A RARE CASE OF GLOBOID CELL LEUCODYSTROPHY
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Abstract: Krabbe disease (also known as globoid cell leukodystrophy or galactosylceramide lipidosis) is a fatal degenerative disorder that affects the myelin sheath of the nervous system. We present a rare case of Krabbe leukodystrophy in an 8 month old child who presented with features of hypertonia, generalized seizures, recurrent fever and feeding difficulties and recurrent vomiting. Examination revealed classical features of spasticity and hypertonia and swallowing difficulty, on evaluation for neurological illness, MRI revealed characteristic bilateral symmetrical hyperintensities involving the cortical white matter. Enzyme assay confirmed the diagnosis of Krabbe leukodystrophy.

Keyword: Globoid Cell Leukodystrophy, Beta Galactocerebrosidase, Hematopoiteic Stem Cell Transplantation

CASE REPORT:
A 8 months old male child 1st born out of 2nd degree consanguineous parentage was admitted with complaints of not attaining head control, stiffness of all four limbs while crying and generalized seizures and feeding difficulties with frequent regurgitation of milk since 3 months and recurrent episodes of fever treated in private clinics. There was no significant antenatal history. He was delivered as labour naturale at term with APGAR 1 min 6/10 and 5 min 8/10. B.wt was 2.1 kg. The child had attained social smile by 3 months and cooing by 3/2 months other milestones were not yet attained. The child was appropriately immunized. On Examination there was no facial dysmorphism, no external neurocutaneous markers, head circumference was 41 cm. Neurological examination revealed a generalized hypertonia involving all four limbs with extensor plantar response, bilateral pupils equal and reacting to light + dolls eye movements. Initial differential diagnosis of a form of leukodystrophy and storage disorder was made and the child was investigated further. On work up hemogram, renal and liver function tests, routine urine analysis, skeletal survey and thyroid function test were normal. Urine metabolic screening was negative. Serum lactate 4.8 mg/dl and Serum ammonia was normal ECG/ECHO and cardiac work up was normal. BMA revealed a cellular marrow M:E 3:1 BLAST CELLS <25% NO STORAGE CELLS. Neurological evaluation Two MRI were taken initial MRI: Symmetrical diffuse T2 FLAIR hyperintensities in bilateral cerebral hemispheres sparing the subcortical U fibres, diffuse hyperintensities also noted in corpus callosum, pons, cerebral peduncles similar symmetrical hyperintensities noted in bilateral pyramidal tracts and in gangliocapsular regions consistent with KRABBE LEUKODYSTROPHY. A repeat MRI taken three months later: Interval increase in white matter hyperintensities, diffuse hyperintensities in bilateral denatate nuclei and cerebellar white matter is a new finding. Enzyme assay for Beta Galactocerebroside was 1.1 nmoles /17 hrs /mg(normal 8 -42) . Nerve conduction study to rule out peripheral neuropathy was normal. Ophthalmology opinion was obtained, and found to be normal. Otorhinolaryngologist opinion was Normal. Gastroenterologist suggested regression of developmental milestones with heptosplenomegaly indicating neurodegenerative pathology probably leukodystrophy. Hematologist suggested features consistent with leukodystrophy. The child was treated with anticonvulsants and supportive management. The child is on follow up requiring recurrent admissions for aspiration pneumonia and feeding difficulties for which child has been put on tube feeds.

DISCUSSION:
Krabbe disease is caused by mutation in the GALC gene located on chromosome 14 (14q31), which causes a deficiency of an enzyme called galactocerebrosidase. The build-up of unmetabolized lipids affects the growth of the nerve's protective myelin sheath (the covering that insulates many nerves), and causes severe degeneration of motor skills. Symptoms begin between the ages of 3 and 6 months with irritability, fever, limb stiffness, seizures, feeding difficulties, vomiting, and slowing of mental and motor development. In the first stages of the disease, doctors often mistake the symptoms for those of cerebral palsy. Other symptoms include muscle weakness, spasticity, deafness, optic atrophy, optic nerve enlargement, blindness, paralysis, and difficulty when swallowing. Prolonged weight loss may also occur. In our case the initial presentation is classical of Krabbe disease. Krabbe disease has the following 4 clinical subtypes, distinguished by age of onset: Type 1 - Infantile, Type 2 - Late infantile, Type 3 - Juvenile, Type 4 - Adult.
DIFFERENTIAL DIAGNOSIS INCLUDE

- Gauchers disease
- GM2 gangliosidosis
- Metachromatic leukodystrophy
- Niemann-Pick disease

Several previous studies suggest that in the absence of confirmatory evidence of low or absent GALC levels, the characteristic distribution of lesions and MRI signal patterns on 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 which are classically present in our case. Before the advent of an enzyme assay, definitive diagnosis was based on histopathological demonstration of globoid cells by brain biopsy. Enzyme estimation in cultured skin fibroblasts or peripheral blood leukocytes accurately identifies homozygotes, which is positive in our case clinching diagnosis. GALC assay for the diagnosis is expensive and not widely available because of this constraints the mutational analysis could not be ventured in our case.

TREATMENT OPTIONS

The hematopoietic stem cell transplantation (HSCT) is a potential treatment option for Krabbe disease, when transplanted within the first month of life it has given excellent prognosis. Various studies have shown varying degrees of benefit with HSCT, with greatest benefit occurring in patients who are asymptomatic or mildly symptomatic cases. HSCT should be considered in individuals with late-onset or slowly progressive Krabbe disease and in individuals with infantile-onset disease, in the early neonatal asymptomatic period. Short-term benefits with HSCT include delayed progression and improved survival. Long-term post transplant neurocognitive developmental and survival outcomes are not known at present. Symptomatic treatment for some neurologic sequelae is also available but has no significant effect on the clinical course of the disorder. Research still continues on treatments targeting inflammatory markers, enzyme replacement therapy, gene therapy, and neural stem cell transplantation. No medications that alter the natural history of Krabbe disease is currently available. Early hematopoietic stem cell transplantation (HSCT) is the only treatment that has been shown to significantly alter the disease progression.

COMPILATIONS:
Irreversible neurologic deterioration and death can occur. Patients are at risk for aspiration pneumonia and recurrent respiratory infections caused by neurologic compromise.

PROGNOSIS:
In patients with type 1 infantile Krabbe disease, the average lifespan is 13 months. Most patients with type 2 disease die within 2 years of disease onset. With both juvenile-onset and adult-onset Krabbe disease, progression of disease and lifespan reduction vary. HSCT results indicate markedly improved short-term survival for individuals who are treated while asymptomatic during the early neonatal period.

REFERENCES:


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