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Case Report

Early infantile form of Krabbe disease: a case report

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ABSTRACT

A 7-month-old female child, born to 2nd degree consanguineous marriage brought with complaints of gross developmental delay. Her examination revealed spasticity in all 4 limbs with brisk deep tendon reflexes with intact primitive reflexes and exaggerated startle reflex. Her MRI brain showed demyelination signs in bilateral thalami, dentate hila, and thickened optic chaisma. Age of presentation, clinico-radiological findings were suggestive of early infantile form of Krabbe disease.

Keywords: Developmental delay, Spasticity, Primitive reflexes, Demyelination, Krabbe disease

INTRODUCTION

Leukodystrophies are a group of inherited neurodegenerative disorders which primarily affect white matter of the central nervous system. These disorders are broadly classified as hypomyelinating or demyelinating depending on myelin synthesis or break down of existing myelin, respectively.

Krabbe disease or globoid cell leukodystrophy is an autosomal recessive demyelinating disorder. This disease is characterized by deficiency of galactocerebrosidase (GALC), a lysosomal enzyme responsible for the hydrolysis of psychosine and galactosylceramide. This enzyme is located on chromosome 14 and is responsible for the accumulation of galactosylceramide.[1]

The incidence of Krabbe disease has been estimated as 1 in 100,000 live births.[2] True incidence is unknown. Very limited cases have been reported till now with early infantile form of Krabbe disease in India. The diagnosis can be made with clinical suspicion, laboratory diagnosis includes brain magnetic resonance imaging (MRI), enzyme levels and detecting a mutation in genes coding for GALC.

Here, we report a 7-month-old female child who has presented with typical clinical and radiological features suggestive of Krabbe disease.

CASE REPORT

A 7-month-old female, 2nd degree consanguineous born child, 3rd in birth order with normal antenatal and natal history was brought by her parents with complaints of not yet attained neck holding. Mother also complained that she is always irritable, cries out suddenly which is inconsolable at times and difficulty in feeding. There was no history of fever and seizures. There was no history of neuro-infection, trauma in the past.

Physical examination revealed a normal weight, length and head circumference. There was no head control. She had severe hypertonia in all limbs; opisthotonus posturing, abducted thumbs, increased deep tendon reflexes with bilateral extensor plantars and clonus. Her primitive reflexes like Moro's, asymmetrical tonic neck reflex, palmar and plantar grasp; rooting and sucking reflexes were not disappeared. There was an exaggerated startle reflex with tactile, sound and light stimuli. She had poor eye to eye contact with poor visual tracking. Her

developmental age is less than 1 month of age in all domains.

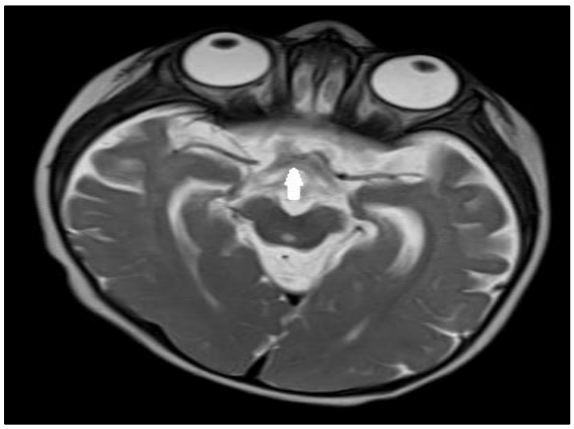

Figure 1.

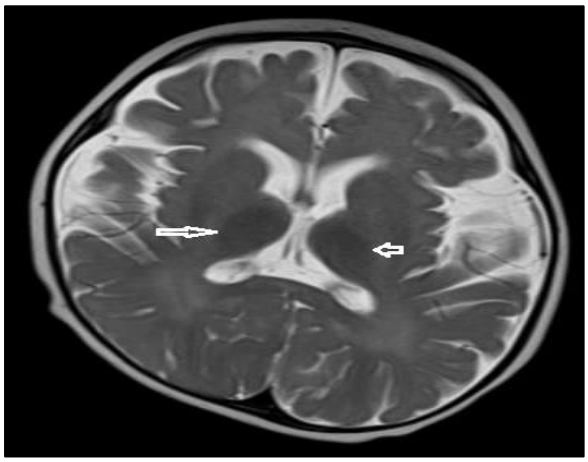

Figure 2.

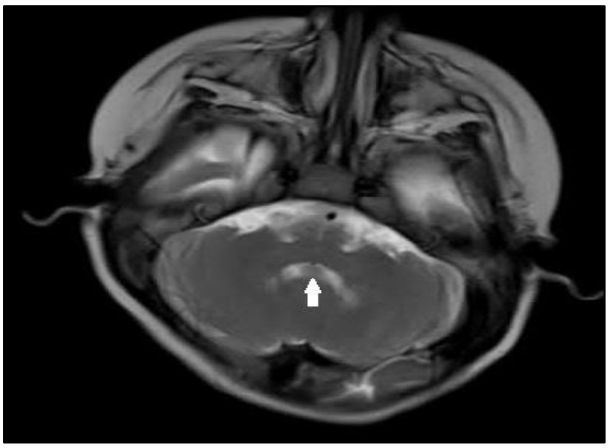

Figure 3.

Her ophthalmological examination revealed pale fundus in both eyes with no cherry red spot. There was a history of unexplained neonatal death of a sibling. With the above history and clinical findings, we suspected a neurodegenerative disorder most likely a white matter disease with early infantile onset variant. Her MRI brain showed diffuse white matter hypomyelination with thickened optic chaisma (Figure 1), mild T2 hypointensity on bilateral thalami (Figure 2), with hyperintensity of dentate hila on T2 weighted images (Figure 3). These MRI findings are characteristic of Krabbe disease. Other findings seen are myelin sparing areas in deep white matter giving a tigroid pattern (Figure 4). Parents were not willful for further investigation and treatment, they left against medical advice.

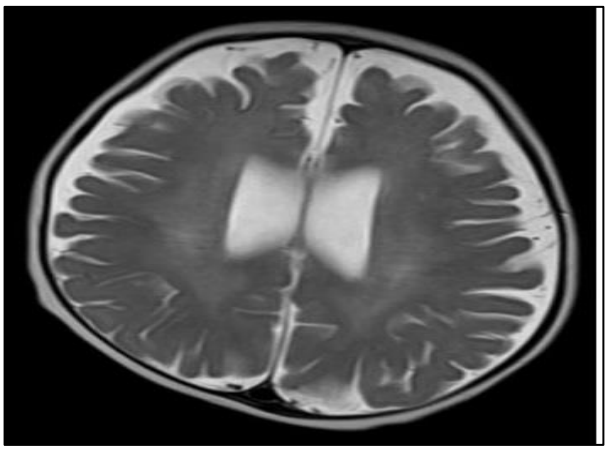

Figure 4.

DISCUSSION

Krabbe disease, also known as globoid cell leukodystrophy, is a rare, fatal, autosomal recessive metabolic disorder caused by the deficiency of galactocerebrosidase (GALC). It is a lysosomal enzyme responsible for the hydrolysis of psychosine and galactosylceramide. The incidence of Krabbe disease has been estimated as 1 in 100,000 live births.[2]

It was described for the first time by Knud Krabbe, a Danish neurologist, in 1916.[3]

Krabbe disease is characterized by the accumulation of globoid multinucleated cells, demyelination, loss of oligodendrocytes, and gliosis in the CNS.

Psychosine is the primary component responsible for the destruction of oligodendrocytes and Schwann cells, which produce myelin, resulting in demyelination of the central and peripheral nervous systems.[4] Peripheral nerve damage occurs due to endoneurial fibrosis, proliferation of fibroblasts, infiltration with histiocytes/ macrophages, and finally segmental demyelination.[5]

The disease is typically divided into four subgroups based on age at symptom onset: early-infantile (birth–5 months), late-infantile (6–36 months), juvenile (37 months–16 years), and adult (>16 years).[6] Early infantile type of Krabbe disease presents within first 6 months of life and is the most common and severest form, which

progresses rapidly. Presenting symptoms include hyper-irritability, stiffness, and hyperactive reflexes, episodes of elevated temperature; followed by psychomotor deterioration, seizures, spasticity, and loss of vision; and usually succumb by 2 years of age.[7]

Late infantile group frequently present with irritability, psychomotor regression, stiffness, ataxia, and loss of vision. The disease has progressive course, resulting in death in approximately 2 or 3 years after the onset. Patients with juvenile group, commonly develop loss of vision, together with hemiparesis, ataxia, and psychomotor regression.[8]

Estimation of galactosyl ceramidase in a fibroblast and leukocyte culture is confirmatory.[9] In our case, we couldn't get the enzyme level estimation due to lack of parent's cooperation. In the absence of confirmatory evidence of low or absent GALC levels, the characteristic distribution of lesions on CT and MRI T2-weighted images can be diagnostic. Involvement of pyramidal tracts, parieto-occipital white matter, posterior corpus callosum, and cerebellar white matter involvement as well as lesions of deep grey matter and cerebral atrophy may be seen.[10, 11]

Thickening of the intracranial optic nerves and chiasm on MRI was a neurodiagnostic sign that antedated the development of other central nervous system signal abnormalities of Krabbe disease. This finding was observed in our case.[12] Tried therapeutic modalities include Enzyme replacement therapy (ERT), gene therapy, chaperone therapy, Hematopoietic stem cell transplantation, umbilical cord stem cells transplantation and cytokine therapy. These therapies did not show alteration in the course of the disease or any substantive neurologic improvement.[13-15.]

CONCLUSION

Infants born to consanguineous parents presenting with global delay in milestones with features of central and peripheral nerve involvement and characteristic clinico-radiological and/or with low glucocerebrosidases enzyme levels is diagnostic of Krabbe disease. Early infantile is the most common and severe form with fatal outcome with minimal response to current available therapy.

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