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# Early Infantile Form of Krabbe Disease with Optic Hypertrophy: Serial MR Examinations and Autopsy Correlation

K. Hittmair, D. Wimberger, P. Wiesbauer, M. Zehetmayer, and H. Budka

**Summary:** The development of white matter lesions in a case of autopsy-proved early infantile form of Krabbe disease was monitored by serial MR examinations. Hypertrophy of the optic nerves was present late in the course of the patient's disease and is a remarkable feature in this case.

**Index terms:** Krabbe disease; Infants, diseases; Nerves, optic (II); Brain, magnetic resonance

Krabbe disease (globoid cell leukodystrophy or galactosylceramide lipidosis) is an autosomal recessively inherited metabolic disease involving a deficiency of galactocerebrosidase, an enzyme that degrades cerebroside to galactose and ceramide. Cerebroside then accumulates in the brain and elicits the typical "globoid cell response" (1). Because cerebroside is practically absent in immature brains, the lack of galactocerebrosidase is of little consequence in very early infancy. As soon as myelination begins and myelin undergoes its normal turnover, cerebroside from catabolized myelin cannot be degraded and produces its fatal effect (2). At autopsy, the brain is reduced in size, with marked loss of white matter, whereas the cortex is relatively normal. There is diffuse demyelination of the cerebral and cerebellar white matter; U fibers are usually normal. Peripheral nerves are also affected and feature markedly reduced conduction velocity. The cerebrospinal fluid contains abnormally high protein levels; the electroencephalogram reveals slow activity and high voltage (2). The clinical course of the disease can be divided into three clinical stages according to Hagberg (3), beginning with a period of hyperirritability and finally resulting in a vegetative or burnt-out stage.

Magnetic resonance (MR) provides an unique opportunity to see abnormal myelination (4), but reports on MR findings in early infantile form of Krabbe disease are rare (5). This case demonstrates the MR appearance of early brain abnormalities and their temporal development, which might be helpful for diagnosing the disease early. We also describe our observation of optic hypertrophy as opposed to atrophy elsewhere in the brain.

## Case Report

Pregnancy and delivery of this boy were normal, as was early development. Hyperirritability, listlessness to drink, and frequent crying were the first symptoms, beginning at the age of 4 months and leading to hospital admission at 5 months; then the first MR examination was performed. Neuromotor development retrospectively can be classified as Hagberg's stage 1 or early stage 2 at that time. Protein content of the cerebrospinal fluid was elevated (192 mg/dL); the electroencephalogram did not reveal major abnormalities.

A period of consequent deterioration with loss of mental and neuromotor skills, increasing muscular hypertension, and increasing hyperirritability with constant crying followed. Hypersalivation and frequent attacks of apnea were observed. Cerebral seizures occurred with increasing frequency. The electroencephalogram now revealed increased excitability with high-voltage spike-and-wave complexes.

At 12 months, clinically late Hagberg's stage 2, severe aspiration caused another admission to the hospital under emergency conditions. After initial recovery, the second MR examination was done at 13 months. The child died soon afterward, at an age of 15 months, from recurrent aspiration.

MR examination was done on a 1.5-T system. T1-weighted and T2-weighted spin-echo sequences were obtained. Gadopentetate dimeglumine (0.1 mmol/kg body weight) was administered during both examinations.

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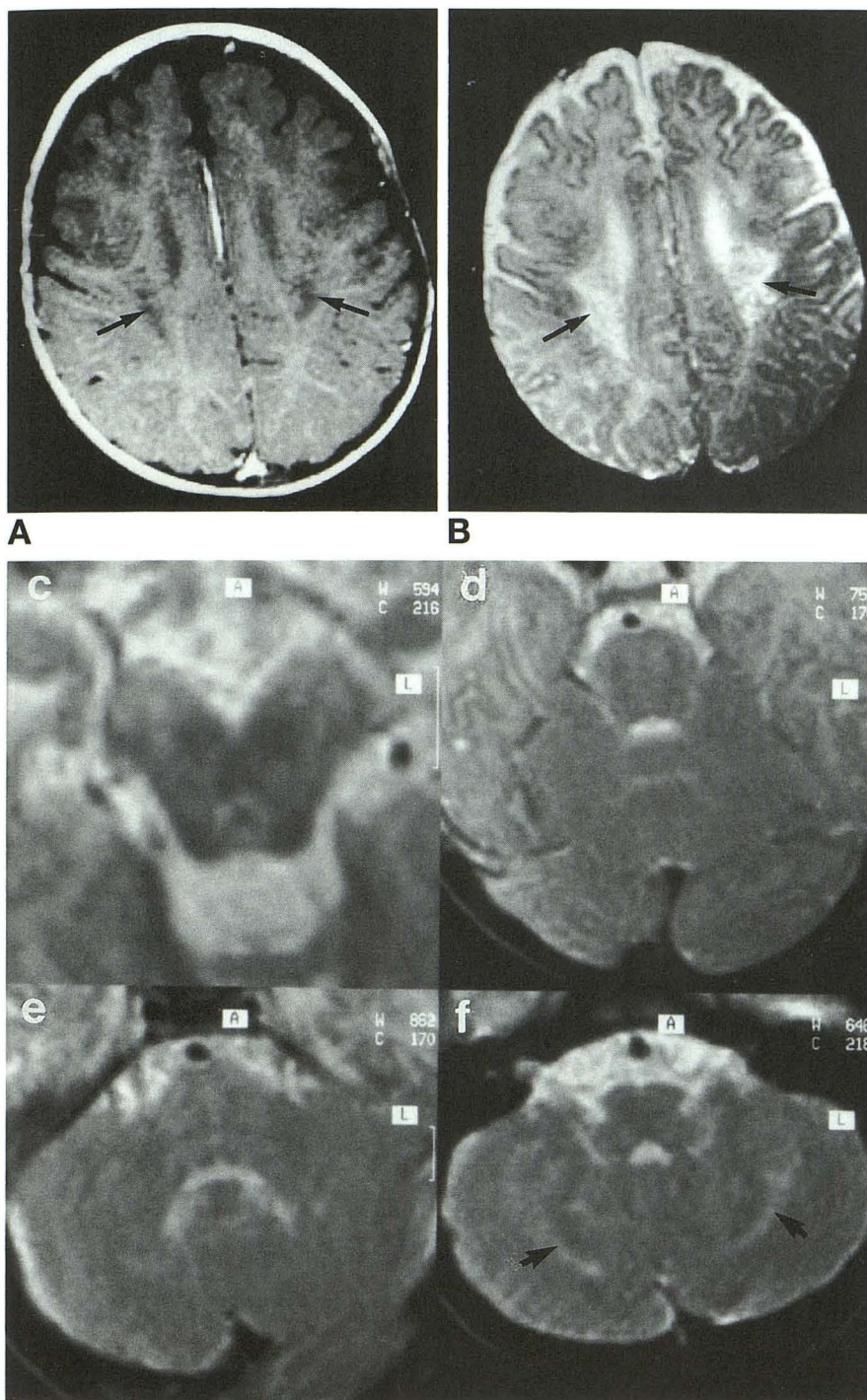


Fig 1. MR at 5 months.

A and B, Symmetric, periventricular, patchy, and confluent white matter lesions and frontally accentuated atrophy. White matter lesions (*large arrows*) can be better delineated on T1-weighted 600/15/2 (repetition time/echo time/excitations) (A) than on T2-weighted 2500/90/1 (B) spin-echo sequences.

C-F, T2-weighted 2500/90 images. C, Nuclei of the quadrigeminal plate and red nuclei are visible as hypointense structures; crura cerebri and substantia nigra cannot be delineated (stage 2 of Martin et al [7]). E, The basilar pons and tegmentum are isointense. E and F, The midcerebellar peduncles are isointense to cerebral hemispheres; the peripheral cerebellar white matter is still hyperintense to gray matter (*small arrows*) (stage 2 of Stricker et al [8]).

The most significant MR findings at 5 months were symmetric, patchy, and confluent white matter lesions in the periventricular regions with hyperintensity on T2-weighted and hypointensity on T1-weighted images (Figs 1A and B). White matter age (6) was determined as 3 to 4 months. There were enlargements of the subarachnoid spaces in the frontal region and in the region of the cisterna insulae, indicating cerebral atrophy (Figs 1A and B). Below the tentorium only a slight to intermediate retardation

of brain maturation was found without focal lesions. The signal intensity pattern of the brain stem corresponded to stage 2 of Martin et al (7) (Figs 1C-F), which is observed between 37.5 and 56.4 weeks of postconceptual age in healthy persons. Maturation of the cerebellum could be classified as stage 2 of Stricker et al (8) (Figs 1E and F), as in healthy individuals from 37.0 to 48.6 weeks after conception. The optic nerves did not feature abnormalities at 5 months.

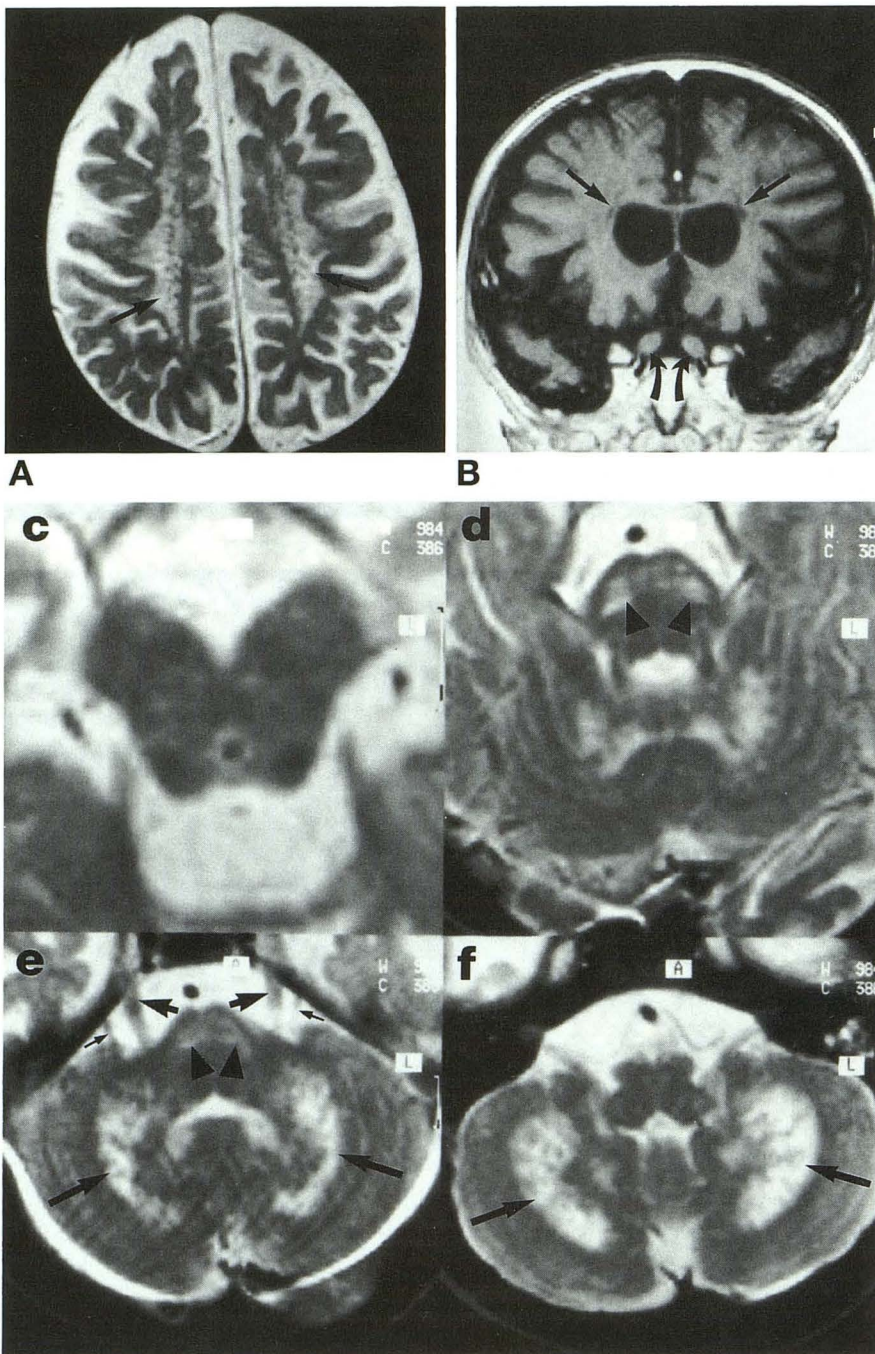


Fig 2. MR at 13 months.

A, Slight enlargement but similar appearance of periventricular white matter lesions (*large arrows*) on T2-weighted 2500/90 images at 13 months. Subcortical white matter had become myelinated, and U fibers are spared from lesions.

B, Optic hypertrophy (*curved arrows*), well demonstrated on coronal T1-weighted 600/15 contrast-enhanced spin-echo images, is opposed to brain atrophy, which has become striking. Contrast of periventricular white matter lesions is poor (*large arrows*).

C-F, T2-weighted 2500/90 images. C, Crura cerebri and substantia nigra are now hypointense and indistinguishable from the red nuclei (stage 3 of Martin et al [7]). Peripheral cerebellar white matter now features low signal intensity, whereas patchy confluent white matter lesions can be observed within the midcerebellar peduncles (*long arrows*) and the corticospinal tracts (*arrowheads*). The fourth (*thin arrows*) and fifth (*short arrows*) cranial nerves are prominent.



At 13 months, MR revealed pronounced cerebral atrophy, predominantly involving the supratentorial white matter. Supratentorial white matter lesions had progressed only slightly and continued to be patchy and confluent (Fig 2A). Maturation of subcortical white matter had progressed since the first examination; U fibers were spared from white matter lesions. A hyperintense line in the thin corpus callosum was found on T2-weighted images. Basal ganglia were normal. Progression of myelination since the first examination was also noted below the tentorium, but patchy and confluent hyperintense white matter lesions of

the midcerebellar peduncles, the deep cerebellar white matter, and the corticospinal tracts were seen on T2-weighted images at 13 months (Figs 2D-F).

The optic nerves were markedly enlarged (Fig 2B); a tendency to enlargement was also observed in other cranial nerves (Fig 2E). There was strict symmetry of lesions and no pathologic contrast enhancement anywhere in the brain at both examinations.

At autopsy, a pronounced atrophy of the entire brain was found macroscopically, whereas the optic nerves and, to a lesser degree also other cranial nerves, were enlarged.



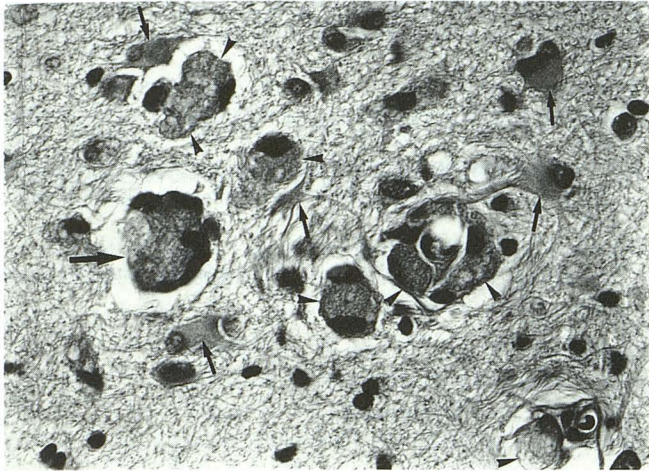


Fig 3. Hematoxylin and eosin stain of the left optic nerve, original magnification  $\times 850$ . Histologic examination of the damaged white matter including the enlarged optic nerves reveals reactive astrocytes (small arrows) and the pathognomonic accumulation of mononuclear (arrowheads) and multinuclear (large arrows) globoid cells with fine granular cytoplasm and perivascular clustering.

Microscopically there were extensive white matter lesions with demyelination, gliosis, and typical globoid cell response (Fig 3). Lesions were pronounced periventricularly; U fibers were relatively normal. The enlarged optic nerves did not feature deviating histologic features, although globoid cells were more numerous, and gliosis was extensive in the optic nerves. Because diagnosis of Krabbe disease was established only at autopsy, the enzyme deficiency could not be proved, which, however, does not make diagnosis doubtful.

## Discussion

White matter lesions on MR images corresponded to extensive gliosis and globoid cell response on histologic sections and were predominantly found in areas where myelination takes place early during brain maturation. At these sites cerebroside from catabolized myelin appears first and produces its fatal effect. This pathophysiologic mechanism explains the distribution and time of development of white matter lesions.

Appearance of lesions, symmetrical distribution, and involvement of the corpus callosum are in agreement with previous observations (4, 9). Atrophy, which is a secondary change, is another characteristic feature of the early-infantile form of Krabbe disease (5, 10, 11) and becomes striking in later stages of the disease (5). Appearance and distribution of white matter lesions with progressive atrophy were ob-

served in the early stages of the disease in our patient and therefore may provide a diagnostic hint. The development of bone marrow transplantation as a treatment for patients with Krabbe disease has made early and accurate diagnosis particularly important (12).

Previous investigators found high-attenuation areas on computed tomography in the posterior limb of the internal capsule and the posterolateral thalami (11, 13). Because these areas were isointense to slightly hyperintense on T1-weighted images, calcium deposits were considered a less probable explanation. However calcification may appear isointense or even hyperintense on T1-weighted images because of surface-relaxation mechanisms, as shown by Henkelman et al (14). We did not have the opportunity to do a computed tomographic scan with our patient, but there was no abnormal signal intensity at the thalami or at the internal capsule on MR images. Moreover, no calcifications were seen at autopsy.

Optic hypertrophy has, to our knowledge, never been described in Krabbe disease. In our case optic hypertrophy was predominantly caused by the space-occupying effect of an extensive gliosis. This observation, underlined by the tendency of enlargement in other cranial nerves, suggests that neuronal tissue, in particular neuronal tissue outside the brain, may react alternatively with enlargement rather than atrophy to the presence of cerebroside in Krabbe disease. This enlargement was significant only in the later stage of the disease, although the optic nerves myelinate early. This suggests that, similar to brain atrophy, the enlargement of neuronal tissue takes time to develop and cannot serve as a criterion for early diagnosis of Krabbe disease.

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