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Original Article

Patterns of Magnetic Resonance Imaging Abnormalities in Symptomatic Patients With Krabbe Disease Correspond to Phenotype

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ABSTRACT

BACKGROUND: Initial magnetic resonance imaging studies of individuals with Krabbe disease were analyzed to determine whether the pattern of abnormalities corresponded to the phenotype. **METHODS:** This was a retrospective, nonblinded study. Families/patients diagnosed with Krabbe disease submitted medical records and magnetic resonance imaging discs for central review. Institutional review board approval/informed consents were obtained. Sixty-four magnetic resonance imaging scans were reviewed by two neuroradiologists and a child neurologist according to phenotype: early infantile (onset 0-6 months) = 39 patients; late infantile (onset 7-12 months) = 10 patients; later onset (onset 13 months-10 years) = 11 patients; adolescent (onset 11-20 years) = one patient; and adult (21 years or greater) = three patients. Local interpretations were compared with central review. **RESULTS:** Magnetic resonance imaging abnormalities differed among phenotypes. Early infantile patients had a predominance of increased intensity in the dentate/cerebellar white matter as well as changes in the deep cerebral white matter. Later onset patients did not demonstrate involvement in the dentate/cerebellar white matter but had extensive involvement of the deep cerebral white matter, parieto-occipital region, and posterior corpus callosum. Late infantile patients exhibited a mixed pattern; 40% had dentate/cerebellar white matter involvement while all had involvement of the deep cerebral white matter. Adolescent/adult patients demonstrated isolated corticospinal tract involvement. Local and central reviews primarily differed in interpretation of the early infantile phenotype. **CONCLUSION:** Analysis of magnetic resonance imaging in a large cohort of symptomatic patients with Krabbe disease demonstrated imaging abnormalities correspond to specific phenotypes. Knowledge of these patterns along with typical clinical signs/symptoms should promote earlier diagnosis and facilitate treatment.

Keywords: Krabbe disease, MRI, magnetic resonance imaging, Krabbe phenotypes, age-related findings

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Introduction

Krabbe disease is a rare, autosomal recessive neurodegenerative disease that involves both the central and peripheral nervous system. It results from a deficiency of the enzyme galactocerebrosidase that, under normal circumstances, is responsible for myelin turnover by breaking down galactocerebroside. Galactocerebrosidase is also responsible for the breakdown of galactosylsphingosine (psychosine), a substance that is highly toxic to oligodendroglia and myelin. Interest in Krabbe disease has increased in the past 7 years because of the advent of universal newborn screening for Krabbe disease in New York. It had been anticipated that the incidence of Krabbe disease would have been 1/100,000, with 90% of children having the early infantile phenotype.[1] After 7 years and

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>1.8 million babies tested, however, only five infants have been identified as having early infantile Krabbe disease, whereas the majority of children with positive newborn screens, confirmatory low galactocerebrosidase activity, and two mutations have so far remained clinically normal.

These findings are of more than academic interest because the only treatment for Krabbe disease is hematopoietic cell transplantation, a procedure associated with significant morbidity and a 10% to 15% mortality rate. Moreover, to be effective in children with the early infantile phenotype, transplantation must be performed before symptom onset. To further complicate the situation, there are five different phenotypes of Krabbe disease, including early infantile (onset 0-6 months), late infantile (onset 7-12 months), later onset (onset 13 months-10 years), adolescent (onset 11-20 years), and adult (onset 21 years or greater).[2-4] Unfortunately, neither low galactocerebrosidase activity nor most mutations reliably predict phenotype. Therefore an infant identified by the newborn screening program with low galactocerebrosidase activity and two mutations may have early infantile Krabbe disease, necessitating emergent hematopoietic cell transplantation, may have a later onset phenotype that may not become clinically manifest for decades, or may remain unaffected.

In response to the perceived need to identify predictors of phenotype in this rare disease, the World-Wide Krabbe Registry was opened in 2008. The registry has previously provided data on the results of neurodiagnostic studies in early and later onset phenotypes of Krabbe disease as well as the role of galactocerebrosidase in predicting phenotype.[2,3,5] In our previous reports, the descriptions of initial magnetic resonance imaging (MRI) were based on the interpretations done in each patient's local medical center. We now describe the results of a central review of initial MRI in this symptomatic population to determine whether the pattern of MRI abnormality corresponds with phenotype.

Methods and Materials

This retrospective nonblinded study was approved by the Children and Youth Institutional Review Board of the University at Buffalo School of Medicine. Informed consents were obtained from the patients' parents or from the patients themselves if they were adolescent and adult-onset patients. All patients were enrolled in the World-Wide Krabbe Registry. Initial MRI scans and official reports were requested from the hospitals at which the scans were performed. Scans had been obtained before definitive diagnosis. Scans were reviewed by two pediatric neuroradiologists (11 and 30 years of experience) and one child neurologist (30 years of experience). One of the pediatric neuroradiologists (A.A.) and the child neurologist (P.K.D.) reviewed the scans together, whereas the second pediatric neuroradiologist (R.A.) reviewed the scans separately. If the interpretation of the scans differed, the scans were re-reviewed and consensus was achieved. The reviewers were aware of the patient's age at symptom onset (to determine phenotype), duration from symptom onset to MRI (to determine duration of illness), and age at time of MRI scan. Sixty-four MRI scans were reviewed centrally. The scans were grouped according to age at onset of symptoms and phenotype: 0-6 months = early infantile; 7-12 months = late infantile; 13 months-10 years = later onset; adolescent = 11-20 years; and adult 21 years or greater. Age at symptom onset, age at first MRI, age at diagnosis, and duration from MRI to diagnosis were recorded.

Most scans were performed without contrast. T1, T2, and fluid-attenuated inversion recovery images were reviewed. Although some patients also received diffusion-weighted imaging, these results were not included in the study. Scans were coded as follows: isolated corticospinal tract involvement, deep cerebral white matter (periventricular/centrum semiovale), parieto-occipital, posterior corpus callosum, posterior internal capsule, thalamus, brainstem, cerebellar white matter, dentate nucleus, atrophy, optic nerves/chiasm, and other.

Reports of MRI scans from local institutions were compared with results of central neuroradiologic review. Whereas scans performed at local institutions were obtained before diagnosis of Krabbe disease, the central readers were aware of the age at symptom onset, duration from onset of symptoms to MRI, and age at time of MRI.

Results

Early infantile Krabbe disease

MRI scans were available on 39 children whose symptom onset was 0-6 months. The ages at symptom onset, initial MRI, and diagnosis are provided in Table. Sixty-four percent (25/39) of children received their initial MRI between 3 and 6 months of age. The time between symptom onset and MRI was 3 months or less in 27/39 (69%). The first MRI was not obtained until at least 6 months after symptom onset in three children.

The initial MRI was abnormal in 38/39 children (Fig 1). The most common abnormalities were increased T2 intensity in the deep cerebral white matter (periventricular/centrum semiovale) and involvement of the dentate hilum and cerebellar white matter. A pattern of increased T2 intensity of the hilum of the dentate surrounded by decreased intensity in the peridentate area and increased T2 in the cerebellar white matter was found in 21 (54%) scans (Fig 2). No child had isolated corticospinal tract involvement, but involvement of the motor cortex, posterior corpus callosum, posterior internal capsule, and/or brainstem was found in 10/39 (25%) scans. Atrophy was identified in seven, and four had a tigroid appearance to the white matter.

Thirty-seven MRI reports from local institutions were compared with the results of central review of the MRI images. MRI scans (27/37) were read as abnormal by the

TABLE.
Patient characteristics

Phenotype	n	Age at Onset (Months)		Age at Initial MRI (Months)		Age at Diagnosis (Months)		Most Common Initial Symptoms
		Mean	Range	Mean	Range	Mean	Range	
Early infantile	39	3.14	0.5-5.5	6.37	3-19	7.23	2-20	Crying, irritability
Late infantile	10	9.2	7-12	15.10	8-48	17.45	8-48	loss of milestones, poor feeding
Later onset	11	35.18	9-60	47.64	14-144	49.91	14-144	Change in gait
Adolescent/adult	4	255	192-336	456	216-696	423	204-504	Change in gait