CASE REPORT

MRI EVALUATION OF A CASE OF KRABBE DISEASE

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ABSTRACT: Krabbe disease, or globoid cell leukodystrophy, is a demyelinating disorder caused by a genetic deficiency of lysosomal enzyme galactocerebrosidase (GALC), a key component in metabolic pathways of myelin turnover and breakdown. The GALC gene maps to chromosome 14q24. 3 to 14q32. 1. The most frequent form of Krabbe disease has an infantile onset, whereas the late-onset form is rare. We present the MR imaging findings in a 5 month old male baby presenting with features of spastic paraplegia diagnosed biochemically as Krabbe Disease. Their MR images showed selective, increased signal intensity on T2- weighted sequences along the corticospinal tracts. Proton MR Spectroscopy showed increased choline and myo-inositol peaks in the affected white matter. The MR imaging pattern is characteristic and, in the appropriate clinical setting, may suggest the diagnosis.
KEYWORDS: Globoid cell leukodystrophy, galactocerebrosidase, Krabbe, MRI.

INTRODUCTION: Globoid cell leukodystrophy (GLD) was first described by Krabbe in 1916.(1) It is a rare autosomal recessive disease with an incidence ranging from one in 100,000 to one in 200,000 live births.(1,2) It is caused by congenital deficiency of a lysosomal enzyme, galactosylceramidase I, which is responsible for hydrolyzing the galactose moiety in galactocerebroside and for the hydrolysis of galactosylphingosine (psychosine).(1-4) The defect is due to a mutation in the GALC gene locus which has been mapped to chromosome 14 by genetic linkage studies.(1-4) The enzyme deficiency causes abnormal accumulation of galatosylcerebrosides, which induce macrophages to become globoid cells. The same deficiency also causes accumulation of galactosylphingosine (psychosine) which is extremely toxic to oligodendroglia. The cumulative effect of multinucleated globoid cells and the direct toxic effect of psychosine results in extensive demyelination and severe astrogliosis.(4,5)

Here we report the MRI features in a 5 month old male baby presenting with features of spastic paraplegia diagnosed biochemically as Krabbe Disease.

CASE REPORT: A 5month old male child was brought by his parents with history of excessive crying, recurrent seizures and tonic posturing since birth. There was distinct history of delayed mental and physical milestones in the baby. On examination, he had hypertonicity in all four limbs with bilaterally up-going plantars and brisk deep tendon reflexes.

On MR imaging, bilateral basal ganglia and thalami were hyperintense on T1 W and hypointense on T2W images. The periventricular and cerebellar white matter showed hyperintensity on T2W FLAIR images. The clinical and neuroimaging findings were consistent with infantile Krabbe's disease.

DISCUSSION: Krabbe's disease is one of the more common leukodystrophies, inherited in an autosomal recessive fashion. It is caused by a deficiency in the lysosomal enzyme galactocerebroside beta-galactosidase, with the genetic locus mapped to chromosome14.[6] Galactocerebroside beta-galactosidase is responsible for the conversion of galactosylceramide to ceramide and psychosine to sphingosine. There are alternative enzymes that can break down galactosylceramide when galactocerebroside betagalactosidase is deficient. However, this is not the case for psychosine.[7] Psychosine accumulates at toxic levels in Krabbe's disease, resulting in oligodendrocyte death and impaired Schwann cell function.[8,9] The normal harmonious relationship between myelin breakdown and production is therefore disturbed, causing a severe demyelination involving both the central and peripheral nervous system.[6] Histologically, there is myelin destruction, gliosis, and the presence of the characteristic multinucleated "globoid" cells (macrophages) within the perivascular regions of the affected white matter.[10]

The disorder is present at birth, with exclusively neurological clinical presentation consisting of prominent white matter signs including early onset seizures, spasticity, psychomotor deterioration and optic atrophy.[2-4] It is clinically classified into early infantile form, which presents between 1 to 12 months of age, the late infantile form (early childhood form), presenting between 1-3 yrs of age and the juvenile variety, manifesting in older children.[1] The early infantile form is most common and the late onset form is rare.[3] The infantile (early and late) forms of Krabbe's disease show increased CSF proteins and delayed nerve conduction, whereas in the juvenile form, CSF findings remain normal with minimal peripheral neuropathy.[1]

The infantile form has 3 clinical stages. Stage I, is characterized by irritability, unmotivated crying, hypertonicity, recurrent fever and regression of psychomotor development. Within two to four months of onset, most patients reach stage II, which is characterized by opisthotonus, hypertonic flexion of limbs, exaggerated deep tendon reflexes and clonic seizures. Visual failure and optic atrophy now begin to appear and the CSF proteins are elevated. In Stage III or the "burnt out stage" infants are decerebrate and blind and death soon occurs. There is evidence of parallel progression of CT, MR and pathological findings.[1]

Diagnosis is usually suspected on the basis of clinical and radiologic findings, with confirmation by lysosomal enzyme testing revealing a deficiency of galactocerebroside beta-galactosidase. Early in the course of the disease, nonenhanced CT examinations may show areas of symmetrically in creased attenuation within the basal ganglia, thalami, and centrum semiovale.[11,14,15] The pathogenesis of this increased attenuation remains debated, with hypotheses suggesting areas of calcification[13] and grouping of the globoid cells.[15] These areas of increased attenuation may actually precede any identifiable white matter abnormalities on either CT scans or MR images.[15] The middle stages of the disease are characterized by areas of hypoattenuation on CT scans and T2 prolongation on MR images within the periventricular white matter (centrum semiovale).

Progressive cerebral and cerebellar atrophy herald the late stages of the disease. The cranial nerves may be affected, with multiple cases of thickened optic nerves noted at both autopsy[8] and MR imaging.[3] Bernal and Lenn[12] reported a case in which there was abnormal enhancement of multiple cranial nerves.

The abnormalities on CT and MR occur in basal ganglia, cerebellum and white matter. CT features known to characterize early infantile Krabbe disease are increased attenuation in cerebellum, brainstem, thalami, caudate nuclei and corona radiata on non-contrast CT.[4,6,7] Kevan et al in 1984 attributed these hyperdensities to alterations in the ratio of lipids, water and proteins in response to breakdown of myelin and the associated astrogliosis.[4] Some investigators have reported histological evidence of minute calcification in these hyperdense regions.[4] These hyperdensities may precede progressive white matter hypoattenuation and atrophy.[4]

The thalami, central white matter and cerebellum which show hyperdensities on CT, are seen on MR as decreased signal intensity on T2 and increased on T1 W images, possibly due to a paramagnetic effect of calcium deposition. MR also shows abnormalities in the periventricular white matter, which are non-specific and resemble those seen in other dysmyelinating disorders.[4] Paradoxically, MR may be deceptively normal in early infantile Krabbe's disease when basal ganglia hyperdensity on CT may suggest the diagnosis.[4] However, with progression of disease the hyperdense areas seen on CT gradually disappear. The differential diagnosis of CT hyperdensities of basal ganglia and cerebellum include Alexander's disease, Fahr's syndrome, tuberous sclerosis and Cockayne's disease, Sandhoff and Tay Sach's disease.[5,8]

To the best of our knowledge, there has been only one previously reported case of the spinal involvement of Krabbe's disease with imaging.[6] Vasconcellos and Smith[6] presented a case of abnormal enhancement involving the lumbosacral nerve roots in a 7-month-old child with an infantile form of Krabbe's disease. Their case had no intracranial manifestations of the disease revealed by either CT or MR imaging at the time of presentation or by follow-up MR imaging performed 1 week later. Because their patient had the classic.

Clinical presentation of Krabbe's disease, it is unlikely that this represented a variation in the enzyme defect that preferentially affected the peripheral nervous system. Instead, it seems more plausible that the spinal involvement preceded any intracranial imaging abnormalities.

Confirmatory diagnosis of Krabbe's disease requires enzymatic assays, for which galactosylceramidase activity is estimated photometrically either in peripheral blood leucocytes or skin fibroblasts.[2] However, in centres where enzymatic assays are not available the neuroimaging diagnosis is considered to suffice. Antenatal diagnosis is performed by enzyme assays or mutation analysis in chorionic villus sampling, which also facilitates antenatal genetic counseling.[2] Bone marrow transplantation is being attempted for the treatment of the more benign, late onset form.[3]

CONCLUSION: In conclusion, therefore, Krabbe's disease should be considered in the diagnosis of early onset infantile seizures and in older children with spasticity and ataxia. Characteristic CT and MR imaging features help to clinch the diagnosis.

REFERENCES:

1. Bernardi B, Fonda C., Franzoni E, Marchiani V, Della GE, Zimmerman RA. MRI and CT in Krabbe's disease: case report. Neuroradiology. 1994; 36(6): 477-9.

2. Kleijer WJ, van Diggelen OP, Halley DJ, van der Ploeg AT, Mancini GM. From gene to disease; Krabbe disease and galactosylceramidase deficiency. Ned Tijdschr Geneeskd. 2004; 148(17): 826-828. (Article in Dutch, English abstract).
3. Suzuki K. Globoid cell leukodystrophy (Krabbe's disease): update. J Child Neurol. 2003; 18(9): 595-603.
4. Finelli DA, Tarr RW, Sawyer RN, Horwitz SJ. Deceptively normal MR in early infantile Krabbe disease. AJNR Am J Neuroradiol. 1994; 15(1): 167-71.
5. Choi S, Enzmann DR. Infantile Krabbe disease: complementary CT and MR findings. AJNR Am J Neuroradiol. 1993; 14(5): 1164-1166.
6. Zlotogora J, Chakraborty S, Knowlton RG, Wenger DA. Krabbe disease locus mapped to chromosome 14 by genetic linkage. Am J Hum Genet 1990; 47: 37–44.
7. Jones BV, Barron TF, Towfighi J. Optic nerve enlargement in Krabbe's disease. AJNR Am J Neuroradiol 1999; 20: 1228–1231.
8. Ida H, Kawame F, Kim SU, Eto Y. Abnormality in cultured oligodendrocytes and Schwann cells isolated from the twitcher mouse. Mol Chem Neuropathol 1990; 13(3): 195–204.
9. Jacobs JM, Scaravilli F, De Aarnda FT. The pathogenesis of globoid cell leukodystrophy in peripheral nerve of the mouse mutant twitcher. J Neurol Sci 1982; 55(3):285–304.
10. Vasconcellos E, Smith M. MRI nerve root enhancement in Krabbe's disease. Pediatr Neurol 1998; 19(2):151–152.
11. Robbins SL, Cotran RS, Kumar V. Pathologic Basis of Disease. 3rd ed, Phliladelphia: W. B. Saunders Company; 1984: 1424–1425.
12. Krabbe K. A new familial, infantile form of diffuse brain-sclerosis. Brain 1916; 39: 74–114.
13. Bernal OG, Lenn N. Multiple cranial nerve enhancement in early infantile Krabbe's disease. Neurology 2000; 54: 2348–2349.
14. Choi S, Enzmann DR. Infantile Krabbe disease: complementary CT and MRI findings. AJNR Am J Neuroradiol 1993; 14: 1164–1166.
15. Farina L, Bizzi A, Finocchiaro G, et al. MR imaging and proton MR spectroscopy in adult Krabbe disease. AJNR Am J Neuroradiol2000; 21: 1478–1482.

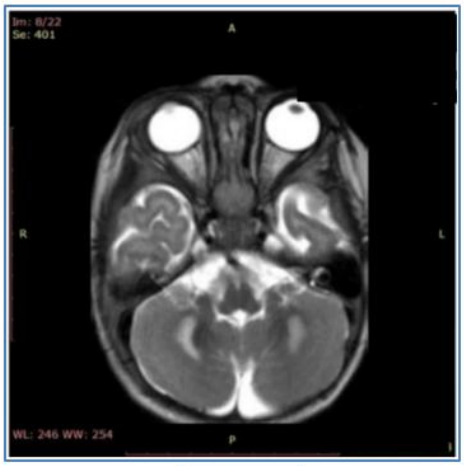

Fig. 1

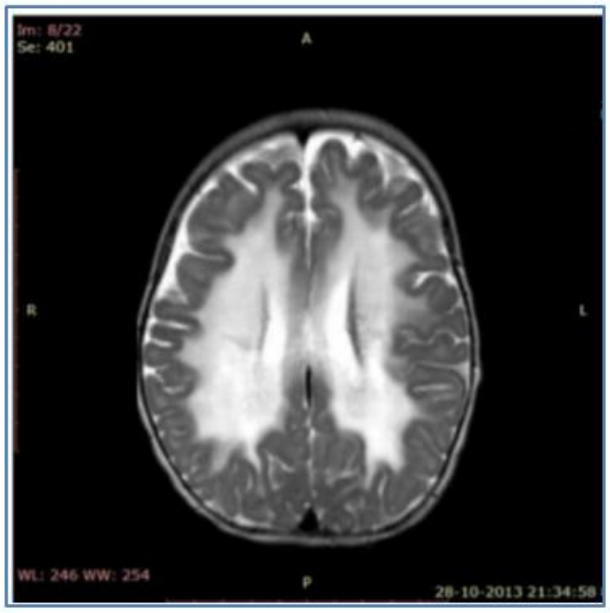

Fig. 2

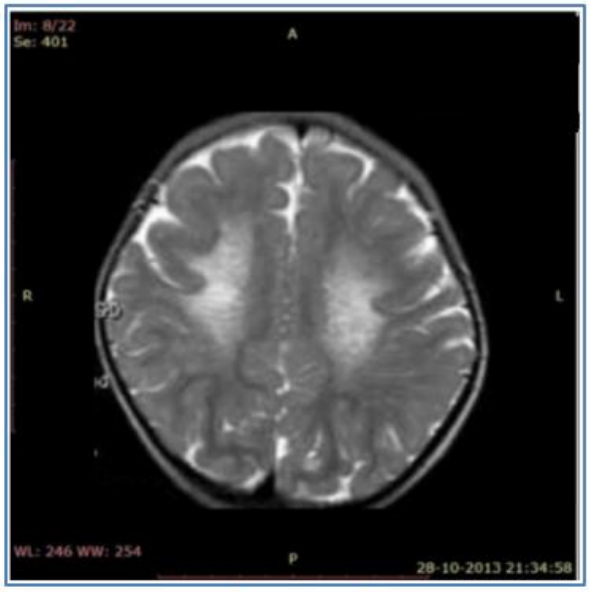

Fig. 3

Axial T2 weighted images show bilateral parietal, occipital, deep gray matter and cerebellar white matter hyperintensities with spared subcortical white matter.

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