselors and the value of a provider's clinical acumen in interpreting genetic testing results. Furthermore, the importance of considering mucopolysaccharidosis type IIIA when adult patients present with new-onset isolated retinitis pigmentosa is emphasized.

Keywords

mucopolysaccharidoses, retinitis pigmentosa, mucopolysaccharidosis type III, Sanfilippo syndrome, lysosomal storage disorders

Introduction

Mucopolysaccharidoses are a group of rare inherited disorders characterized by defective degradation and consequent accumulation of glycosaminoglycans in bodily tissues.[1] At least 11 known enzymes are involved in the breakdown of glycosaminoglycans, which can cause various types of mucopolysaccharidosis if deficient.[1]

Mucopolysaccharidosis type III is caused by deficiencies in enzymes involved in the heparan sulfate degradation cascade, and patients commonly present with progressive neurocognitive deterioration. Depending on the unique enzyme affected, there are 4 known subtypes of mucopolysaccharidosis type III (A, B, C, and D).[2] Mucopolysaccharidosis type IIIA, also known as Sanfilippo syndrome, is the most disabling, presenting early in childhood with difficulties with sleep and behavior. It is an autosomal recessive disease caused by biallelic mutations in the *SGSH* gene.[3] This results in a deficiency of heparan-N-sulfatase (ie, sulfamidase), causing an accumulation of heparan sulfate in various tissues.[4] Cognitive challenges can progressively become more severe. In the teenage years, motor deterioration begins to take place, and most patients die by the second or third decade of life.[2] There have been recent reports of milder, non-neuronopathic forms of mucopolysaccharidosis type III.[5] Here, we describe a patient with mucopolysaccharidosis type IIIA who presented with isolated retinopathy.

Case Report

A 36-year-old man with a medical history notable for attention-deficit/hyperactivity disorder presented with 5 years of worsening peripheral vision and night vision. He reported that he had always struggled with his vision in dim lighting but had only recently noticed the visual field changes. In previous years, eye examinations were performed sporadically by outside providers. Retinal changes consistent with retinitis pigmentosa (RP) were first seen at age 16 and noted again on subsequent examinations; however, there was no consistent follow-up. Before referral to our clinic, the patient had a sponsored genetic test evaluating for X-linked RP, which was negative. Otherwise, the patient's ocular history was notable only for myopia and bilateral laser-assisted in situ keratomileusis at age 29.

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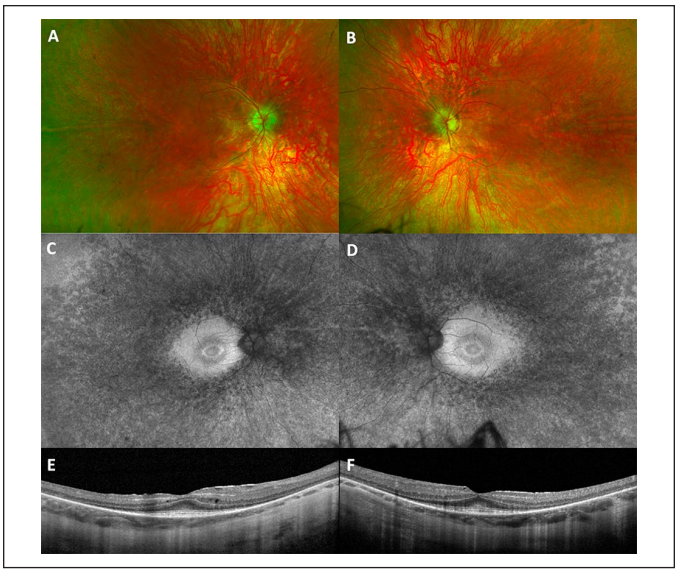

Figure 1. (A and B) Fundus photography shows mild attenuation of vessels with midperipheral atrophy and retinal pigment epithelium changes in both eyes. (C and D) Fundus autofluorescence shows macular hyperautofluorescence with a foveal ring of hypoautofluorescence and hypoautofluorescence of the midperiphery outside the arcades in both eyes. (E and F) A B-scan through the fovea shows internal limiting membrane thickening, rare cystic changes, and paracentral ellipsoid zone loss but a preserved foveal contour in both eyes.

The patient's presenting visual acuity was 20/20 OD and 20/25 OS. The pupils were round and reactive without an afferent pupillary defect. The intraocular pressure was within normal limits, and the extraocular motility was full. Confrontational visual fields were notable for constriction of peripheral visual field bilaterally. A slit lamp examination was notable for mild cortical changes of the left lens but otherwise unremarkable. A fundus examination was notable for mild attenuation of vessels with midperipheral atrophy and retinal pigment epithelium (RPE) changes in both eyes (Figure 1, A and B). Autofluorescence photographs showed macular hyperautofluorescence with a foveal ring of hypoautofluorescence and hypoautofluorescence of the midperiphery outside the arcades in both eyes (Figure 1, C and D). Optical coherence tomography imaging was notable for a mild epiretinal membrane, rare cystic changes, and paracentral ellipsoid zone loss, but with a preserved foveal contour in both eyes (Figure 1, E and F). A full-field electroretinogram showed undetectable photopic and scotopic responses in both eyes.

In consideration of the patient's ocular findings, an advanced rod-cone dystrophy was deemed the most likely diagnosis. The patient underwent genetic testing to evaluate for inherited retinal disorders (IRDs) using the Invitae Genetic Testing Panel.[6] This panel sequences more than 300 genes typically associated with diseases such as RP, cone–rod dystrophy, and Leber congenital amaurosis.[6] The Invitae clinical reporting team only labels sequence changes as "pathogenic" if they have been shown to directly contribute to the development of disease by multiple pieces of evidence.[7] In our patient's case, the panel did not reveal mutations commonly associated with IRD. However, genetic testing did identify 1 pathogenic variant mutation, c.1139A>G (p.Gln380Arg), and 1 variant of unknown significance, c.539C>T (p.Pro180Leu), in the *SGSH* gene, which is associated with autosomal recessive mucopolysaccharidosis type IIIA. The patient was heterozygous for both mutations identified.

Mucopolysaccharidosis type IIIA was thought to be an unlikely cause of the patient's retinopathy given his late ophthalmic presentation and overall systemic health. He and his parents denied learning difficulties or regression, and he denied experiencing cardiac symptoms at any point. In addition, the patient only had 1 known pathogenic *SGSH* mutation, while most confirmed cases of mucopolysaccharidosis type IIIA would show biallelic pathogenicity. In light of the genetic testing results showing only 1 pathogenic mutation and 1 variant of unknown significance, further testing was pursued to investigate the possibility of mucopolysaccharidosis type IIIA as a diagnosis. Both of the patient's parents subsequently had genetic testing to classify the configuration of the variants, showing that our patient had inherited 1 allele from each parent, confirming in trans position of the mutations and supporting an autosomal recessive inheritance pattern. Furthermore, none of the patient's healthy siblings were found to have *SGSH* mutations in both alleles.

Quantitative urine assays and mucopolysaccharidosis enzyme blood panels were performed to assess levels of heparan-N-sulfatase, a mucopolysaccharidosis enzyme, and heparan sulfate, a breakdown product of heparan-N-sulfatase. The patient's heparan-N-sulfatase levels were low while his heparan sulfate levels were elevated, findings that further supported the diagnosis of mucopolysaccharidosis type IIIA.

Additional literature review found cases of mild attenuated non-neuronopathic forms of mucopolysaccharidosis type IIIA with associated cardiac findings. Notably, it cannot be ruled out that our patient may have had additional contributory pathogenic mutations in genes that are not included on the standard IRD panel. However, the mucopolysaccharidosis enzyme levels and existing body of literature support the likelihood of isolated RP in the context of mucopolysaccharidosis type IIIA without other pathogenic variants.

The patient subsequently had cardiac and neuropsychology evaluations, which did not reveal other findings of mucopolysaccharidosis type IIIA. An abdominal ultrasound was notable only for minimal liver enlargement, which was not thought to be a result of the disease.

Conclusions

For many decades, the only reported form of mucopolysaccharidosis type IIIA was the severe form with an onset in childhood and neurocognitive decline. The most prominent ocular symptom of the disease is retinopathy, which results from heparan sulfate accumulation within the RPE, ultimately causing death of the photoreceptors and retinal degeneration.[8] Cases of isolated, nonsyndromic RP have been reported in patients with mucopolysaccharidosis type IIIC.[9,10] In mucopolysaccharidosis type IIIA, retinopathy is often seen in conjunction with cardiac

findings of hypertrophic cardiomyopathy or left ventricular hypertrophy.

Reports in recent years have described a later onset, milder form of mucopolysaccharidosis type IIIA, also known as an attenuated form.[11,12] Nijmeijer et al[5] reported 12 individuals from 6 different families with adult-onset mucopolysaccharidosis type III. Of the 12 patients, 11 had mucopolysaccharidosis type IIIA and 1 had mucopolysaccharidosis type IIIB. The median age of these patients at diagnosis was 43 years. Two of the patients presented with retinal dystrophy as their only symptom at the time of diagnosis. Further retinal examination found 9 of the 12 patients had signs of retinopathy. One of the 12 patients had hypertrophic cardiomyopathy as the presenting symptom at the time of diagnosis, and 8 had signs of hypertrophic cardiomyopathy or left ventricular hypertrophy on further cardiac examination. Only 1 of 12 patients presented with neurocognitive decline in adulthood. All 12 patients completed secondary education, and many held independent jobs. Eight had a cognitive evaluation after diagnosis. Four of the 8 patients were found to have no cognitive defects, and 3 had high verbal comprehension but slower processing speeds.

Reverse phenotyping played a prominent role in the clinical course of these patients. Typically, patients present with a constellation of symptoms and undergo genetic testing to confirm a certain diagnosis. In reverse phenotyping, a known genomic variant prompts a targeted phenotypic workup.[13] In a study by Wilczewski et al,[13] many cardiac abnormalities and retinopathies were discovered only because of targeted testing in the context of the known mucopolysaccharidosis type IIIA genotype. Reverse phenotyping can guide diagnostic decision-making and help identify subclinical abnormalities before they progress and cause harm.

In our patient's case, retinopathy was the only symptom present at diagnosis at 36 years of age. The neuropsychologic and cardiac examinations were unremarkable. Although the patient did report a history of attention-deficit/hyperactivity disorder, he had no history of cognitive or learning difficulties, making this a challenging diagnosis. Genetic testing was a crucial diagnostic step in initially considering mucopolysaccharidosis type IIIA as a possible diagnosis. Further laboratory workup and input from a genetic counselor confirmed the expected sulfamidase enzyme deficiency.

This case highlights the importance of considering mucopolysaccharidosis type IIIA in the differential diagnosis when adult patients present with new-onset isolated RP. Furthermore, this case emphasizes the necessity of working closely with genetic counselors and the value of a provider's clinical acumen in interpreting genetic testing results. This team-based approach to reverse phenotyping allows swift diagnosis and effective counseling of patients with non-neuronopathic mucopolysaccharidosis type IIIA and other genetic disorders.

Ethical Approval

This case report did not require institutional review board approval given that the research did not involve human subjects.

Statement of Informed Consent

The patient provided written informed consent for the publication of this case report.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of the article.

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