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Case Report

Optic Nerve Enlargement in Krabbe's Disease

Blaise V. Jones, Todd F. Barron, and Javad Towfighi

Summary: We report imaging and gross pathologic findings from two cases of Krabbe disease in which there was marked enlargement of the intracranial optic nerves. Numerous globoid cells were observed in the optic nerves at autopsy in one case. Krabbe disease should be included in the differential diagnosis of children with enlargement of the optic nerves.

Krabbe's disease (globoid cell leukodystrophy) is a disorder of lysosomal function that results in accumulation of galactocerebroside and psychosine in macrophages and is associated with demyelination and dysmyelination of cerebral white matter. Previously described imaging findings with Krabbe's disease include foci of increased attenuation on CT scans early in the disease, patchy foci of abnormal signal in the white matter on MR images, and white matter volume loss later in the disease. We present two cases of Krabbe's disease in which there is striking enlargement of the optic nerves in association with foci of abnormal signal on MR images. Histologic analysis of one of the cases shows the enlargement to occur because of the presence of numerous globoid cells.

Case Reports

Case 1

A 5-month-old male patient presented with marked irritability since birth, characterized by unremitting crying and episodes of whole-body stiffening with arching of the back. Developmental milestones initially had been appropriate but more recently had plateaued. Birth and family history were noncontributory. A neurologic examination revealed that the patient was extremely irritable. He had increased truncal and appendicular tone, with bilateral Babinski signs but absent deep tendon reflexes. MR imaging of the brain showed discrete foci of abnormal hyperintense signal in the deep cerebellar gray matter on T2-weighted images (Fig 1). The optic chiasm and prechiasmatic optic nerves were enlarged symmetrically; this enlargement did not extend to the intraorbital optic nerves. Blood test for lysosomal enzymes showed low galactocerebrosidease. The patient was taken to another institution for further treatment.

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From the Department of Radiology, Neuroradiology (B.V.J.), Children's Hospital Medical Center, Cincinnati, OH, and the Departments of Pediatrics, Pediatric Neurology (T.F.B.), and Pathology (J.T.), M.S. Hershey Medical Center, Penn State Geisinger Health System, Hershey, PA.¹

Case 2

A 5-month-old female patient presented with developmental delay. MR imaging of the brain at 6 months of age showed scattered foci of abnormal hyperintense signal on T2-weighted images in the cerebellar peduncles, midbrain, and brain stem, in addition to abnormal enlargement of the optic chiasm and prechiasmatic optic nerves. Her neurologic status continued to decline, and she was admitted to the hospital at 10 months of age in status epilepticus. Repeat MR imaging of the brain showed progression of the white matter lesions and development of diffuse atrophy, which was complicated by respiratory difficulties and bronchiolitis, and the decision was made to extubate the child and make her a "no code." She died as a result of respiratory arrest shortly thereafter. Autopsy confirmed diffuse cerebral and cerebellar atrophy. In addition, there was enlargement and grayish discoloration of the optic chiasm and prechiasmatic optic nerves. Microscopic examination showed numerous globoid cells (Fig 2) in the enlarged optic nerves.

Discussion

Krabbe's disease is an inherited disorder of lysosomal function. Previously described imaging findings in Krabbe's disease include foci of abnormally high attenuation in the thalami, corona radiata, and body of the caudate nuclei on CT scans, scattered foci of abnormal hyperintense signal on T2-weighted MR images, and diffuse cerebral and cerebellar atrophy in the latter stages of the disease. To the best of our knowledge, optic nerve enlargement has not been reported as an imaging finding in cases of Krabbe's disease.

Krabbe's disease most commonly presents in the first 6 months of life, manifested by hyperirritability, increased muscular tone, fevers, and developmental arrest and regression. As the disease progresses, there is greater cognitive decline, myoclonus and opisthotonus, nystagmus, and optic atrophy. Symptoms eventually progress to spasticity with loss of responses to peripheral stimuli and lack of spontaneous movement. Less frequently, the disease may present in later childhood or even in adulthood. These later presentations may be from a lesser degree of enzyme deficiency (1). More pronounced involvement of the peripheral nervous system leads to a clinical presentation characterized by hypotonia rather than irritability (2, 3).

The genetic basis for the enzymatic defect in Krabbe's disease has been traced to a faulty gene on chromosome 14 (4). It is inherited in an autosomal recessive pattern. The enzymatic deficiencies in Krabbe's disease cause lysosomal dysfunction, resulting in the accumulation of

FIG 1. Case 1: MR imaging of enlarged optic nerves and white matter lesions in a 5-month-old male patient with Krabbe's disease.

A, Axial T1-weighted image shows symmetrical enlargement of the prechiasmatic intracranial optic nerves (*arrow*).

B, Sagittal T1-weighted image shows symmetrical enlargement of the prechiasmatic intracranial optic nerves (*arrow*).

C, Axial T2-weighted image shows symmetrical enlargement of the prechiasmatic intracranial optic nerves (*arrow*).

D, Axial T2-weighted image through the posterior fossa shows abnormal hyperintense foci in the region of the dentate nuclei (*arrows*), with some surrounding hypointensity.

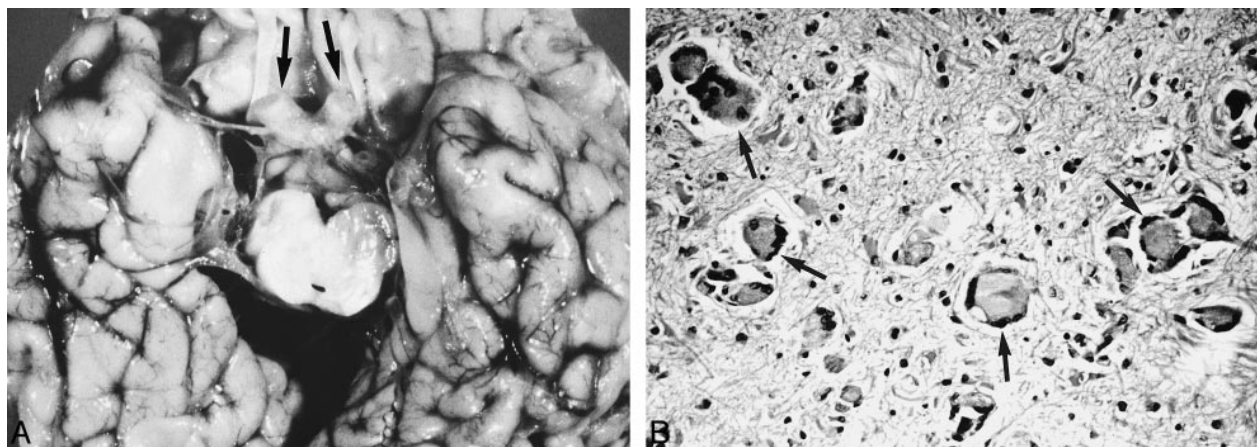
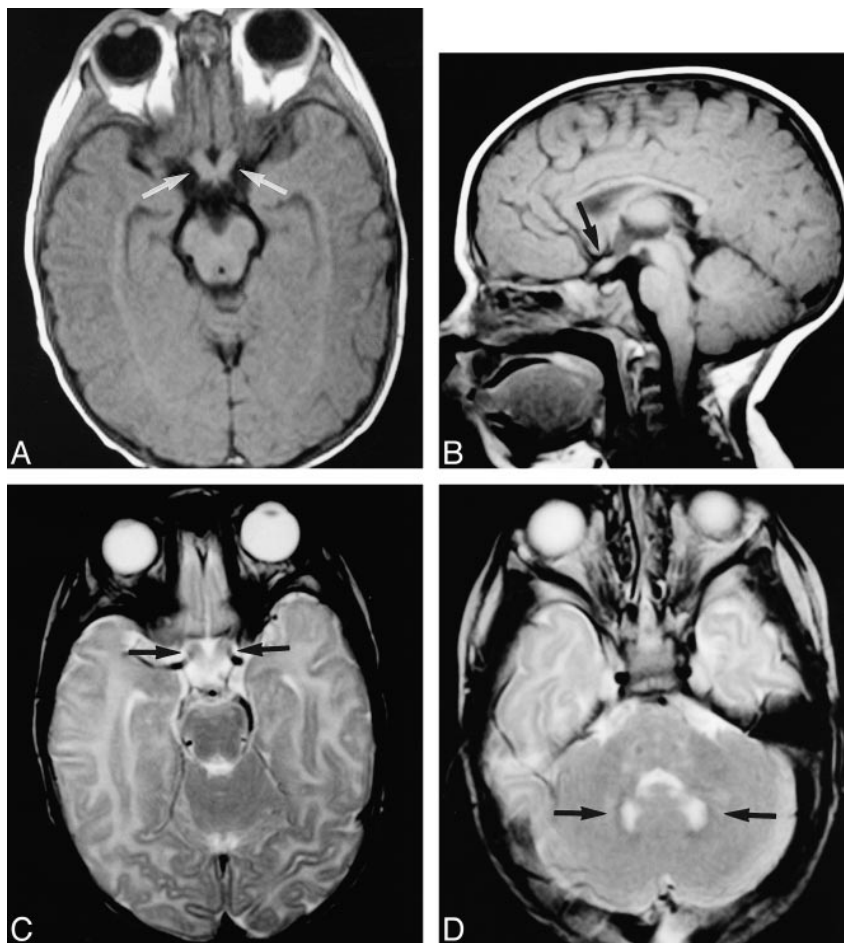


FIG 2. Case 2: Gross anatomy and histopathologic presentation of optic nerves in an 11-month-old female patient with Krabbe's disease.

A, Photograph of the base of the brain obtained at autopsy with the pons and posterior fossa contents removed. Arrows point to the symmetrically enlarged optic nerves.

B, Photomicrograph of a section from the optic nerve (hematoxylin and eosin stains; original magnification, $\times 100$) shows numerous multinucleated globoid cells (*arrows*).

psychosine (galactosylsphingosine). The amount of psychosine found in the brain of patients with Krabbe's disease can be 100 times greater than normal (5). Normally, the enzyme galactosylceramidase I (galactocerebroside beta-galactosidase)

aids in the removal of galactose from psychosine and from galactosylceramide, leaving sphingosine and ceramide, respectively. This enzyme is deficient in Krabbe's disease. The enzymes galactosylceramidase II and III are capable of

catalyzing the breakdown of galactosylceramide but not psychosine. Psychosine is toxic to the brain, oligodendroglia in particular, but the mechanism by which it causes demyelination and dysmyelination is unclear (2). The two major histopathologic characteristics of Krabbe's disease are severe loss of oligodendrocytes and the presence of globoid cells (1). The latter represent macrophages laden with accumulated galactocerebroside. Buildup of psychosine is the likely cause of oligodendrocyte loss, with the intracellular accumulation of galactosylceramide accounting for the formation of globoid cells. The secondary enzyme sulfotransferase also may be deficient in Krabbe's disease, suggesting that the disruption of enzymatically controlled galactosylceramide degradation may be more complex (3).

With the widespread use of CT and MR imaging, several articles have reported imaging findings in the brains of patients with Krabbe's disease (1, 6–8). One of the more characteristic abnormalities is abnormal high attenuation seen on CT scans of the thalami, corona radiata, and body of the caudate nuclei. The histopathologic substrate of this increased density is unknown, although one case has been reported with numerous fine periventricular calcifications (8). Signal abnormalities on MR images in a similar distribution also have been reported; the lesions were described as hypointense on T2-weighted images and possibly hyperintense on T1-weighted images (5). These signal characteristics also would be consistent with the presence of fine calcifications. This finding seems to be limited to the early stage of the disease; as the disease progresses, white matter hypointensity (on CT scans) and subsequent atrophy (7) dominate the imaging picture. Because of this, pathologic confirmation of the true nature of the hyperdensities is difficult to obtain. Patchy hyperintense signal on T2-weighted MR images and decreased attenuation in the white matter on CT scans seem to be the most common imaging findings in the more intermediate stages of the disease (1, 5). These abnormalities are thought to reflect demyelination and dysmyelination. Late-stage Krabbe's disease is characterized by marked cerebral atrophy on CT scans and MR images.

Of note, one of the five children originally described by Krabbe was noted to have optic nerves that were "solid, hard, and thickened" (9). In addition, one of the two children reported by Ieshima et al (6) was noted to have enlarged optic nerves at autopsy. In our second case, the enlargement of the optic nerves was shown to arise from the presence of numerous globoid cells. Because globoid cells are a persistent and constant feature of Krabbe's disease, there is no reason to suspect that this finding would be transient, as the hyperdensities on CT scans seem to be.

Although enlargement of the optic nerves would seem to be in conflict with the diffuse atrophy seen in cases of Krabbe's disease, it may be a reflection

of the two dominant histologic effects of the enzyme deficiency. The diffuse atrophy could be a result of oligodendrocyte loss from psychosine toxicity. The pathologic abnormality in our second case showed that the enlargement of the optic nerves arises from the accumulation of globoid cells. Why this enlargement is apparent only in the optic nerves is unknown.

The differential diagnosis of optic nerve enlargement in children is dominated by optic nerve glioma, with dural ectasia, nerve sheath meningioma, and histiocytic or granulomatous infiltration of the optic nerves being less common. Other entities to be considered in the differential diagnosis include leukemia, orbital pseudotumor, juvenile xanthogranuloma, postviral optic neuritis, medulloepithelioma of the optic nerve and optic nerve head, and optic nerve involvement with retinoblastoma. Both optic nerve glioma and ectasia of the optic nerve sheath can be seen in neurofibromatosis-1 (NF-1). Considering that NF-1 is many times more common than Krabbe's disease, the combination of patchy white matter signal abnormalities and optic nerve enlargement logically would lead to that diagnosis by imaging criteria. In both of the presented cases, NF-1 was the suggested diagnosis at the time of initial review of the MR images. Nevertheless, the clinical presentation of the two entities is markedly different. Although children with NF-1 may have seizures or developmental delay, they do not present with the severe hyperirritability characteristic of Krabbe's disease, and some characteristic skin lesions invariably can be found.

The increased use of MR imaging may result in more frequent recognition of optic nerve enlargement in children with Krabbe's disease. With the use of sagittal and coronal imaging planes, routine MR imaging of the brain easily depicts optic nerve size. To obtain the same degree of sensitivity, a CT examination would have to be tailored to evaluate specifically the optic nerves. Krabbe's disease should be included in the differential diagnosis of optic nerve enlargement in children. Although the combination of patchy hyperintense lesions in the white matter and optic nerve enlargement is still more likely attributable to NF-1, the distinctive clinical presentations of these two entities should allow a correct diagnosis to be proposed.

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