

Krabbe disease - a rare lysosomal storage disease

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Abstract

Krabbe disease a rare and fatal lysosomal storage disease that results in progressive damage, demyelination of central, and peripheral nervous system. It involves the dysfunctional metabolism of sphingolipids; characterized by the deficiency of enzyme galactocerebrosidase (galactosylceramidase, GALC). Krabbe disease is an extremely rare condition with an incidence of 1 in 1,00,000 live births. Typically, the disease has an infantile-onset, with rapid deterioration in the first few months, leading to death before the age of 2 years. The late-onset forms (late-infantile, juvenile, and adult forms) are rare with variable clinical outcomes, presenting spastic paraplegia as the main symptom. It is inherited in an autosomal recessive pattern. Early diagnosis of Krabbe disease can be made by measuring the activity of galactocerebrosidase in a sample of a dried spot of blood during the screening of new-born infants. Radiological investigations can show diffuse brain and cerebellar atrophy, and demyelination can be identified by magnetic resonance imaging (MRI). Authors report a case of a 10-year-old female child presented with feeding difficulties excessive irritability, global developmental delay, and progressive loss of hearing and sight. On examination had peculiar facial features, hypertonia, and hyper reflexes. No neurocutaneous stigmata were found. Diagnosed as Krabbe's disease on the basis of peculiar clinical features and confirmed diagnosis on MRI and spectrophotometric and spectrofluorometric enzyme assay. There's no cure for Krabbe disease, and treatment focuses on supportive care. However, stem cell transplants have shown some success in infants who are treated before the onset of symptoms and in some older children and adults.

Keywords: Krabbe disease, Autosomal recessive, Progressive neurologic degeneration, GALC, Globoid cell leukodystrophy, Enzyme assay

Introduction

Krabbe disease or globoid cell leukodystrophy or Galactosylceramide Lipidosis is a rare inherited metabolic, autosomal recessive, neurodegenerative disorder affecting the myelin sheath of the nervous system. It is a lipid storage disorder responsible for sphingolipidosis (dysfunctional metabolism of sphingolipids) usually noticed among children. It is characterized by the defective functioning of lysosomal enzyme β -galactocerebrosidase (β -GALC) [1,2]. This enzyme is located on chromosome 14 and is responsible for the accumulation of galactosylceramide.

This produces a toxic compound psychosine, is cytotoxic at enhanced concentrations which seem to explain the rapid degeneration of myelin-generating cells in Krabbe [3].

The diagnosis of this disease can only be made with clinical suspicion. Laboratory diagnosis includes brain magnetic resonance imaging (MRI), magnetic resonance (MR) spectroscopy, biochemical analysis of cerebrospinal fluid, and genetic analysis for detecting a mutation in genes coding for GALC.

Case Report

Authors report a case of a 10-year-old female child born of third degree consanguineous marriage with normal birth history, at 4 months age, parents observed that child had episodes of excessive crying, irritability, feeding difficulties, vomiting and not

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able to hold the neck, not reaching for an object and social smile was not achieved like other children of her age suggestive of global developmental delay associated with rigid posture. Seizures a common presentation in this condition which is absent in this patient. Now presented with the global developmental delay with generalized rigidity, visual abnormalities, and loss of hearing, functional urinary incontinence, and dependence on the mother for most daily activities. On physical examination, the patient had protruding ears, malocclusion of teeth, microcephaly, cortical thumb with hypertonicity, and hyper reflexes in both upper and lower limbs with a positive Babinski sign with genu valgum and ankle valgus with Grade 3 PEM. She was unable to speak but otherwise appeared to have the normal intellectual ability

MRI brain showed diffuse abnormal T2 hyperintensity in bilateral periventricular and subcortical cerebral white matter as well as cerebellar white matters as well as the pons. Peritrigonal white matter reveals hypointensity with increased diffusion on T1 weighted images. Bilateral thalamic and basal ganglia appear hypointense on T2 weighted image- Figure 1-4 suggestive Krabbe disease.

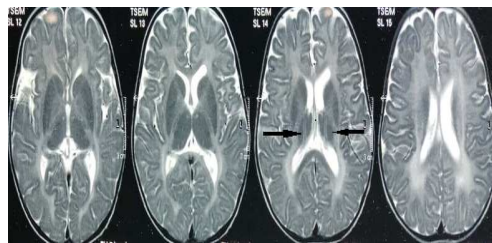


Fig-1: T2W-bilateral basal ganglia and thalami hypointensity.

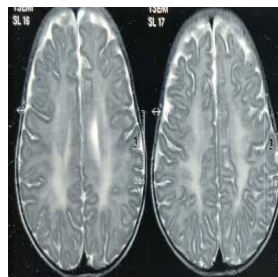


Fig-2: Bilateral basal ganglia and thalami hypointensity.

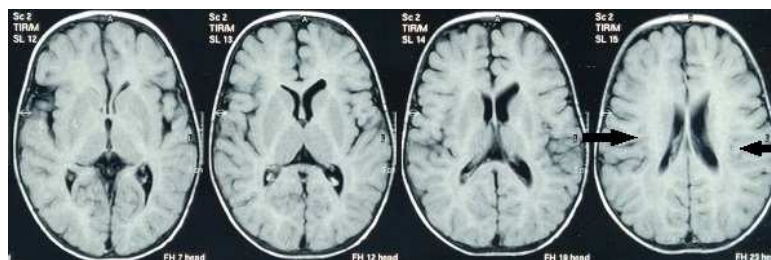


Fig-3: T2W/FLAIR-hyperintensity in bilateral periventricular and subcortical cerebellar white matter.

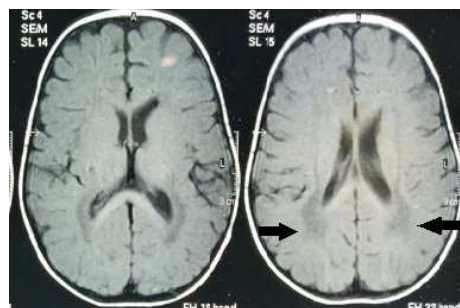


Fig-4: T1W-peritrigonal hypointensity.

Lysosomal storage disorder analysis on plasma and leukocytes using spectrophotometric and spectrofluorometric enzyme assays showed low activity for β -galactocerebrosidase-10 for a control of 36 and high activity of plasma chitotriosidase-1710 nmol/hr/ml plasma; thus confirming the diagnosis of Krabbe disease.

Brainstem Auditory Evoked Potential showed normal wave I but absent waves III and V at the maximum intensity of stimulation from both ear suggestive of a lesion affecting both auditory pathways at lower brainstem level between acoustic nerve and lower pons. Cerebrospinal fluid evaluation, electroencephalography (EEG), and electromyography (EMG) test and genetic testing could not be performed due to patient's concerns.

The patient was prescribed drugs to ease muscle spasticity and advised to undergo physiotherapy to help maintain muscle tone and circulation.



Fig-5: Protruding ears.



Fig-6: Malocclusion off teeth and microcephaly.

Discussion

Krabbe disease (globoid cell leukodystrophy), is a rare autosomal recessive disorder that was first described by Krabbe in 1916 [9]. This is due to a deficiency in the lysosomal enzyme, galactosylceramidase (expressed in oligodendrocytes and Schwann cells), which is responsible for the degradation of galactolipids found in myelin such as galactosylphingosine (psychosine) [10]. Due to mutation in the GALC gene, responsible for the production of enzyme galactosylceramidase. Enzyme deficiency would result in abnormal accumulation of galactosyl cerebroside which is extremely toxic to oligodendroglia and induces macrophages to become globoid cells. This would eventually result in demyelination [4-6].

Krabbe disease in infants is fatal due to a decline in psychomotor activity, and death occurs before two years. This severe lysosomal storage disorder starts in the classical early-infantile form with a rapid downhill course around the first six months of life [7]. Compared to this acute disease form, the late-onset forms have a slower clinical progression [8]. Based on the age of onset there are four forms of Krabbe disease, infantile, late infantile, juvenile, and adult form. Juvenile and adult forms are categorized as late-onset Krabbe disease. Late-onset (juvenile and adult forms) disease has slow progression and the patient has a significantly longer life. The difference in the severity of progression and age of onset

of the disease is due to the difference in the mutational area of this gene and also the turnover of the psychosine.

Early diagnosis of Krabbe disease can be made by measuring the activity of galactocerebrosidase in a sample of a dried spot of blood during the screening of new-born infants [11,12]. Radiological investigations can show diffuse brain and cerebellar atrophy, and demyelination can be identified by magnetic resonance imaging (MRI). Demyelination may also involve the spinal cord and cranial nerves [13]. Other diagnostic neurological investigations include nerve conduction studies, electroencephalography (EEG), auditory evoked responses, visual evoked potentials, and measurement of galactocerebrosidase levels [12].

The definitive diagnosis of Krabbe disease is made by measuring the activity and enzyme levels of galactocerebrosidase, which may show variable degrees of remnant activity of the enzyme. Sequencing studies of the GALC gene, which encodes the galactocerebrosidase enzyme, are also useful [14].

The present case reached the definitive diagnosis for this patient by the blood galactocerebrosidase enzyme levels, which is expected to be below along with the early onset of signs and symptoms and clinical features with which the child presented. In 2012, Jalal et al. investigated the correlation between the galactocerebrosidase enzyme levels and the phenotype and age of presentation of Krabbe disease [15]. They concluded that an increased enzyme level was associated with late-onset of Krabbe disease, but that reduced activity of the enzyme did not determine the phenotype of the disease [15]. Also, the correct type of method used to determine enzyme activity should be selected so that the correct diagnosis is made.

The present case highlights the importance of careful consideration of Krabbe disease among children with defective feeding habits. Although a feeding problem was noticed early in childhood, in this case, it was ignored until later age. Parents may be carriers of the gene responsible for Krabbe disease with no clinical symptoms, and clinical disease can be noted among children born to such parents.

Although hematopoietic stem cell transplantation (HSCT) is seen as a potential treatment for Krabbe disease. A significant benefit of HSCT was noted in patients who were asymptomatic or mildly symptomatic and when transplanted within the first month of life, signifying the importance of diagnosis as early as possible after birth. Other treatment modalities being tried to treat Krabbe disease include enzyme replacement therapy, targeting

inflammatory markers, gene therapy, and neural stem cell transplantation. In conclusion, counseling families about the risk of disease and recommending prenatal testing in future pregnancies could help early diagnosis of Krabbe disease. To reduce the mortality and morbidity, necessary care by a neurologist, ophthalmologist, occupational therapist, audiologist, and physiotherapist is recommended.

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