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Special Article

Krabbe Disease: Severe Neonatal Presentation With a Family History of Multiple Sclerosis

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ABSTRACT

Krabbe disease, also known as globoid cell leukodystrophy, is a rare autosomal recessive disorder caused by a deficiency of a lysosomal enzyme, galactocerebrosidase. This defect prevents normal turnover of the galactolipids and results in progressive demyelination. In the infantile form, symptoms typically present at 3 to 6 months of age with subsequent neurologic deterioration. We report a case with presentation on day 7 of life and rapid progression culminating in death at 10 weeks. Galactocerebrosidase activity was absent in the leukocytes, and a 30 kb deletion in the *GALC* gene was found. To our knowledge, this is the earliest reported death from Krabbe disease. Several family members have multiple sclerosis, which is also a demyelinating disorder. We propose that the neonatal expression could be an example of complementary gene interaction in which coinheritance of a predisposition to multiple sclerosis led to the unusual early manifestation and rapid course of Krabbe disease in this infant. (*J Child Neurol* 2005;20:826–828).

CASE REPORT

A 9-week-old girl was admitted to the hospital for evaluation of failure to thrive and regression of milestones. The patient was the product of an uncomplicated second pregnancy of a nonconsanguineous couple of European ancestry. She was delivered via a cesarean section for dystocia and appeared to be normal at birth. Irritability and episodes of vomiting were first noted on day 7 of life. These symptoms progressed, and intermittent lethargy was also noted. Several formula changes did not relieve the symptoms. At around 7 weeks of age, her suck and grip were observed to be weak and her oral intake was very poor. Upper endoscopy revealed gastrointestinal reflux, and she was started on omeprazole. She appeared to respond initially, but her mother noticed that she was not fixing with her eyes. On the day she was admitted to the hospital for a complete neurologic evaluation, two episodes of twitching of the lower extremities were witnessed.

Initial physical examination revealed an irritable infant with length, weight, and head circumference at the 10th percentile. She lay in bed with her legs extended and arms flexed, which her mother reported had been her preferred posture since birth. She moved her eyes and blinked spontaneously but did not fix and follow or blink to threat. Occasional twitching movements were noted in the lower extremities, especially on handling. Her pupils responded only sluggishly to light, but the fundus was normal. Head lag was present. Her muscle tone fluctuated from hypotonic to hypertonic, especially in the lower extremities. The reflexes were brisk, and right lower extremity clonus was noted.

Her family history was notable in that the paternal great-grandmother, the paternal granduncle, and one of his daughters have multiple sclerosis. (The multiple sclerosis was diagnosed by their respective neurologists based on the clinical presentation and magnetic resonance imaging [MRI] findings.)

Computed tomography (Figure 1) revealed mineralization in the lateral thalami and putamen extending into the corona radiata and lucencies in the perirolandic regions in a pattern suggestive of hypoxic-ischemic injury. Signal abnormalities of the lateral thalami, corona radiata, and dentate nuclei of the cerebellum were noted on MRI (Figure 2). Electroencephalography revealed diffuse slowing with multiple epileptogenic foci. Cerebrospinal fluid analysis was remarkable for elevated protein of 216 mg/dL (normal 15–45 mg/dL). Routine laboratory analyses and ammonia; plasma and cerebrospinal fluid amino acids; toxoplasmosis, rubella, cytomegalovirus, and herpes simplex titers; very-long-chain fatty acids; carnitines; acylcarnitines; organic acids; lactate; transferrin; urinary acylglycines; and human immunodeficiency virus (HIV) titers were normal. Lysosomal enzyme testing revealed no galactocerebrosidase activity, and DNA analysis revealed homozygosity for the 30 kb deletion on the *GALC* gene, confirming the diagnosis of Krabbe disease.

Over the course of the next few days, her seizures became frequent and her condition deteriorated rapidly such that she finally succumbed to the illness at 10 weeks of age.

The 30 kb deletion was detected in the heterozygous form in both parents but was absent in the paternal grandmother. No other family members have been tested for the mutation.

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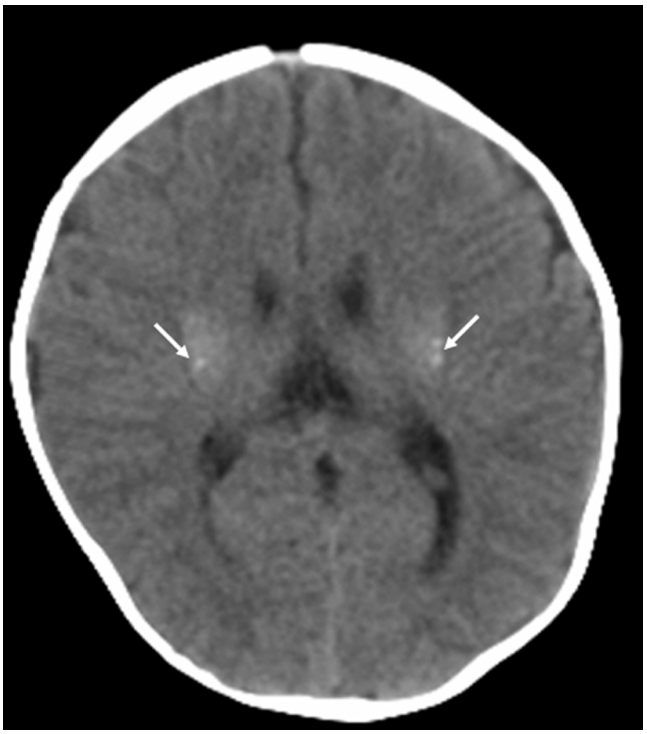
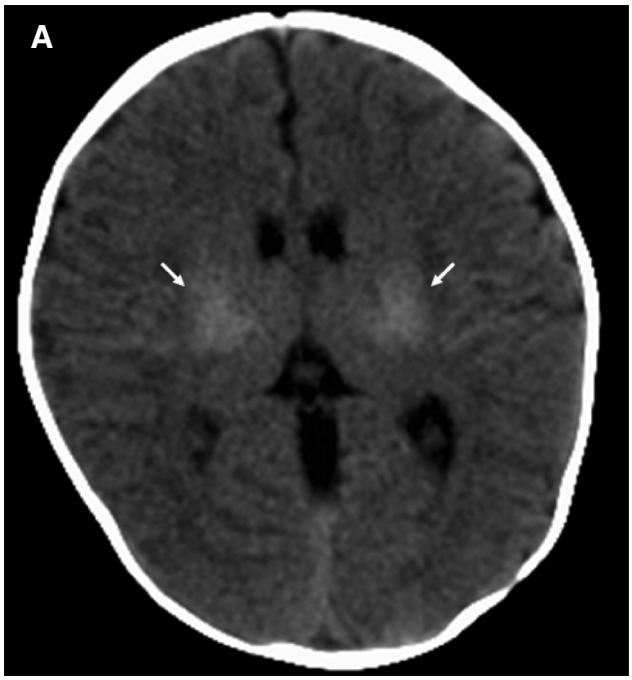


Figure 1. CT scan revealing mineralization in the lateral thalami and posterior putamen.



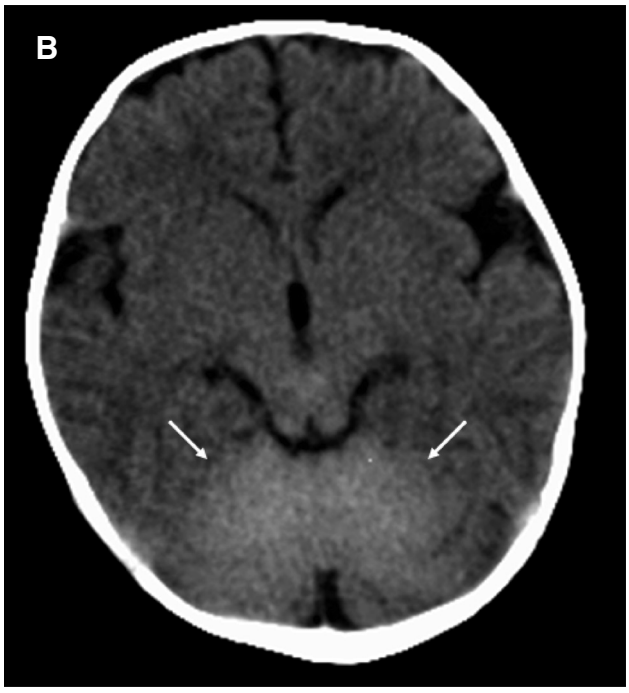


Figure 2. MRI showing signal abnormalities of the putamen and lateral thalami (*A*) and cerebellum (*B*).

DISCUSSION

Krabbe disease, also known as globoid cell leukodystrophy, is a rare autosomal recessive disorder with an incidence estimated at 1 in 100,000 to 200,000 live births. It is caused by a deficiency of a lysosomal enzyme, galactocerebrosidase, which is required for hydrolysis of galactocerebroside and psychosine. Since these galactolipids are found almost exclusively in the myelin, their defective turnover, owing to the deficiency of galactocerebrosidase, results in the progressive destruction of myelin and myelin-forming cells, including oligodendrocytes in the central nervous system and Schwann cells in the peripheral nervous system.[1,2] In addition to myelin destruction, histology reveals astrocytic gliosis and infiltration by unique multinucleated macrophages containing periodic acid–Schiff–positive material (globoid cells). Krabbe disease can be divided into two main clinical forms based on the age at onset of symptoms: an infantile form, accounting for 85% to 90% of the cases, and a late-onset form, accounting for the remaining 10% to 15%.

Patients with the infantile form generally present with irritability, spasticity, and arrested motor development at 3 to 6 months of age followed by rapid progressive neurologic decline and death by 2 years.[3,4] In the initial few months after birth, however, psychologic development proceeds normally, and the median age at onset of symptoms is reported as 4 months. It is possible that clinical manifestations of Krabbe disease in some affected infants are present earlier than reported but are missed owing to a low index of suspicion. For instance, accumulation of galactosylsphingosine (psychosine) in tissues was observed in a 21-week fetus diagnosed prenatally with Krabbe disease, and an asymptomatic child was found to have evidence of peripheral neuropathy at 7 weeks of age, which strengthens this possibility.[5–7] An extremely rare neonatal variant has been mentioned in the literature wherein the symptoms were evident in the neonatal period.[8,9] Even in these cases, the disease progressed over several months before death ensued or the diagnosis of Krabbe disease was unconfirmed. To our knowledge, our case with symptoms noted at 7 days of age and rapid progression to death at age 10 weeks is the earliest reported death from Krabbe disease.

Individuals with Krabbe disease can be diagnosed on the basis of the decreased galactocerebrosidase activity (0–5% of normal) in leukocytes. The galactocerebrosidase (*GALC*) gene has been localized to chromosome 14q31.[10,11] More than 60 mutations associated with Krabbe disease have been reported.[12] A large 30 kb deletion (IVS10del30kb) results in the classic infantile form when present in the homozygous form or with another mutation associated with severe disease. It accounts for 45% of mutant alleles in individuals of European descent and 35% of those of Mexican ancestry.[13,14] Another mutation, G>A809, always results in the late infantile form even when heterozygous with the 30 kb deletion. Even in individuals with an identical genotype, the clinical manifestations and severity can vary. It is interesting to note that the common 30 kb deletion, associated with the classic infantile presentation, was identified in the present case rather than a novel or rare variant, which might have offered an explanation for the early presentation and rapid progression. In the late-onset form of Krabbe disease, patients can be normal until almost any age. They usually present with weakness, vision loss, and intellectual regression, but the clinical manifestations are extremely variable, and the course is more protracted.

Multiple sclerosis, another demyelinating disorder, is an autoimmune disorder of the central nervous system characterized by multifocal areas of demyelination, loss of oligodendrocytes, and occurrence of astroglial scarring. Symptoms of multiple sclerosis are extremely diverse, and although vision disturbances, spasticity, paresthesias, and cognitive impairment are frequently seen, they are not specific to this disorder. Genetic epidemiologic and molecular studies suggest a role of both genetic and nongenetic factors in the causation and outcome of multiple sclerosis. Genomic screening studies have excluded a single major locus for multiple sclerosis, although several genes appear to be associated with this disorder.[15]

No association of the *GALC* gene with multiple sclerosis has been reported thus far, but it seems reasonable to propose that genes associated with multiple sclerosis could modify the expression of the *GALC* gene. In the infant we described, the neonatal expression and the rapid progression of Krabbe disease could be an example of such complementary gene interactions wherein a coinheritance of a predisposition to multiple sclerosis led to this very profound clinical course. We concede that because it is impossible to determine if, indeed, this infant had inherited a predisposition to multiple sclerosis, it is difficult to verify our hypothesis. However, through identification of individuals with multiple sclerosis and subsequent retrospective analysis of the clinical presentations of their family members with Krabbe disease, this hypothesis could be evaluated. Alternatively, encountering other patients with an early presentation of Krabbe disease and a family history of another demyelinating disorder would certainly substantiate our hypothesis.

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