Child Neurology: Exaggerated dermal melanocytosis in a hypotonic infant

A harbinger of GM1 gangliosidosis

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Gangliosidoses are a group of rare lysosomal storage diseases (LySD) involving the accumulation of lipids in multiple organ systems, including the central and peripheral nervous systems. These disorders are inherited in an autosomal recessive pattern and are broadly grouped into 2 types. GM1 gangliosidoses (GM1) are due to a deficiency of the enzyme β -galactosidase, and GM2 diseases (Tay-Sachs, AB variant, and Sandhoff disease) are due to a deficiency of the enzyme β -hexosaminidase. GM1, first described biochemically by Dr. John S. O'Brien in the 1960s, is estimated to occur in 1 in 100,000–200,000 newborns.¹ Despite being the first of the gangliosidoses identified as well as the most prevalent, GM1 often presents a diagnostic challenge to the child neurologist. GM1 type 1, the infantile form, is the most common and the most severe. Patients present with nonspecific neurologic features including hypotonia, sensory impairment, and developmental regression within the first year of life; thus, a broad differential diagnosis is often entertained. We report a complex case of infantile GM1 diagnosed following identification of an extensive dermal melanocytosis on physical examination. This distinguishing feature has been increasingly recognized as a harbinger of GM1.^{2–5} In rare disorders where expensive genetic testing and invasive procedures are often used to reach a diagnosis, recognition of unique clinical features on the physical examination can be a great asset.

Clinical case: Part 1. A 5-month-old girl was admitted to our pediatric ward for evaluation of persistently elevated liver enzymes and developmental regression. Born full term to nonconsanguineous Brazilian parents, she was first admitted to the hospital at 2 months of life for poor feeding in the context of a febrile illness. At that time, she was noted to have normal tone and a normal skeletal survey. During that admission, she was found to have hepatomegaly and markedly elevated alkaline phosphatase levels as well as a mild transaminitis and was ultimately diagnosed with cytomegalovirus hepatitis. Three weeks after successful treatment with valganciclovir, her viral load was undetectable but her liver enzymes remained elevated. In addition, her pediatrician had noted loss of developmental milestones since

4 months of age, including her social smile and tracking abilities. She had never been able to roll over or hold her head steady.

On admission, the patient's vital signs were significant for hypertension. On physical examination, she was noted to have a large anterior fontanel, hypertelorism, and a broad nasal bridge. Her dilated ophthalmologic examination results were normal. Her abdomen was distended, and her liver could be palpated 2 cm below the costal margin. She did not track light or blink to threat. She did not startle to loud sound. She responded to tactile stimulation with active exploration and had a responsive sucking reflex. She was diffusely hypotonic with decreased deep tendon reflexes. She had an extensive, patchy dermal melanocytosis covering most of her back, buttocks, lower extremities, and diffusely over her abdomen (figure, A). These discolorations were noted by her pediatrician to have progressed from birth to 2 months of age and then stabilized.

Initial laboratory studies revealed a mild transaminitis with markedly elevated alkaline phosphatase and normal bilirubin levels. Visual evoked potential showed a marked delay in conduction time. MRI of the brain revealed marked hypomyelination with no visible myelination of subcortical U-fibers and scant myelination in the perirolandic areas and corticospinal tracts, as well as elevated T2 signal in the basal ganglia (figure, B and C). An echocardiogram demonstrated mild left ventricular dilation with mildly depressed global systolic function and symmetric left ventricular hypertrophy. An initial metabolic screening revealed normal urine organic acids and glycosaminoglycans.

DISCUSSION The differential diagnosis of a hypotonic infant with regression in milestones and hepatomegaly includes LySD such as gangliosidoses (i.e., GM1 type I, Tay-Sachs, Sandhoff), fucosidosis, α -mannosidosis, mucopolipidoses (i.e., sialidosis, I-cell disease, multiple sulfatase deficiency), mucopolysaccharidoses (i.e., Hurler syndrome), and glycogen storage disorders (i.e., Pompe disease).^{6,7} Tay-Sachs is the only LySD without liver involvement. Normal glycosaminoglycans essentially

(A) Extensive dermal melanocytosis present since birth. (B) Axial T1 brain MRI demonstrates marked hypomyelination diffusely throughout subcortical white matter and scant myelination in the internal capsule. (C) Axial T2 brain MRI demonstrates patchy T2 hyperintensity in the basal ganglia.

rule out Hunter and Hurler syndromes. Age at onset within the first 6 months of life makes several potential diagnoses less likely, including Hurler syndrome, Pompe disease, and multiple sulfatase deficiency. Extensive dermal melanocytosis, a distinguishing feature in our patient, is associated with several LySD, most frequently Hurler syndrome and GM1.^{2,4} Given our patient's history and clinical presentation, including Brazilian heritage, MRI findings, and extensive dermal melanocytosis, GM1 was determined to be the most likely diagnosis. Targeted gene testing was sent, confirming a compound heterozygote mutation in the *GLB1* gene of R59H and W527LfsX5. As 2 disease-causing mutations on the same allele (cis location) do not result in the disease phenotype, our patient's parents must have each contributed mutations on different alleles (trans location) to produce the disease.

In addition to the delayed development, hypotonia, and hepatosplenomegaly seen in GM1 type 1, additional features include dysostosis multiplex, seizures, joint stiffness, exaggerated startle response, and coarsening of facial features. Macrocephaly, secondary to increased lysosomal storage and calvarial thickening, may be present. Half of infants diagnosed with the condition have cherry-red spots on ophthalmologic examination, and most are deaf and blind by age 1. Death occurs by 3 years of age, most commonly from aspiration pneumonia or cardiac problems. Prenatal presentation, though uncommon, can occur in the form of hydrops fetalis and intrauterine growth retardation.⁶

Diagnosis involves clinical evaluation as well as targeted testing. Enzyme assay demonstrating a deficiency of lysosomal β -galactosidase in fibroblasts or leukocytes provides a definitive diagnosis. Enzyme levels vary, with lower levels associated with more

severe disease. *GLB1* sequence analysis, which has 99% specificity, can be used to diagnose the condition if enzyme testing is not available or not definitive. If a diagnosis is suspected or confirmed, multiorgan involvement should be evaluated with ECG, echocardiogram, EEG, brain MRI, and complete ophthalmologic examination.

Certain populations have a much higher prevalence of GM1, such as people from the Maltese Islands (1:3,700), of Roma ancestry (1:10,000), and from Brazil (1:17,000), which is suspected to represent a founder effect.⁷ Because GM1 is an autosomal recessive disorder, future pregnancies have a 25% chance of homozygosity. Antenatal diagnosis is possible through custom laboratory tests or preimplantation genetic diagnosis.

The *GLB1* gene on chromosome 3p21.33 codes for lysosomal β -galactosidase. With more than 150 disease-causing mutations, most patients are compound heterozygotes.⁷ The most common mutations involve changes in *GLB1*'s tertiary structure, leading to alterations in the enzyme's ligand binding pocket. Patients are most severely affected when these changes affect the triosephosphate isomerase (TIM) barrel domain, which is critical for catalysis.⁸ Without a functional enzyme, the breakdown of ganglioside GM1 and keratan sulfate cannot occur. These substances accumulate in toxic levels throughout the body, most significantly in the brain, where ganglioside synthesis is greatest. This accumulation leads to gray matter expansion and marked myelin deficiency, possibly related to neuronal dysfunction and subsequent disruption of axonal transport.⁹

In addition to her neurologic findings, our patient's examination showed extensive dermal melanocytosis. There are now 54 reported cases of extensive dermal melanocytosis in children with LySD, with 17

occurring in GM1, 25 in Hurler syndrome, 9 in Hunter syndrome, 2 in α -mannosidosis, and 1 in Niemann-Pick disease.^{2–5} Despite similar histology between typical dermal melanocytosis and those associated with LySD, the latter persist and even progress over time rather than fading.² Both Schwann cells and melanocytes derive from the neural crest during embryologic development. The accumulated metabolites in GM1 are hypothesized to bind tightly to tyrosine kinase protein, resulting in increased nerve growth factor. This factor then binds to chemotactic melanocyte receptors, leading to abnormalities in melanocyte migration and producing the large dermal melanocytosis seen.⁴

Clinical case: Part II. After her initial decline in development between 3 and 5 months of age, the patient's development remained stagnant through the present time, age 11 months. Although her weight has remained in the 10th percentile, her head circumference climbed from the 25th percentile at birth to the 95th percentile by 7 months. At 8 months of age, she had a generalized tonic-clonic seizure in the context of a febrile illness. EEG showed marked high-amplitude disorganization of the background with multifocal sharp waves. At age 10 months, she was hospitalized for respiratory syncytial virus bronchiolitis and continues to require oxygen at night.

Treatment of GM1 is symptomatic and not curative. Specialists in genetics, cardiology, neurology, and orthopedics are often necessary to manage care of these patients. Physical, occupational, and speech therapists also play important roles in facilitating the patient's daily activities. Many children with GM1 develop seizures requiring anticonvulsant treatment. Feeding difficulties and subsequent weight loss are common and preventable with proper nutrition and at times, gastric tube placement. As neurologic decline progresses, managing the patient's airway and preventing infections becomes paramount. In-home hospice care is often utilized when a patient's end of life approaches.

Current research efforts in animals are focused on using small molecule chaperones to transport functional enzymes across the blood–brain barrier to slow neurologic decline.¹⁰ While bone marrow transplant has successfully treated patients with Hurler syndrome, only one article has been published on a patient with GM1 type II disease, demonstrating no effect of transplant on slowing cognitive decline.¹¹

DISCUSSION GM1 is a rare but universally fatal LySD with particularly devastating consequences on

the neurologic system. Though treatment is largely supportive, earlier diagnosis could enhance the patient and his or her family's quality of life and allow for informed decisions about future pregnancies. In this case, the patient's distinctive birthmark in the context of other clinical features was instrumental in reaching a diagnosis.

AUTHOR CONTRIBUTIONS

Dr. Armstrong-Javors prepared the first draft and revisions of the manuscript. Dr. Chu prepared revisions of the manuscript.

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DISCLOSURE

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