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Case Report

A rare case of Sandhoff disease: two in the same family

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ABSTRACT

Sandhoff disease is a rare lysosomal storage disorder which is inherited in an autosomal recessive pattern. Prevalence of Sandhoff disease is 1 in 384000 live births. Here we report a 14 month old male child who presented with macrocephaly, regression of developmental milestones and seizures. Fundus examination showed macular cherry red spot. Enzyme studies revealed reduced levels of beta hexosaminidase A and B, following which a diagnosis of Sandhoff disease was made. Mother was offered prenatal diagnosis of the fetus in the subsequent pregnancy, which was also found to have the same enzyme deficiency and the pregnancy was medically terminated. Early identification of this neurodegenerative disorder, helped in preventing the birth of subsequent affected children in the same family, thereby reducing the burden on the family as well as the society.

Keywords: Lysosomal storage disorder, Macrocephaly, Cherry red spot, Beta hexosaminidase A and B

INTRODUCTION

Sandhoff disease is a lysosomal storage disorder. The mode of inheritance is autosomal recessive. Prevalence of Sandhoff disease is 1 in 384000 live births.[1] The Sandhoff carrier frequency in non-Jewish population (36 in 10000) is higher than the Jewish population (20 in 10000). There are more than 30 diverse groups of lysosomal storage disorders; one among them is GM2 gangliosidoses. This group includes only two diseases, Taysach and Sandhoff disease. They result from the deficiency of β-hexosaminidase activity and the lysosomal accumulation of GM_2 gangliosides, particularly in the central nervous system.[2] Sandhoff disease represents 7% of GM2 gangliosidoses.[3] Here we report one such rare case of Sandhoff disease.

CASE REPORT

A 14 months old male child, presented with complaints of disproportionately increasing size of the head and multiple episodes of seizures. The child was first born of a non-consanguineous marriage with an uneventful antenatal period. The perinatal transition was uneventful and there was no family history of seizures. The child had a delay in attaining age appropriate milestones. Head control, recognition of mother and social smile were attained by 6 months of age and sitting with support by 9 months. There was no language development. After 10 months of age, there was regression of the above milestones and by 1 year, all were lost. With regression and loss of developmental milestones, a neurodegenerative disorder was considered.

General examination revealed an awake child, not responding to commands, no gaze fixation with an occasional startle response to sounds (Figure 1 and 2). Head appeared large and the head circumference was 51 cm. This was >+2 SD for age, suggestive of macrocephaly. Anterior fontanel was wide open with frontal bossing. There was no dentition and child also had bilateral undescended testes.

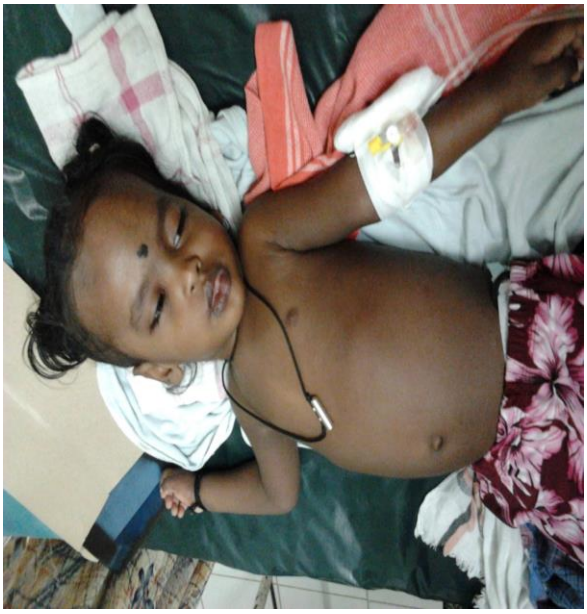

Figure 1: Macrocephaly, frontal bossing.

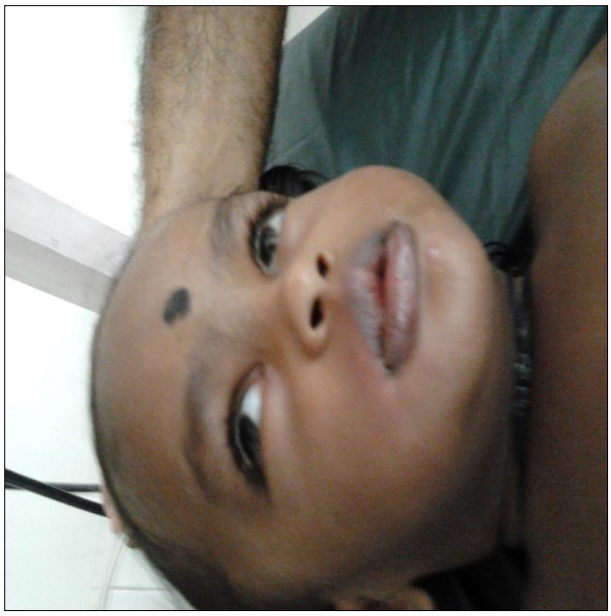

Figure 2: Vacant stare.

Neurological examination revealed generalised hypotonia, exaggerated deep tendon reflexes, clonus, and extensor plantar response. The abdomen examination revealed hepatosplenomegaly, with liver enlarged 4cm below right costal margin and spleen 3 cm below left costal margin. The liver span was 8 cm which was increased for age. Fundus examination revealed a macular cherry red spot (Figure 3). Cardiovascular and respiratory system examination were clinically normal.

The basic investigations were within normal limits. ECHO and thyroid profile were normal. MRI brain showed hypomyelination with increase in T2 signal intensity in bilateral frontoparietal areas, temporal lobe, subcortical deep white matter, periventricular white matter and bilaterally in basal ganglia (Figure 4).

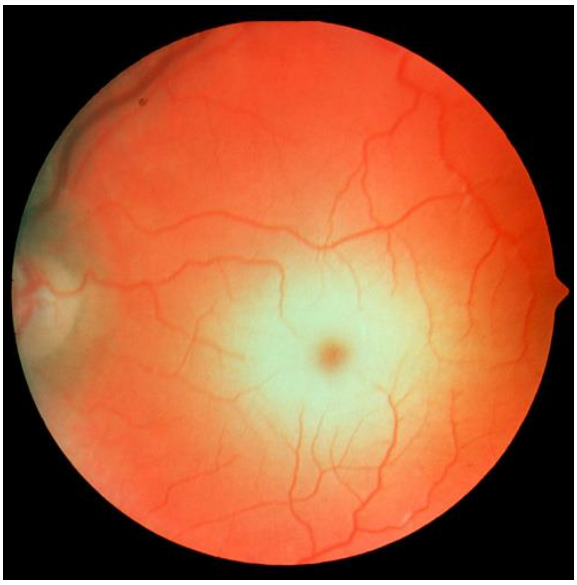

Figure 3: Cherry red spot.

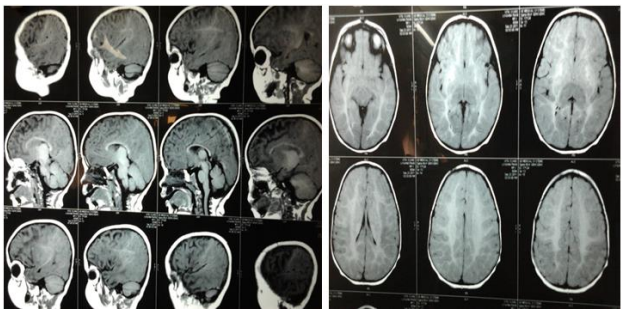

Figure 4: MRI showing increase in T2 signal intensity of the brain.

Enzyme studies

With macrocephaly, regression of milestones and cherry red spot, Taysach's disease and Sandhoff disease were considered and enzyme studies were sent.

Enzyme levels in our case were as follows:

Beta hexosaminidase A and B: 230 nmol/hr/mg (N: 905-2878 nmol/hour/mg) suggesting Sandhoff disease.

Beta hexosaminidase A: 101 nmol/hour/mg (N: 62-310 nmol/hour/mg) ruling out Taysach's disease.

The child was given supportive management with antiepileptics for control of seizures, antibiotics for respiratory infections and multivitamins for general health. Genetic counselling was given to the parents. Thereafter the child had frequent admissions for seizures and pneumonia .He gradually deteriorated and died at 3 years of age.

The mother conceived 6 months later and chorionic villus sampling was done, which also showed reduced levels of beta hexosaminidase A and B in the fetal cells. The pregnancy was thereby medically terminated.

DISCUSSION

Sandhoff disease is a lysosomal storage disorder. The disease is named after Konrad Sandhoff, a German chemist. It is characterised by exaggerated startle reaction, regression of milestones, hepatosplenomegaly, skeletal dysplasia, cherry red spot and seizures. The early symptoms of hypotonia and acoustic hypersensitivity are followed by spasticity and hearing loss. Seizures are usually a late manifestation of the disease. It is estimated that early seizures indicate severity of the disease and are associated with poor developmental outcomes.[4] There is no correlation between the severity of neuroimaging and clinical picture.[5]

The gene that causes Sandhoff is located on chromosome 5, specifically 5q13. It is called HEX B gene. This gene provides instructions for making a protein that is part of two critical enzymes in the nervous system, beta-hexosaminidase A and beta-hexosaminidase B. These enzymes are located in lysosomes. Mutations in the gene lead to reduced enzyme levels, such that GM2 gangliosides accumulate in the neurons of brain and spinal cord producing the symptoms.

Sandhoff disease has been classified into three forms as infantile, juvenile and adult onset type based on the age of onset and clinical features. The most common type is the infantile form. Here the child is normal at birth, with disease onset between 3-9 months of age. The disease course is severe leading to death before 3 years of age. Juvenile and adult onset Sandhoff disease are very rare. Children with juvenile Sandoff, do not exhibit the tell-tale sign of cherry red spot which can make the diagnosis challenging.

Definitive diagnosis is by determination of the deficient levels of the enzyme. A diagnostic neuroimaging marker of Sandhoff disease is bilateral thalamic involvement.[3] A recent advanced diagnostic modality for this disease is proton Magnetic Resonance Spectrography (MRS) of the cerebral metabolites. Wilken et al. in their study identified increased levels of inositol (glial marker) and reduced amount of total N-acetylaspartate which is a neuroaxonal marker in a proved case of Sandoff disease.[6]

Sandhoff disease 'breeds true' in a family. If one child is diagnosed with infantile Sandhoff, then the other children are at risk only for the infantile form. One set of parents cannot have children with both the infantile and juvenile forms of the disease.

Our case falls under the category of infantile type of Sandoff disease with classical clinical presentation and confirmatory enzyme deficiency. This clearly indicates that the next sibling which was medically terminated would have been of the same infantile type.

Sandhoff disease needs to be differentiated from the other conditions with similar neuroimaging findings like Taysach's disease, GM1 gangliosidoses, Alexander disease, late stages of Canavan and Krabbe's disease.

Both Taysach and Sandhoff have similar clinical presentation with the exception of hepatosplenomegaly and skeletal dysplasia which are absent in Taysach's. Cherry red spot is present in both these conditions. The two conditions are differentiated by the specific enzyme deficiency. Beta hexosaminidase occurs as 2 isoenzymes. Beta hexosaminidase A is composed of 1alpha and 1beta subunits, whereas beta hexosaminidase B has 2 beta subunits. Mutation in alpha subunit causes deficiency of Beta hexosaminidase A and results in Taysach's disease. On the other hand, mutation in beta subunit causes deficiency of both beta hexosaminidase A and B and leads to Sandhoff disease.

GM1 gangliosidoses are characterised by deficient levels of beta galactosidase with neuroimaging findings similar to GM2 gangliosidoses. This is because both GM1 and GM2 gangliosides structurally differ only in the terminal N-acetyl galactosamine. They are identified by specific enzyme assay.

In Alexander disease the white matter degeneration is most prominent in the frontal areas.

Late stages of Canavan disease is characterised by white matter necrosis with cavitation, atrophy of brainstem, cerebellum and dense T1 signals in thalami. Magnetic resonance spectroscopy in this disease shows high peak of N-acetyl aspartic acid.

In Krabbe's disease, there is extensive white matter involvement, more brain structures show high density on CT and it does not spare the corpus callosum.[7]

Our case had classical clinical phenotype, cherry red spot and enzyme deficiency suggestive of Sandhoff disease. We did not have thalamic involvement which is characteristic of GM2 gangliosidoses especially Sandhoff disease.[8] A similar case of late onset GM2 gangliosidoses without thalamic involvement was reported by Nassogne et al., where the abnormality was localised to the brain stem.[9]

Management

There is no specific treatment for Sandhoff disease. Management is mainly supportive. Research in this area includes gene therapy, substrate inhibitors and pyrimethamine chaperone, which crosses the blood brain barrier and binds with the inactive enzyme so that it takes a correct functional shape. The other research aspects are stem cell therapy, and enzyme replacement therapy. All

the above said modalities are in clinical trials. Recent studies include bone marrow transplantation and therapy with Tumor Necrosis Factor-α (TNFα).

CONCLUSION

The prevalence of Sandhoff disease is very rare. Early diagnosis is of prognostic value and helps in preventing the disease in subsequent pregnancies. This case is presented for its rarity, the early prenatal diagnosis of which helped in termination of the next pregnancy. This throws light on the importance of early recognition of genetic disorders, knowledge of the pattern of inheritance, genetic counselling and the definite need for prenatal diagnosis to prevent birth of subsequent affected children.

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