Abstract:
Sandhoff disease is a type of GM2 gangliosidoses. It occurs due to the deficiency or reduced activity of the enzyme beta hexosaminidase A and B. The prevalence of the disease is 1 in 384000 live births. (1) Here we are presenting a case report of Sandhoff disease.

Case report:
A 14 months old male child first born of a non-consanguineous marriage presented with complaints of increasing size of the head, inability to hold his head and failure to recognize mother for the past six months along with multiple episodes of seizures. There was no birth asphyxia with uneventful antenatal, natal and post natal history. There was a developmental delay with head control, social smile, recognition of mother being attained at 6 months of age. There was no language development and after 10 months of age, there was regression of the milestones and by 1 year, all the attained milestones were lost.
Examination revealed an awake child, not responding to commands with no gaze fixation and an occasional startle response to sounds (fig. 1 and 2). Anterior fontanel was wide open. The child had a macrocephaly with head circumference measuring 51 cm (> +2 standard deviation). There was no dentition and bilateral undescended testes.

Vitals were normal. Systemic examination showed a generalised hypotonia, exaggerated deep tendon reflexes, clonus and extensor plantar response with hepatosplenomegaly. Cardiovascular and respiratory system were clinically normal. Fundus showed a macular cherry red spot (fig. 3). Basic investigations, thyroid profile, echocardiogram were normal. MRI brain had hypomyelination with increase in T2 signal intensity in bilateral frontoparietal and temporal lobe subcortical deep white matter, periventricular white matter and in bilateral basal ganglia.

Figure 1: Macrocephaly

Figure 2. Vacant stare

Figure 3. Cherry red spot
ENZYME STUDIES:

With macrocephaly, regression of milestones and cherry red spot, Taysach’s disease and Sandhoff disease were considered and enzyme studies were sent. It showed reduced levels of beta hexosaminidase.

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

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

The child was treated with anti convulsants and antibiotics for seizures and respiratory tract infections respectively. Drug prophylaxis for seizures was advised on discharge. Genetic counselling was given to parents.

The child had got frequent admissions to hospital for seizures and pneumonia and was adequately treated. He gradually deteriorated and died at 3 years of age. Chorionic villus sampling was done for the mother during her second pregnancy which also showed reduced levels of beta hexosaminidase A and B in the fetal cells and then the pregnancy was medically terminated.

DISCUSSION:

Sandhoff disease is a lysosomal storage disorder. It is an autosomal recessively inherited GM2 gangliosidoses. It is prevalent in Creole population of northern Argentina, Indians in Saskatchewan, Canadians, and people from Lebanon, people of Eastern European and Ashkenazi Jewish descent.

Prevalence of Sandhoff disease is 1 in 384,000 live births.(1) The Sandhoff carrier frequency in non-Jewish populations (36 in 10,000) is slightly higher than Jewish populations (20 in 10,000).Both Taysach and Sandhoff disease are GM2 gangliosidoses. They result from the deficiency of β-hexosaminidase activity and the lysosomal accumulation of GM2 gangliosides, particularly in the central nervous system.(2)

β-Hexosaminidase occurs as 2 isozymes: β-hexosaminidase A, which is composed of 1 α and 1 β subunit, and β-hexosaminidase B, which has 2 β subunits. β-Hexosaminidase A deficiency results from mutations in the α subunit and causes Tay-Sachs disease, whereas mutations in the β-subunit gene result in the deficiency of both β-hexosaminidases A and B and cause Sandhoff disease.(2)

The disease is named after Konrad Sandhoff, a German chemist. It has been classified into three forms as infantile, juvenile and adult onset type based on the age of onset and clinical features. The gene that causes Sandhoff is located on chromosome 5, specifically 5q13.(3)It is called HEX B gene.
The HEX B 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. Within lysosomes, these enzymes break down fatty substances, complex sugars, and molecules that are linked to sugars. Mutations in the gene leads to reduced enzyme levels so that GM2 gangliosides accumulate in the neurons of brain and spinal cord producing the symptoms. (4)

Sandhoff disease ‘breeds true’ in a family. If one child is diagnosed with infantile Sandhoff, then the other children are only at risk for the infantile form. One set of parents could not have children with both the infantile and juvenile forms of the disease. (3).

INFANTILE SANDHOFF:

A baby with infantile Sandhoff appears normal at birth and typically develops normally for the first six months of age. As development slows, parents may notice a reduction in vision and tracking. They gradually regress, losing skills one by one and eventually are unable to crawl, turn over, sit or reach out. Other symptoms include loss of coordination, progressive inability to swallow and difficulty breathing. They also develop an exaggerated startle reaction to loud noises. Most children experience recurrent seizures by age 2 and eventually lose muscle function, mental function and sight, becoming mostly non-responsive to their environment. They usually will die due to respiratory problems and refractory seizures.

JUVENILE SANDHOFF:

Early symptoms of Juvenile Sandhoff include lack of coordination or clumsiness and muscle weakness such as struggling with stairs. A child may also exhibit slurred speech, swallowing difficulties and muscle cramps. They also slowly decline losing their ability to walk, eat on their own and communicate. Children are prone to respiratory infections and often experience recurrent bouts of pneumonia. Many children will have seizures.

Juvenile Sandhoff has a broad range of severity. In most cases, the earlier the first signs are observed, the more quickly the disease will progress. These children do not exhibit the tell tale sign of cherry red spot. This can make the diagnosis challenging. (3)

ADULT ONSET SANDHOFF:

They present with clumsiness and muscle weakness. Later they develop speech difficulties and mental health problems. Adults frequently require more mobility assistance. This type is often misdiagnosed as Multiple sclerosis or Amyotrophic Lateral Sclerosis.
MANAGEMENT:

There is no cure for Sandhoff disease. Only supportive management with anti convulsants and antibiotics are given.

RESEARCH:

Gene therapy: Introducing the correct genetic code with a viral vector to produce a proper enzyme.

Molecular Chaperone: Pyrimethamine chaperone is tried in late onset Sandhoff disease. It crosses the blood brain barrier and binds with the inactive enzyme so that it takes a correct functional shape.

Substrate inhibition: Substrate inhibitors are small molecules that pass the blood brain barrier into the central nervous system and decrease the amount of substrate or waste product that accumulates.

Stem cell therapy, bone marrow replacement, enzyme replacement therapy and the above said modalities are all in clinical trials.

RECENT STUDIES:

1) During neuronal cell death in Sandhoff mice, there was an upregulation of genes related to an inflammatory process dominated by activated microglia. Activated microglial expansion was found to precede massive neuronal death. Extensive microglia activation also was detected in a human case of Sandhoff disease. Bone marrow transplantation of Sandhoff disease mice suppressed both the explosive expansion of activated microglia and the neuronal cell death.(5)

2) Tumor necrosis factor-alpha (TNFα), a key modulator of the CNS immune response is involved in microglial activation and neuronal cell death. The deletion of TNFα ameliorates neurodegeneration in Sandhoff mice. This points to TNFα as a potential therapeutic target to attenuate neuropathogenesis.(6).

CONCLUSION:

The prevalence of Sandhoff disease is very rare. This case is presented for its rarity.
References:


