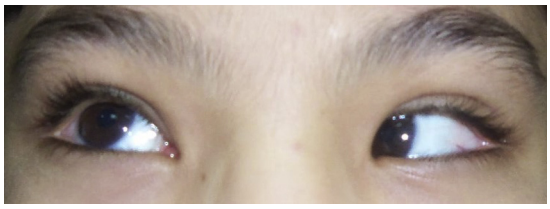

FIG. 1. During version up and to the right, the left eye has limited supraduction. This persisted with left duction up and to the right.

Both geleophysic dysplasia and Weill-Marchesani syndrome are acromelic dysplasias, which are characterized by short stature, brachydactyly, and joint contractures.[2] The recessive forms are caused by biallelic mutations in, respectively, the *ADAMTSL2* and *ADAMTS10* genes.[3,4] Findings more characteristic of geleophysic dysplasia include a round "happy" face (from *geleos*, meaning "happy" in Greek), recurrent middle ear and respiratory infections, cardiac valve anomalies, hepatomegaly, and tracheal stenosis.[2,3] Spherophakia with resultant progressive angle-closure glaucoma is a well-defined feature of Weill-Marchesani syndrome,[5] while most prior reports of genetically confirmed recessive geleophysic dysplasia either do not state whether there was ophthalmic phenotyping or simply mention the presence of "ophthalmic symptoms," with no further details.[3,6] There is one prior report of an adult diagnosed as geleophysic dysplasia for whom blue sclera, keratoglobus, and microspherophakia were mentioned as findings.[7] These ocular findings have never been reported in any other patient with geleophysic dysplasia. That patient also had recurrent intussusception, another finding which has not been reported in any other patient with geleophysic dysplasia. This raises the possibility that she may have had a different underlying diagnosis. That patient did have compound heterozygous *ADAMTLS2* variants, but both were intronic.

In the current genetically confirmed case, we specifically looked for and found no evidence for zonular weakness. As spherophakia is a consistent feature of Weill-Marchesani syndrome,[5] a lack of zonular weakness can be a useful feature to help distinguish geleophysic dysplasia from Weill-Marchesani syndrome. Although there are no data regarding age at which spherophakia develops in Weill-Marchesani syndrome, it is typically in early childhood.

Short eyes and resultant hyperopia were notable ophthalmic features in our case and are potentially additional useful distinguishing features from Weill-Marchesani syndrome. These features were also noted in a clinically diagnosed but not genetically confirmed 9-year-old girl who developed anterior chamber shallowing.[8] Hyperopia may be useful as a distinguishing feature from Weill-Marchesani syndrome, because Weil-Marchesani patients are typically myopic secondary to their spherophakia. We are unaware of any studies of axial length in Weil-Marchesani syndrome.

The high corneal astigmatism and Brown syndrome in our case could be coincidental or could be potentially be recurrent features of geleophysic dysplasia. Additional reports with detailed ophthalmic phenotyping of children with confirmed biallelic *ADAMTSL2* mutations are needed to definitively define the ocular phenotype for recessive geleophysic dysplasia.

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Infantile sialidosis: natural history in a preterm infant with two new pathogenic mutations and new ocular findings

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Sialidosis is a rare lysosomal storage disease caused by an α-N-acetyl neuraminidase-1 deficiency due to mutations of the *NEU1* gene (6p21). Disease severity varies among patients and is linked to the level of residual neuraminidase activity in vivo. At least 40 disease-causing mutations in the *NEU1* gene have been reported. Sialidosis occurs in two main clinical variants: type I, the milder form of the disease, and type II, which is subdivided into congenital, infantile, and juvenile forms. We report the clinical, biochemical, and molecular characterization of a patient with infantile sialidosis type II. The abnormal urinary oligosaccharide profile is described for the first time. The genetic characterization of the patient showed two previously unreported missense mutations in the *NEU1* gene: p.R78C (c.232C>T) and p.R290Q (c.869G>A).

Case Report

A 20-month-old girl of Moroccan origin, the third child of healthy, nonconsanguineous parent, born at 29 weeks' gestation and weighing 1900 g, was found to have retinopathy of prematurity at birth. The medical history of the pregnancy was unremarkable. At 4 months of age, mild bilateral capsular/subcapsular diffuse lens opacity and high hyperopia were observed on ophthalmological examination (Figure 1A). She seemed to have developed slightly coarse facial features. At 9 months of age, she had bilateral cherry-red spots in the macula (Figure 1B). Magnetic resonance imaging at 12 months of age showed normal images of the brain.

Oligosaccharidosis was suspected, and this possible diagnosis was supported by elevated urinary sialylated oligosaccharide levels, measured at 12 months of age by tandem mass spectrometry: Neu5Gc-HexNAc-Hex3: 0.37 mmol/mol creat (normal, <0.03), Hex2-Neu5Ac: 3.17 mmol/mol creat (NV: 0.33-1.27), Hex-HexNAc-Neu5Ac: 0.89 mmol/mol creat (normal, 0.08-0.34), Hex3-HexNAc2-Neu5Ac: 0.08 mmol/mol creat. (normal, <0.02), Hex4-HexNAc2-Neu5Ac: 0.05 mmol/mol creat (normal, <0.01). A peripheral blood smear showed 15% lymphocytes with many small, cytoplasmic, irregular vacuoles.

In cultured skin fibroblasts, α-neuraminidase activity was low (6.2 nmol/h/mg protein; normal, 27-82), at 8% of the control activity. Sequencing of the coding region of the patient's *NEU1* gene revealed two previously unreported missense mutations in the catalytic domain which are likely pathogenic: p.R78C (c.232C>T) in the maternal allele and p.R290Q (c.869G>A) in the paternal allele. The segregation analysis was performed by sequencing the parents' DNA. These results confirmed the diagnosis of sialidosis, a rare metabolic lysosomal storage disease (OMIM #256550).[1]

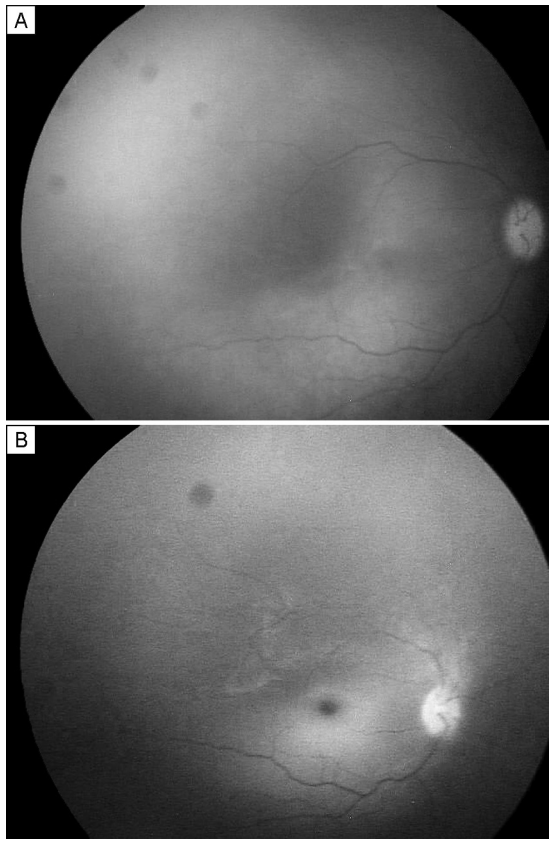

FIG 1. Fundus photographs of patient at 4 months, showing a diffuse, central spot produced by the shadow of the lens opacity (A), and at 9 months, showing a cherry-red spot in the macula (B).

Now 2 years of age, the patient has mild psychomotor retardation and progressive mucopolysaccharidosis-like features. She suffers from recurrent upper respiratory infections and mild hepatomegaly. She now has more evident bilateral cherry-red spots due to the accumulation of metabolic substrates and punctate lenticular opacities, grouped following a stellate-shaped lineal pattern. She has not developed corneal opacities.

Discussion

Sialidosis, an autosomal recessive disease caused by deficiency of the enzyme neuraminidase, is characterized by the progressive lysosomal accumulation of sialylated glycopeptides and oligosaccharides (OMIM #

256550). In sialidosis type II, which has a worse prognosis, there is an early onset (<12 months of age) of symptoms, including coarse facies, dysostosis multiplex, hepatosplenomegaly, and macular cherry-red spots as well as psychomotor and developmental delay. Patients with type I sialidosis present later in life, with a mild form of the disease that is mostly confined to ophthalmologic features, myoclonus, and minor or absent neurologic manifestations.[2-4]

We describe the biochemical and clinical phenotype associated to two novel mutations. No effective therapy is yet available for this rare disease; therefore, treatment is focused on symptoms. This case illustrates the importance of early diagnosis of lysosomal storage diseases through the ophthalmological examination. Because the patient was in ophthalmological follow-up for retinopathy of prematurity, it was possible to trace the natural history of the onset of macular cherry-red spots in sialidosis type II. This sign, caused by the accumulation of storage material in the macula, should raise suspicion for a lysosomal storage disease, especially oligosaccharidosis. The differential diagnosis of macular cherry-red spots mainly involves GM2 gangliosidoses, GM1 gangliosidosis, sialidosis, metachromatic leukodystrophy, Niemann-Pick type A, and Farber lipogranulomatosis. Other typical ocular manifestations in sialidosis type II are corneal whorling or opacities. The presence of punctate lenticular opacities in our patient, which are grouped into a stellate-shaped lineal pattern resembling the pattern seen in alpha-mannosidosis, is, to our knowledge, the first report of this characteristic in a patient with sialidosis type II. Punctate opacities have recently been described in a 15-year-old boy with sialidosis type I.[5]

The finding of an altered urinary profile of oligosaccharides would indicate the subsequent enzymatic and/or genetic study to confirm the causing metabolic disorder. To date, at least 40 disease-causing mutations in the *NEU1* gene have been reported.

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Unilateral cone-rod dysfunction and retinal thinning in a child carrying the 14484 mutation of Leber hereditary optic neuropathy

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Leber hereditary optic neuropathy is a mitochondrial disorder that presents with bilateral, usually sequential, central vision loss from optic nerve damage. We report the case of an 11-year-old girl with the 14484 mutation who developed significant, unilateral visual loss secondary to retinal thinning and abnormal cone-rod responses on electroretinography, with no evidence of optic nerve damage. Patients carrying the 14484 mutation may also develop cone-rod dysfunction.

Leber hereditary optic neuropathy (LHON) is a mitochondrial disorder that presents as acute or subacute visual loss secondary to optic nerve dysfunction. Classically, rapid vision loss in one eye is followed, sometimes quickly, by involvement of the fellow eye within 1 year. Three primary mitochondrial DNA point mutations comprise over 90% of cases: 11778 (69%), 3460 (13%), and 14484 (14%).[1] Rarely, retinal dysfunction has been reported among patients carrying an LHON mutation.[2-4]

Case Report

An 11-year-old girl suffered syncope 7 weeks prior to presentation at the University of Minnesota. On awakening, she had noted poor vision in the left eye, which remained subjectively stable. She denied photopsias. Her presenting visual acuity was 20/20 in the right eye and 4/200 in the left eye. There was an afferent pupillary defect and decreased color vision in the left eye. Dilated fundus examination

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