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Deceptively Normal MR in Early Infantile Krabbe Disease

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Summary: The authors present two cases of 5-month-old children with early infantile Krabbe disease studied by CT and MR. Both infants had characteristic CT scans for the disease consisting of symmetric hyperdensity involving the cerebellum, thalami, caudate, corona radiata, and brain stem. One of the infants had a deceptively normal initial MR examination, with dramatic progression of the white-matter disease over the following 4 months.

Index terms: Krabbe disease; Infants, diseases; Brain, magnetic resonance; Brain, computed tomography; Brain, white-matter disease

Magnetic resonance (MR) imaging has been shown to be exquisitely sensitive to the patterns of normal myelination in the infant brain and to the occurrence of white-matter abnormalities (1, 2). The leukodystrophies are a group of disorders characterized by a failure to form or maintain normal myelin, usually secondary to a metabolic defect. Krabbe disease (also known as globoid

cell leukodystrophy) is a lethal, hereditary leukodystrophy caused by a deficiency of galactocerebroside β -galactosidase (3–5). Characteristic findings on unenhanced computed tomography (CT) have been described in early infantile Krabbe disease (6–8), consisting of symmetric hyperdensity involving the cerebellum, thalami, caudate, corona radiata, and brain stem, which may appear before the observation of diffuse decreased attenuation and atrophy of the white matter. We recently have examined by CT and MR two 5-month-old infants with early infantile Krabbe disease. One of the infants, despite a CT appearance suggesting the disorder, had a deceptively normal initial MR examination.

Case Reports

Case 1

A 5-month-old white boy, product of a normal term pregnancy and delivery, presented with a 1-month history

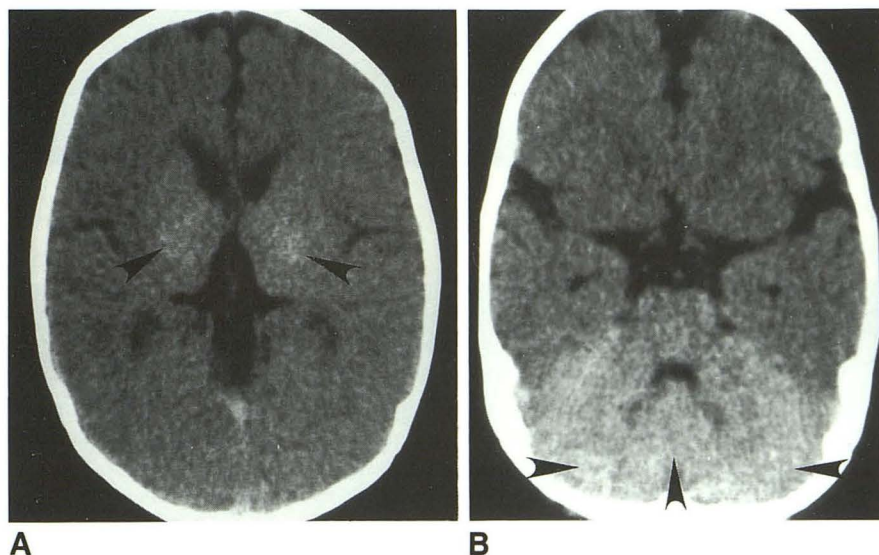


Fig. 1. Case 1.

A, CT scan of the brain without contrast at the level of the thalami demonstrates bilateral, symmetric regions of mild hyperdensity (arrowheads) within the thalami.

B, Scan of the posterior fossa shows increased attenuation within the cerebellar hemispheres and vermis (arrowhead).

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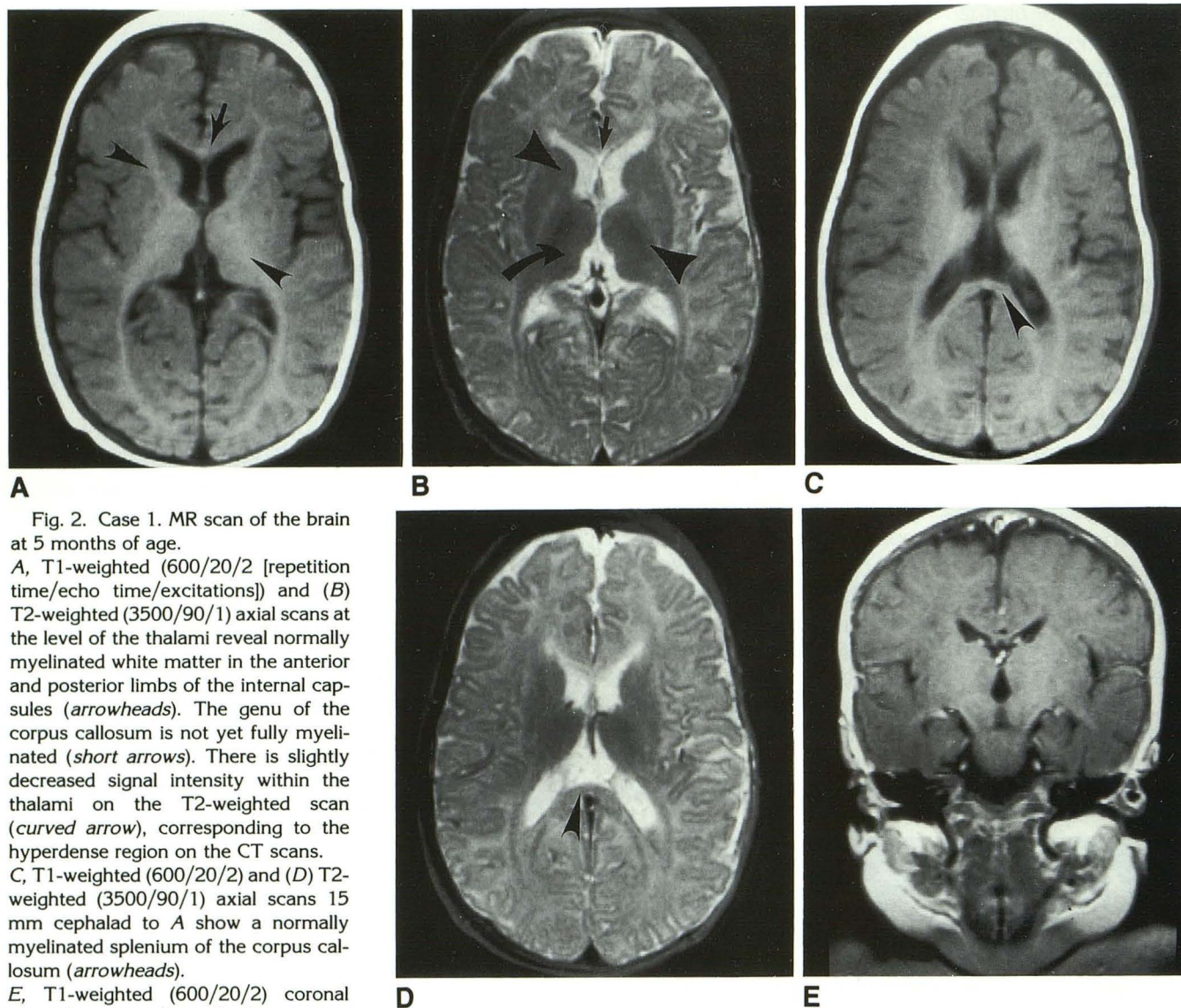


Fig. 2. Case 1. MR scan of the brain at 5 months of age.

A, T1-weighted (600/20/2 [repetition time/echo time/excitations]) and (B) T2-weighted (3500/90/1) axial scans at the level of the thalami reveal normally myelinated white matter in the anterior and posterior limbs of the internal capsules (arrowheads). The genu of the corpus callosum is not yet fully myelinated (short arrows). There is slightly decreased signal intensity within the thalami on the T2-weighted scan (curved arrow), corresponding to the hyperdense region on the CT scans. C, T1-weighted (600/20/2) and (D) T2-weighted (3500/90/1) axial scans 15 mm cephalad to A show a normally myelinated splenium of the corpus callosum (arrowheads).

E, T1-weighted (600/20/2) coronal scan shows myelinated white matter within the cerebral peduncles and internal capsules. The volume of the brain parenchyma is within normal limits.

of difficulty with feeding, motor deterioration, and hyper-tonicity. A barium-swallow examination was normal. The CT examination revealed a normal brain, with mild hyper-intensity in the thalami bilaterally and cerebellum on the unenhanced scans (Fig 1). An MR examination performed the following day was normal (Fig 2). The myelination pattern was normal for a child with a chronologic age of 5 months (1), with myelinated white matter in the brain stem, cerebral peduncles, anterior and posterior limbs of the internal capsule, and the splenium of the corpus callosum. There was no definite T1 signal abnormality corresponding to the hyperdense regions on CT, but there was decreased signal intensity on the T2-weighted scans within the central thalamus. Laboratory evaluation of the child revealed an elevated cerebrospinal fluid protein of 235 mg/dL, slowed peripheral nerve conduction studies, abnormal electromyography, and a leukocyte β -galactocerebrosidase level

markedly decreased, confirming a diagnosis of Krabbe disease. The infant was seen at age 9 months for follow-up MR examination, by then having a clinical history of marked neurologic deterioration and the onset of seizures. The examination revealed interval progression of the disease, with prominent atrophy and hyperintensity of the white matter on the T2-weighted scans (Fig 3). White-matter tracts that had been myelinated on the previous examination, such as the internal capsules, now showed hyperintensity, indicating abnormal myelination. The infant died before the age of 2 years.

Case 2

A 5-month-old white girl, product of a normal term pregnancy and delivery, was referred for evaluation of mental and motor developmental delay, irritability, and failure to thrive. CT scan revealed increased attenuation in

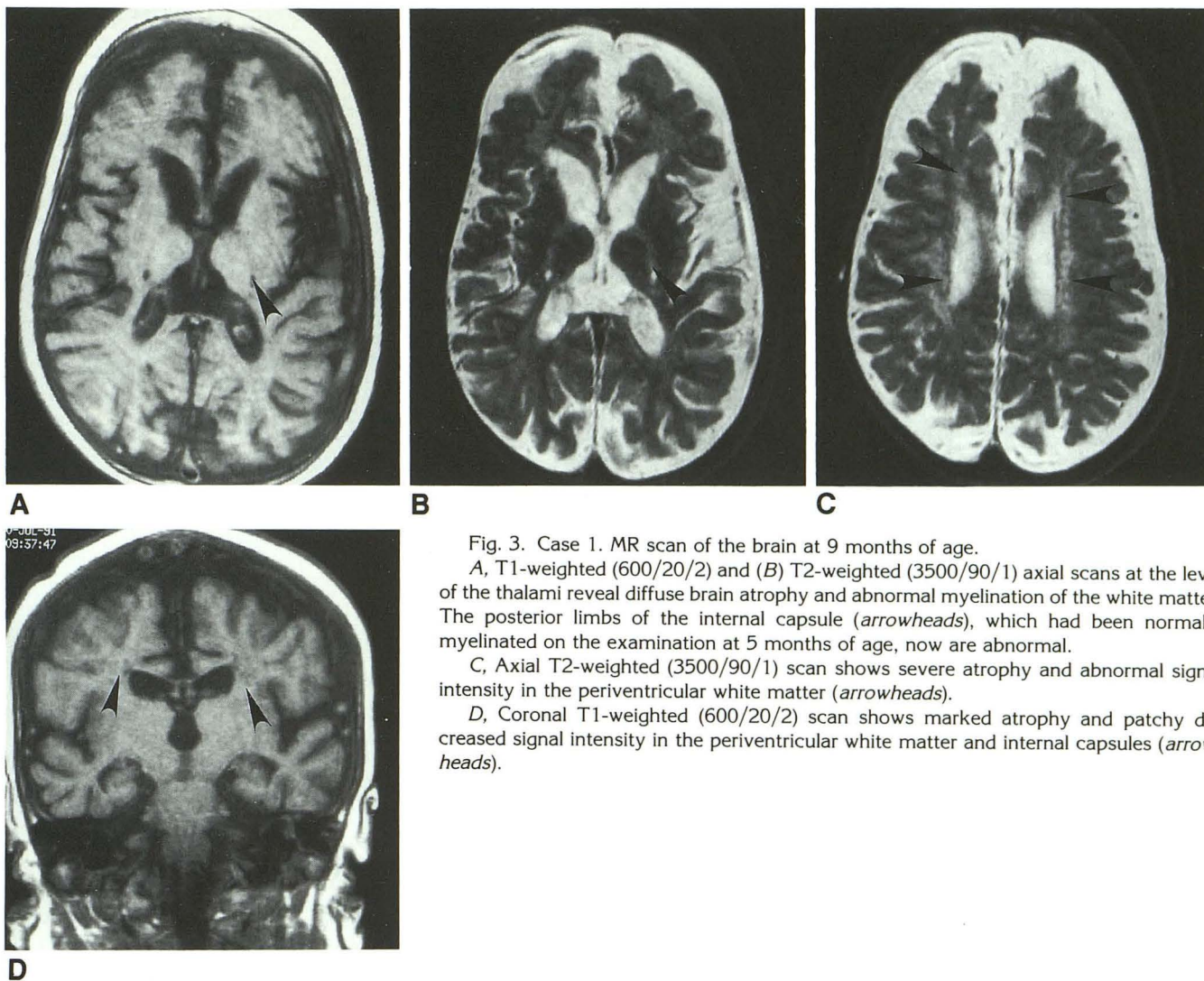


Fig. 3. Case 1. MR scan of the brain at 9 months of age.

A, T1-weighted (600/20/2) and (B) T2-weighted (3500/90/1) axial scans at the level of the thalami reveal diffuse brain atrophy and abnormal myelination of the white matter. The posterior limbs of the internal capsule (*arrowheads*), which had been normally myelinated on the examination at 5 months of age, now are abnormal.

C, Axial T2-weighted (3500/90/1) scan shows severe atrophy and abnormal signal intensity in the periventricular white matter (*arrowheads*).

D, Coronal T1-weighted (600/20/2) scan shows marked atrophy and patchy decreased signal intensity in the periventricular white matter and internal capsules (*arrowheads*).

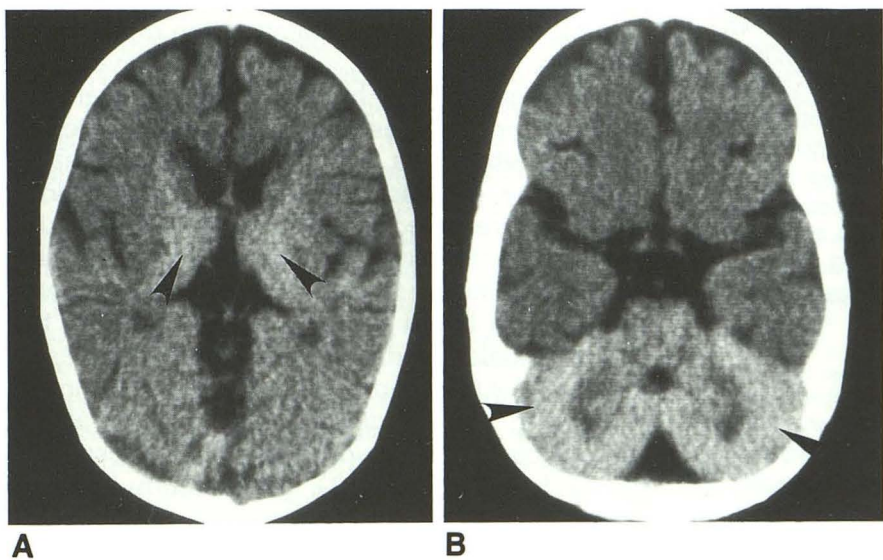


Fig. 4. Case 2. CT scans at the level of the thalami (A) and cerebellum (B) reveal mild hyperdensities (*arrowheads*) within the thalami and cerebellar hemispheres. There is mild generalized atrophy.

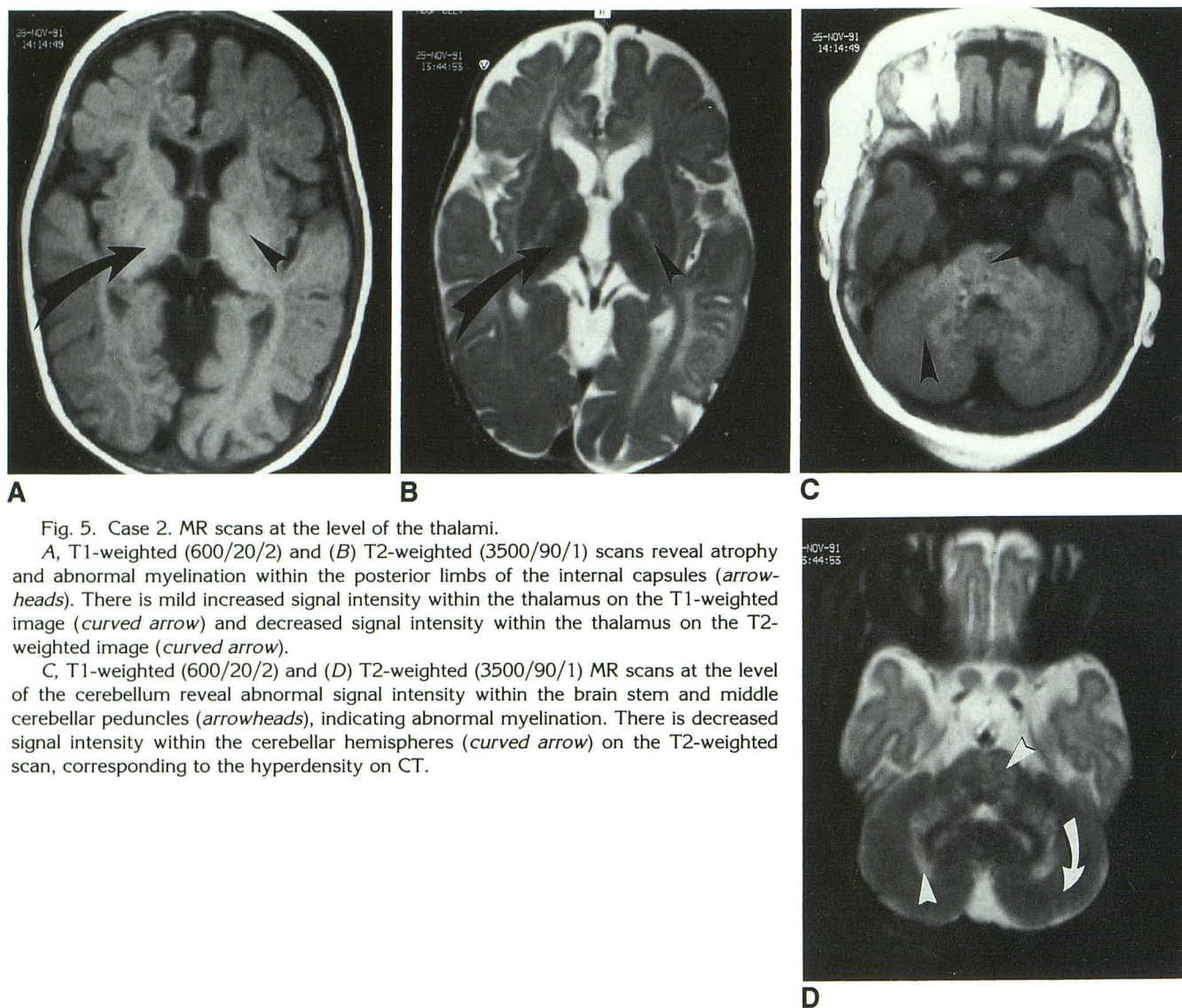


Fig. 5. Case 2. MR scans at the level of the thalami.

A, T1-weighted (600/20/2) and (B) T2-weighted (3500/90/1) scans reveal atrophy and abnormal myelination within the posterior limbs of the internal capsules (*arrowheads*). There is mild increased signal intensity within the thalamus on the T1-weighted image (*curved arrow*) and decreased signal intensity within the thalamus on the T2-weighted image (*curved arrow*).

C, T1-weighted (600/20/2) and (D) T2-weighted (3500/90/1) MR scans at the level of the cerebellum reveal abnormal signal intensity within the brain stem and middle cerebellar peduncles (*arrowheads*), indicating abnormal myelination. There is decreased signal intensity within the cerebellar hemispheres (*curved arrow*) on the T2-weighted scan, corresponding to the hyperdensity on CT.

the cerebellum, brain stem, and thalami, with moderate atrophy and decreased attenuation within the central white matter (Fig 4). MR examination (Fig 5) revealed moderate atrophy, with abnormal myelination in the brain stem, middle-cerebellar peduncles, internal capsules, and corpus callosum. The T1-weighted scans revealed mildly increased signal intensity within the thalami. The T2-weighted scans showed decreased signal intensity within the thalami and cerebellum, which corresponded well to the hyperdense regions on CT. The leukocyte β -galactocerebrosidase assay was markedly low, confirming the diagnosis of Krabbe disease. The child died at age 16 months.

Discussion

Krabbe disease, or globoid-cell leukodystrophy, is a rare, autosomal-recessive disease resulting from a deficiency of galactocerebroside β -galactosidase activity. The disease locus has recently been mapped to chromosome 14 by ge-

netic linkage (9). Pathologically, there is a profound loss of myelin and destruction of oligodendrocytes. The little detectable myelin is morphologically and biochemically normal. The enzymatic defect results in an accumulation of galactocerebrosides, which induce macrophages to become globoid cells. Galactocerebrosides, however, are not toxic to oligodendroglia, the destruction of which is essential to the pathogenesis of the disease. It has been shown by Suzuki and Suzuki (4) and others (10) that there are two distinct β -galactosidases, galactosylceramidase I and II. Galactosylceramidase I is deficient in patients with Krabbe disease; this enzyme also is responsible for the hydrolysis of galactosylsphingosine (psychosine) (11). The accumulation of galactosylsphingosine is extremely toxic to oligodendroglia, and this mechanism is currently

thought to explain the histopathologic and biochemical changes seen in Krabbe disease (11–13).

Characteristic CT changes in early infantile Krabbe disease were described in 1984 by Kwan et al (6), including increased attenuation in the cerebellum, brain stem, thalami, caudate, and corona radiata on unenhanced scans. These findings may be transient and can occur before the development of progressive white-matter hypodensities and atrophy. Kwan et al (6) suggested that the hyperdensities may be caused by alterations in the ratio of lipids, water, and proteins in response to the breakdown of myelin and astrogliosis. Baram et al (7) described three infants, 4 to 8 months of age, with infantile Krabbe disease that also showed symmetric "calcific like" hyperdensities in the thalami, deep white matter, and cerebellum on CT. Intracranial calcifications are not a histologic feature in Krabbe's initial description of the disease (3) or in several subsequent neuropathologic texts (4, 5). However, Feanny et al (8) reported six infants with Krabbe disease, two of which had paraventricular hyperintensities on CT. One of these infants provided histopathologic proof at autopsy of numerous fine calcifications in the paraventricular hyperintense regions seen on CT. The rarity of the disease, the transient nature of the hyperdensities, and the fact that brain tissue is not needed for definitive diagnosis probably have hampered efforts to establish the cause of the CT findings.

Baram et al (7) in 1986 described the MR findings in two cases of early infantile Krabbe disease, consisting of two basic types of lesions. The first lesions are the symmetric, patchy lesions in the periventricular white matter, similar in appearance to lesions of many other dysmyelinating or demyelinating diseases, such as multiple sclerosis. These lesions, and progressive generalized atrophy, have been described later in the course of Krabbe disease (7, 14, 15). The second lesions were regions of decreased signal intensity on T2-weighted scans and possibly increased signal intensity on T1-weighted scans in the thalami, central white matter, and cerebellum, raising the possibility of a paramagnetic effect (7). These regions correspond closely to the hyperdensities present on CT (7). Both of our cases showed regions of decreased signal intensity on T2-weighted scans in the thalami and, in case 2, within the cerebellum, corresponding to their CT hyperdensities. In case 2, mildly increased signal intensity was shown on T1-weighted scans within the thalamus. These findings again suggest, but

do not confirm, the deposition of a paramagnetic substance such as calcium within those regions.

In conclusion, despite the extreme sensitivity of MR for the diagnosis of white-matter diseases, early in the course of even a lethal leukodystrophy such as Krabbe disease, an examination may be deceptively normal. A spectrum of MR abnormalities occurs over several months as the disease progresses, including atrophy and typical bilateral, symmetric white-matter lesions reflecting abnormal myelination. Regions of decreased signal intensity on T2-weighted scans and normal to increased signal intensity on T1-weighted scans may be seen in the thalami and cerebellum in early infantile Krabbe disease. These abnormalities correspond to the distinguishing CT feature of hyperdensities in the thalami, caudate nuclei, deep central white matter, and cerebellum, and provide further confirmation of the diagnosis of infantile Krabbe disease.

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