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Case Report

ADULT ONSET KRABBE'S DISEASE WITH GALC ENZYME DEFICIENCY: A RARE CASE REPORT

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A R T I C L E I N F O

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A B S T R A C T

Krabbe's disease (globoid cell leucodystrophy) is a disorder involving the white matter of the peripheral and central nervous systems. Mutations in the gene for the lysosomal enzyme galactocerebrosidase (GALC) result in low enzymatic activity and decreased ability to degrade galactolipids found in myelin. The disease is classically of infantile onset, but adult onset cases have been reported. A 30 year old female with Krabbe's disease is described, with proven GALC deficiency. Patient is a young female with the history of gradual onset and gradually progressive executive dysfunction for last 4 years associated with difficulty in walking since 4 years and behavioural abnormalities since 2 years and two episodes of seizures. On examination there was no dysmorphic features apparent, spasticity was present in both the legs with brisk reflexes and few cerebellar signs with with Impairement in all the lobar functions. She was suspected case of leukodystrophy and MRI suggestive of hyperintensities in periventricular white matter. Her opthalomological evaluation normal. VEP/BERA/ NCV was normal. Her routine investigations was normal and enzyme assay for leukodystrophy suggestive of decrease level of galactocerebrocidase, suggestive of krabbe's disease.

INTRODUCTION

Krabbe's disease, or globoid leucodystrophy, is an autosomal recessive disorder caused by a deficiency in the activity of the enzyme galactocerebrosidase (GALC). The condition has been mapped to chromosome 14q24.3- q32.1 and the GALC gene has recently been cloned. Deficiency of GALC impairs cleavage of the galactose moiety from galactosylceramide. This leads to accumulation of galactosylceramide within multinucleated macrophages of the white matter, forming globoid cells. A metabolite of galactosylceramide, psychosine, also accumulates and is toxic to oligodendroglia. This ultimately results in damage to the white matter of both peripheral and central nervous systems. The disease is confirmed by markedly reduced GALC activity in peripheral blood leucocytes. The disease may be subdivided into three types: the more common infantile form with onset within the first six months 4; a juvenile form presenting between two and 10 years; and a rarer adult form with onset after 10 years. The infantile form is the most severe, with central demyelination causing irritability, spasticity, ataxia, and seizures. Blindness from optic atrophy, cortical blindness, and deafness may all occur. Peripheral demyelination presents with limb weakness and areflexia. Progressive psychomotor decline results in quadriparesis and death within a few years of onset.

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Nerve conduction studies show a demyelinating peripheral neuropathy, and magnetic resonance imaging (MRI) shows central demyelination, most prevalent in the periventricular area and centrum semiovale with sparing of the subcortical U fibres. The cerebrospinal fluid may show increased protein. Juvenile and adult forms of the disease have a milder phenotype and a slower rate of progression. Symptoms and signs include spasticity, dementia, ataxia, peripheral neuropathy, and loss of vision. Investigations may show milder abnormalities, and nerve conduction can be normal or only mildly affected. Cerebrospinal fluid can be normal and MRI may be normal early on in the disease. In this paper, we present the clinical findings of adult onset Krabbe's disease with proven enzyme deficiency and neuroimaging.

Case Report

My patient is 30 year old female done Bsc in biology was a normal full term baby delivered vaginally and had greenish discolouration of lower body at birth and admitted for about 5 days. Academic performance was average and used to pass with 2nd division.

As narrated by the attenders patient was apparently alright four years back when she had difficulty in walking realized by the patient when she was cautious while walking and had tendency to fall and had to take the support to walk since one year. She had change of gait realized by the attenders as difficulty in walking along the straight line. She also has tendency to topple over rough surfaces. She denies any history of stiffening and

loosening of limbs. She also says that she has difficulty in wearing the slippers and slippers tend to slip since 1 year. She also has weakness in the hands and slipping of objects from the hands. She has difficulty in combing hairs, tying the hairs and dressing and undressing. No complaints of any freezing like episodes. But she tends to stop near obstacles. She also tends to frequently bumps during walking.

She also has difficulty in writing. Initially she used to write normally and was a teacher previously and now says that she is not able to write all. Since one and half year complaining of behavioral abnormalities, such that she had difficulty in dressing the children when she make them to wear clothes. She sometimes shouts and sometimes speaks very slowly. She also has repetitive repetitions of words and used to repeat some words for 4 to 5 days, she also has bizarre behavior like she talks irrelevantly with the guest, she also don't bath for many days. She also used to eat from empty utensils. She also has emotional incontinence and used to cry and laugh irrelevantly for trivial reasons. She also speak lies on small things. She used to do repeatedly to the things she asked to not to do.

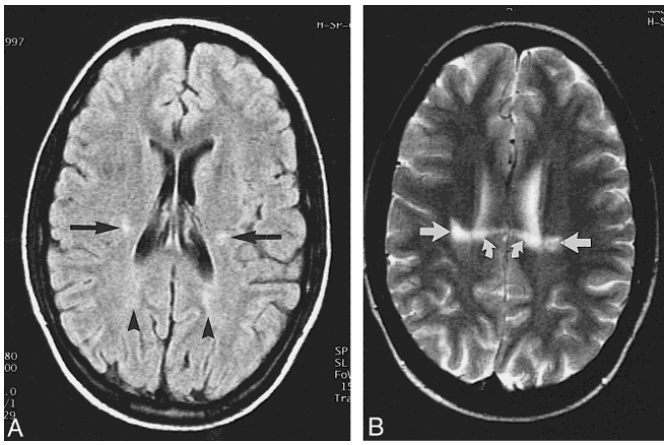
She also has reduced participation in any social function and tends to avoid gatherings and social behavior. She also has difficulty in handling the mobile phone since 32 years. Since 2 to 3 years she also has memory loss realized by the attendees such that she used to forget things put in daily routine. In an incidence she also forget iron while ironing the clothes and burnt them. Attenders also realized that dishes had disproportionate ingredients and uncooked or burnt chapattis. In an incidence she also forgets the LPG gas knob open. This also interfered with daily routine and was gradual in onset and gradually progressive.

She also has history of sudden onset loss of consciousness two episodes, while she was sitting on the ground when she had sudden deviation of neck to the right side with frothing of mouth and up rolling of eye balls, she was not responding to any stimulus, followed by which she had tonic contractions of all the four limbs for about 10 min and post ictal confusion for 20 minutes no fecal and urinary incontinence. Attenders also says that she has slowness of movements and now take double of the time she used to take previously. She is also complaining of decrease vision and saying that difficulty in putting thread in the needle, used to sleep normally in the night and tend to wake up late.

No complaint of change of voice, nasal regurgitation, occasional chocking while drinking, no complaints of dysphasia, dysarthria, no history of muttering in alone, no history of visual and auditory hallucination, no history of jerks in the body, no headache, fever, joint ache. No complaints of any bladder, bowel abnormality. No history of sensory loss or positive sensory phenomenon. No history of any skin lesions.
Examination part:

Head circumference 52cm. Patient was conscious awake, oriented to time place and person, emotional liability, talking irrelevantly sometimes, crying irrelevantly. Speech is normal. MMSE 11/30

Cranial nerve examination was normal, grade 1 spasticity in all four limbs, and power was 5/5 in all the four limbs in all range of motion. Sensory system was intact and having deep tendon reflexes on both the sides were brisk. Superficial reflexes were normal. No frontal release reflexes. Not able to perform the finger nose test but has no nystagmus and no dysdiadochokinesis. Gait is spastic. All the routine blood investigations were in normal limit MRI brain done suggestive of bilateral confluent white matter hyperintensities predominantly periventricular, centrum semiovale and corona radiate suggestive of leukodystrohy. Patient then evaluated for krabbe disease, galactocerebrocidase level was done suggestive of lower limits, the reference range of laboratory was 18 to 45 nmol/ 17hr/ng. and patients found to be 9.81. CSF was normal and nerve conduction studies was also normal.



DISCUSSION

Globoid leukodystrophy is a fatal, genetically determined disorder of myelin which chiefly affects infants and children. Its eponym, "Krabbe's disease," is derived from the report of the late Knud Krabbe who, in 1916, clearly described its infantile form in two siblings.[1] .Distinctive cellular structures are the hall-mark of this disease. These multinuclear and mononuclear structures may be termed "globoid" elements. They are present in large numbers in the devastated white matter who, by this term, drew attention to their globular, distended appearance.

The MR findings in an adult patient with globoid cell leucodystrophy (GLD) or Krabbe's disease are presented. MRI showed a bilateral periventricular hyperintensity of the parieto-occipital white matter on the T2-weighted images. A hyperintense signal was seen bilaterally along the corticospinal tract. There was no immediate nor delayed contrast enhancement.[2]

As with other inherited diseases, advances in molecular biological techniques have enhanced our understanding of the heterogeneous nature of Krabbe's disease.[3] GALC, a highly hydrophobic lysosomal enzyme, is composed of a heterodimeric complex of two subunits of 50 kDa and 30 kDa, derived from an 80 kDa precursor.[4] Recent cloning of the GALC genehas allowed genotypic/phenotypic comparisons to be made in Krabbe's disease, and has shown that different mutations within this gene are associated with differing severity of disease, both in terms of age of onset and subsequent progression. One common mutation has been found in 40-50% of the mutant alleles in infantile cases of European or Mexican ancestry.[5-7] Sixty five disease causing mutations and polymorphic changes within GALC have been described to date.[8]

Polymorphisms within the GALC gene have been shown to decrease the in vitro expression of GALC and may in part be

responsible for pseudodeficiency states.[9]Similarly, expression studies of mutant alleles have suggested that phenotypic variation of cases of Krabbe's disease reflects varying degrees of reduction in GALC activity associated with the differing mutant alleles.[10-11]

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