Child Neurology:

A case of PMM2-CDG (CDG 1a) presenting with unusual eye movements

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Congenital disorders of glycosylation encompass a group of diseases resulting from abnormal protein glycosylation. This group includes more than 20 described diseases.¹ PMM2-CDG, previously referred to as congenital disorder of glycosylation type 1a (CDG 1a), is the most common of the congenital disorders of glycosylation. PMM2-CDG is associated with autosomal recessive inheritance of a mutation in the *PMM2* gene. This mutation causes a deficiency of phosphomannomutase, an enzyme coded by *PMM2*, and results in decreased GDP-mannose production, abnormal glycosylation of N-linked oligosaccharides, and clinical manifestations.

Classically, PMM2-CDG presents in infancy with hypotonia, abnormal fat distribution (accumulation in the buttocks and suprapubic areas), inverted nipples, developmental delay, feeding difficulties, failure to thrive, and esotropia. Infants with PMM2-CDG may have severe multisystemic involvement with up to a 20% mortality rate, but a nonfatal neurologic form has also been observed.² Currently, more than 100 different mutations in *PMM2* have been described and may impact the clinical phenotype.³ We present a patient diagnosed with PMM2-CDG just prior to 4 years of life with primarily neurologic symptoms.

CLINICAL CASE Our patient was born at 37 weeks via spontaneous vaginal delivery with no reported complications. Mother reported normal fetal movement. Birthweight was 4,300 g (97th percentile), length was 48 cm (50th percentile), and head circumference was 34.5 cm (50th percentile). During the newborn period, our patient had a short period of feeding difficulty involving gagging and spitting up which seemed to improve after changing formulas.

Within the first 2 weeks of life, she was observed to have daily episodes consisting of conjugate upward eye movements accompanied with neck extension. At 4 months, she was noted to have jerky eye movements while tracking objects and a resting downbeat nystagmus was observed around 6 months of age.

She otherwise continued to have full range of motion in her extraocular muscles. Her episodes of upward gaze resolved around 1 year of age, at which time the parents began observing inward deviation of each eye separately. This failed to correct with patched eye treatment over 6 months.

In addition, she was noted to be hypotonic since infancy. She had difficulty with lifting her head during the first year of life which gradually improved during her second year of life. She first sat unsupported at 13 months and ambulated with assistance at 3 years of age. Her parents felt she had trouble walking due to clumsy and ataxic movements since 31 months of age. By 4 years of age, her receptive language was at age-expected levels, but her expressive language scores were at a 24- to 30-month age level with only 50% of her speech intelligible. She had no history of language or motor regression. The family was not consanguineous and there were no members with known childhood disability, weakness, or similar neurologic disease. A maternal aunt and her son were reported to have juvenile onset epilepsy.

EXAMINATION Physical examination at 45 months of life revealed height and weight to be in the ninth percentile and head circumference was near the fifth percentile. Previously at 30 months, height and weight were at the 15th percentile and head circumference was measured at the 25th percentile, suggesting suboptimal head growth. General examination was unrevealing with no dysmorphology. Neurologic examination revealed a friendly and interactive youngster who was alert and attentive. She played with her dolls during examination. Cranial nerve examination was significant for impaired smooth pursuit and impaired optokinetic nystagmus in vertical and horizontal planes. She had lateral end gaze horizontal nystagmus and bilateral esotropia (video 1 on the *Neurology*[®] Web site at www.neurology.org). She had mild decreased proximal tone and marked distal hypotonia. She had normal muscle bulk and

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MRI brain with/without contrast at 9 months of age shows slight prominence of cerebellar sulci: (A) sagittal T1, (B) axial T2. Repeat MRI brain at 38 months shows moderate to severe diffuse cerebellar atrophy: (C) sagittal T1, (D) axial T2.

strength. Deep tendon reflexes were normal with downgoing toes bilaterally. She was observed to have truncal titubation while sitting independently, and was dysmetric when reaching for objects bilaterally. Gait was ataxic and broad-based with hyperextension at her knees. She required assistance by her mother, who held her as she walked.

DIAGNOSTIC WORKUP Extensive workup revealed normal complete blood count, chemistry panel, and liver enzymes. Metabolic studies to include ammonia, lactate, plasma amino acids, urine organic acids, acylcarnitine profile, and alpha fetoprotein were normal. Chromosomal microarray (Oligo V8.1) showed no abnormalities. Methylation and DNA sequencing for Angelman syndrome were normal. CSF amino acids and neurotransmitter metabolites were normal. EEG was normal at 10 months in awake and sleep states. MRI of the brain with and without contrast was performed at 9 months of age and showed a slight nonspecific prominence of the cerebral and cerebellar sulci but was otherwise unremarkable. Repeat MRI of the brain performed at 38 months of age showed moderate to severe diffuse cerebellar atrophy with increased T2 hyperintense signal in the cerebellar folia (figure).

Based on MRI findings, a comprehensive spinal cerebellar ataxia panel was obtained and was normal.

Testing for Niemann-Pick type C was also negative. Carbohydrate-deficient transferrin panel showed elevated aglycosylated and monoglycosylated transferrins. (Mono-oligosaccharide/di-oligosaccharide transferrin ratio was $0.172 \mu\text{mol/L}$, normal range $0-0.100$ and a-oligo-/di-oligo-transferrin ratio was $0.082 \mu\text{mol/L}$, normal range $0.00-0.05$.) N-glycan structural analysis showed small amounts of mannose deficient glycans. *PMM2* gene sequencing resulted in detection of 2 heterozygous missense mutations, c.359T>C (p.I120T) and c.682G>T (p.G228C), and confirmed the diagnosis of PMM2-CDG. Both mother and father were found to be carriers of each mutation.

DISCUSSION Our case demonstrates a typical neurologic presentation of a girl with PMM2-CDG with initial clinical findings of ocular motor abnormalities and hypotonia. Ocular motor findings were also first seen in a 10-month-old boy with PMM2-CDG and cerebellar hypoplasia.⁴ He first presented with an ocular motor apraxia, described as jerky, conjugate oscillations of his eyes with awakening or startle. He also had difficulty with initiating voluntary horizontal saccades. It was postulated his eye movements may reflect the diffuse cerebellar hypoplasia seen in PMM2-CDG. Unlike our patient, he was also found to have inverted nipples and abnormal fat distribution.

Three stages of PMM2-CDG have been described: an early infantile stage, late infantile (childhood ataxia-intellectual disability) stage, and adult stable disability stage.⁵ The infantile stage contains 2 forms. A well-known multisystem form exists which may include findings illustrated above with the addition of feeding problems, vomiting, diarrhea, failure to thrive, liver or kidney dysfunction, microcephaly, and developmental delay.⁶ Within the infantile stage, a second nonfatal neurologic form has also been described with predominant symptoms of hypotonia, strabismus, ataxia, and psychomotor retardation.²

The late infantile stage occurs between 3 and 10 years with continued hypotonia, ataxia, delayed language and motor skills, seizures, transient loss of function or stroke-like episodes, retinitis pigmentosa, contractures, and skeletal deformities. Ataxia may initially be progressive and correspond to increasing cerebellar atrophy but may stabilize in early childhood. Additionally, acquired microcephaly may occur.⁶ In the adult stage, patients have been described to have stable cognitive ability, skeletal deformities, coagulopathy, osteopenia, premature aging, and peripheral neuropathy. Also, endocrine abnormalities may occur such as hyperprolactinemia, insulin resistance, and failure to develop secondary sexual charac-

teristics.⁵ Finally, many patients with PMM2-CDG may become myopic, with half of a genetically homogenous group of patients observed to show signs of retinal degeneration.⁷

Congenital disorders of glycosylation should be suspected based on the presence of any of the above clinical findings, especially in the absence of a known underlying diagnosis. In addition to diffuse cerebellar hypoplasia or atrophy, an enlarged cisterna magna or superior cerebellar cistern may be present on MRI of the brain. Like our patient, cerebellar atrophy may worsen during early childhood but usually stabilizes.⁵ Isoelectric focusing of transferrin can show abnormalities in glycosylation and distinguish between types I and II. For example, as in our patient, isoelectric focusing in type I CDG shows an increase in di- or asialotransferrin, reflecting a defect in glycan assembly or transfer. Conversely, type II CDG involves a processing defect and would show increased tri-, di-, mono-, or asialotransferrin on isoelectric focusing studies.

Isoelectric focusing of transferrin is also abnormal in galactosemia, fructosemia, and alcoholism. It is important to note that children younger than 1 month with PMM2-CDG may show false-negative results initially and develop abnormal results after up to 2 months.⁸ Normalization may occur in adulthood or adolescence.^{1,5,8} In PMM2-CDG, *PMM2* gene sequencing is diagnostic and has identified more than 800 patients, but genotype–phenotype relationships are still undergoing investigation.³ A literature search on PubMed failed to reveal a phenotypic description of our patient's genotype.

Upon diagnosis, our patient was sent for further testing to evaluate for any signs of systemic involvement. Ophthalmology follow-up at 46 months confirmed bilateral partially accommodative esotropia and hyperopic astigmatism. Renal ultrasound was

negative for microcystic disease. Echo showed a patent foramen ovale with left-to-right shunting. Random glucose, coagulation studies, liver function tests, and thyroid panel were normal. At this time, the patient exhibits no signs of hormonal or systemic abnormalities. Our patient's disease appears to be limited to neurologic manifestations and will require ongoing monitoring for evolving complications.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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