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Case Presentation

Infantile Neuroregression as a Presentation of Sandhoff Disease: A Case Study

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ABSTRACT

Background: Sandhoff disease is a rare, autosomal recessive lysosomal storage disorder caused by a deficiency in both Hexosaminidase A and B enzymes. This leads to the progressive accumulation of GM2 gangliosides in the central nervous system, typically presenting as infantile neuroregression.

Case Presentation: A 15-month-old female presented with significant loss of achieved milestones, global developmental delay, and generalized spasticity. Clinical examination revealed an absence of social smile and failure to recognize caregivers. MRI of the brain showed T2W hyperintensities in the periventricular white matter and peritrigonal regions, suggesting delayed myelination. Laboratory assays confirmed a deficiency in total Hexosaminidase(357)(Hexosaminidase A (7.38) Hexosaminidase B(349.62)). Fundus examination was negative for cherry-red spot and optic atrophy.

Conclusion:This case highlights that Sandhoff disease must be considered in infantile neuroregression, even in the absence of pathognomonic ocular findings.Any infant presenting with neuroregression, cherry-red spot in the macula, and an increased startle response should raise suspicion of a progressive fatal lysosomal storage disorder (LSD) known as Tay–Sachs disease.In summary, if hepatomegaly is present, it rules out the possibility of Tay–Sachs disease and points towards Sandhoff disease. However, absence of hepatomegaly also helps differentiate Tay–Sachs disease from other LSDs such as Gaucher disease and Niemann–Pick disease.For confirmation, enzyme assay and genetic testing play a pivotal role. Definitive diagnosis relies on enzymatic assays confirming the dual deficiency of Hexosaminidase A and B.

Keywords: *Sandhoff Disease, Neuroregression, Hexosaminidase Deficiency, Lysosomal Storage Disorder, Global Developmental Delay.*

INTRODUCTION

Sandhoff disease is a rare, autosomal recessive lysosomal storage disorder characterized by the progressive accumulation of GM2 gangliosides, primarily within the central nervous system. This metabolic failure arises from mutations in the HEXB gene located on chromosome 5 (5q13.3), which encodes the β-subunit of the β-hexosaminidase enzyme. Unlike Tay-Sachs disease, which involves a deficiency only in Hexosaminidase A, Sandhoff disease results in a global deficiency of both Hexosaminidase A and B isoforms. The worldwide incidence is extremely low, estimated at approximately 1 in 384,000 live births, though it remains a critical differential in cases of pediatric neurodegeneration.

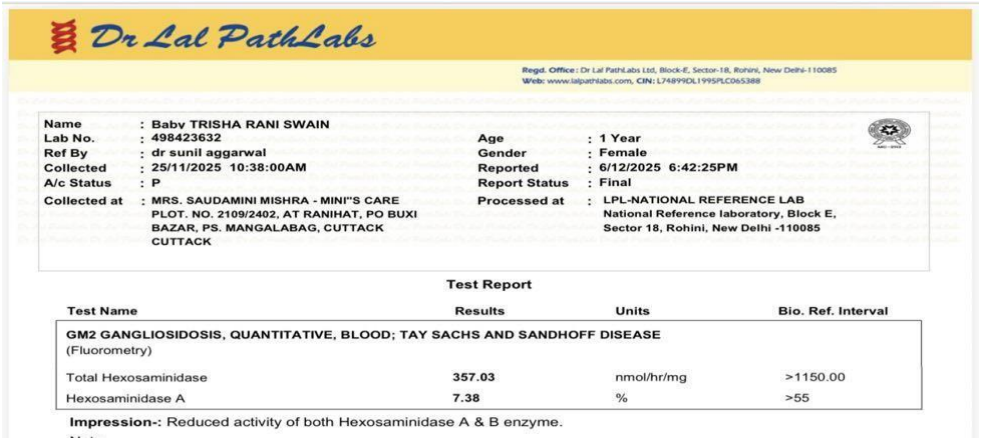
The clinical spectrum of Sandhoff disease is categorized based on the age of onset: infantile, juvenile, and adult-onset forms. The infantile form is the most severe, typically manifesting within the first six months of life with motor weakness, a startle response to sound (hyperacusis), and rapid loss of developmental milestones. As gangliosides accumulate in the neurons, patients progress to develop blindness, seizures, and generalized spasticity. A hallmark finding in many GM2

gangliosidosis patients is the "cherry-red spot" in the macula, though its absence does not definitively rule out the condition. Because the disease involves the β-subunit, it may also present with systemic involvement such as hepatosplenomegaly or skeletal abnormalities, which are absent in Tay-Sachs. Early recognition via enzymatic assays or genetic testing is vital, as the disease is currently progressive and life-limiting.

CASE PRESENTATION

A 15-month-old female child was brought to the hospital with a total duration of illness spanning several months, characterized by a failure to gain age-appropriate milestones and a progressive loss of previously achieved skills. The patient was born via normal vaginal delivery with a birth weight of 2800 g and had an unremarkable perinatal period. However, at the time of presentation, the patient had not achieved a social smile and was unable to recognize her mother or other primary caregivers. Eye-to-eye fixation was absent, and she had not reached markers for cooing, sitting, or rolling over.

On general physical examination, the patient was alert but exhibited significant neurological impairment. Her weight was 10.2 kg and head circumference was 46 cm. Notably, abdominal examination revealed mild hepatomegaly, with the liver span palpable 2 cm below the costal margin. Neurological examination revealed generalized spasticity in all four limbs with a power of 4/5. Deep tendon reflexes were brisk (3+) and symmetrical, and the plantar reflex was bilateral extensor (Babinski sign positive). The patient also exhibited a hyperactive startle response.



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Name	: Baby TRISHA RANI SWAIN		
Lab No.	: 498423632	Age	: 1 Year
Ref By	: dr sunil aggarwal	Gender	: Female
Collected	: 25/11/2025 10:38:00AM	Reported	: 6/12/2025 6:42:25PM
A/c Status	: P	Report Status	: Final
Collected at	: MRS. SAUDAMINI MISHRA - MINI"S CARE PLOT. NO. 2109/2402, AT RANIHAT, PO BUXI BAZAR, PS. MANGALABAG, CUTTACK CUTTACK	Processed at	: LPL-NATIONAL REFERENCE LAB National Reference laboratory, Block E, Sector 18, Rohini, New Delhi -110085

Test Report

Test Name	Results	Units	Bio. Ref. Interval
GM2 GANGLIOSIDOSIS, QUANTITATIVE, BLOOD; TAY SACHS AND SANDHOFF DISEASE (Fluorometry)			
Total Hexosaminidase	357.03	nmol/hr/mg	>1150.00
Hexosaminidase A	7.38	%	>55

Impression-: Reduced activity of both Hexosaminidase A & B enzyme.

Photo-1:Hexosaminidase enzyme assay demonstrating markedly reduced levels of both Hexosaminidase A and Hexosaminidase B

Laboratory investigations, including CBC, LFT, and RFT, were largely within normal limits. MRI of the brain revealed diffuse T2W hyperintensities involving the bilateral periventricular white matter, peritrigonal regions, and the external capsule, suggestive of delayed myelination.,Fundus examination showed no evidence of a cherry-red spot or optic atrophy. To confirm the metabolic etiology, a specific biochemical assay was performed. The results revealed a total Hexosaminidase level of 357 and a significantly low Hexosaminidase A level of 7.38. The dual deficiency confirmed a diagnosis of Sandhoff disease. A treatment regimen was established focusing on supportive care: anticonvulsants (Clobazam and Valproate) for symptom control, along with nutritional supplements and intensive occupational therapy.

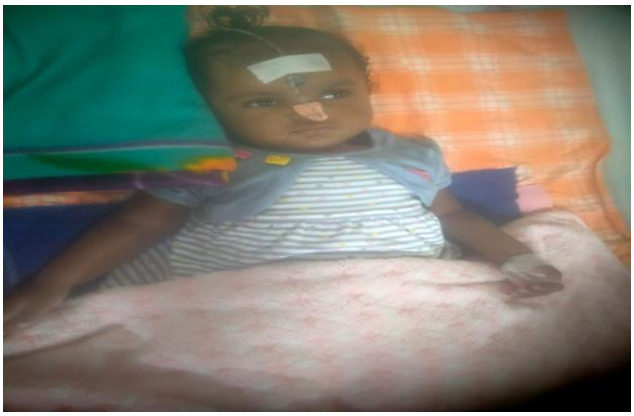

Photo 2:Patient after successful control of seizures; currently stable and receiving nutrition via nasogastric (NG) tube feeding.

DISCUSSION

Sandhoff disease results in the impaired breakdown of fatty substances in the brain, leading to progressive cell death. In

our case, the 15-month-old female presented with a classic triad of neuroregression, spasticity, and hepatomegaly. The presence of hepatomegaly was a crucial clinical clue pointing toward Sandhoff disease rather than Tay-Sachs. However, a major diagnostic challenge was the absence of a cherry-red spot in the macula. Literature suggests that its absence does not exclude the diagnosis, especially in variant forms.

MRI brain findings in this patient showed significant white matter involvement, correlating with the progressive de-myelination seen as gangliosides accumulate. The low serum levels of both Hexosaminidase A and B reinforced that biochemical testing is the "gold standard" when clinical signs are ambiguous. Management remains largely palliative, focusing on seizure control and maintaining quality of life. Early genetic counseling is essential, as there is a 25% recurrence risk in subsequent pregnancies.

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