CASE REPORT

Subacute Juvenile Sandhoff Disease: A Progressive Neurodegenerative Disorder

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Abstract

Aim: To present a case of subacute juvenile Sandhoff disease (SD), a rare neurodegenerative disorder occurring in 1 in 4,00,000.

Background: SD is a rare neurodegenerative disorder grouped under GM2 gangliosidosis that results from a mutation in the *HEXB* gene, which encodes the β-subunit of β-hexosaminidase, leading to a deficiency of hexosaminidases A and B. It affects the metabolism of GM2 gangliosides, causing the enzyme to accumulate within lysosomes in visceral cells as well as the central nervous system (CNS). Depending on the age of onset, the disease presents in three different phenotypes: (1) acute infantile SD, with onset before 6 months; (2) subacute juvenile SD (SJSD), with onset at 2–5 years; and (3) late-onset SD, with onset in late teens or young adulthood.

Care description: A rare case of a 10-year-old female child presented with right lower tooth pain. She had attained developmental milestones normally until about age 4 but later exhibited regressive changes around 4.5–5 years of age. She became progressively slow and unsteady. Investigations, including magnetic resonance imaging (MRI) of the brain, whole-exome sequencing, and biochemical genetic testing, led to a diagnosis of SJSD.

Conclusion: Not much literature has been published to highlight how SJSD impacts daily life and function. However, the functional limitations resulting from neurodegeneration may adversely affect daily activities.

Clinical significance: SJSD needs multidisciplinary involvement, including a physiotherapist, speech therapist, and psychiatrist, to monitor the prognosis regularly, diagnose future manifestations requiring supportive care, and ensure adequate functioning and activity of daily living.

Keywords: Case report, GM2 gangliosidosis, Neurodegenerative disorder, Sandhoff disease.

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Introduction

Several fatal disorders occur due to genetic mutations, with onset in infancy and childhood. Lysosomal storage disorders, caused by inborn errors of metabolism, include GM2 gangliosidosis with the accumulation of GM2 ganglioside in the intracellular organelles of visceral and neural cells.[1] Sandhoff disease (SD) (MIM 268800) is a rare neurodegenerative disorder grouped under GM2 gangliosidosis. SD results from a mutation in the *HEXB* gene, which encodes the β-subunit of β-hexosaminidase. As these mutations affect the metabolism of GM2 gangliosides, they fail to degrade and thus accumulate within lysosomes in visceral cells as well as the central nervous system (CNS).[2] This autosomal recessive disorder progressively destroys the nerve cells in the brain and spinal cord, manifesting as impaired limb coordination.

Depending on the etiopathology and course of the disease, it acquired several synonyms, viz., β-hexosaminidase beta-subunit deficiency, GM2 gangliosidosis type 2, hexosaminidase A and B deficiency, etc. Depending on the age of onset of the disease, SD shows three different phenotypes: (1) acute infantile SD, with onset age <6 months; (2) subacute juvenile SD (SJSD), with onset age 2–5 years; and (3) late-onset SD, with onset in late teens or young adulthood.[3]

Demographics

Sandhoff disease is a rare disorder with a variable frequency among populations. SD is reported to occur in 7% of GM2 gangliosidosis.[1] It is seen in specific ethnic groups living in Eastern Europe, Northern Argentina, Canada, etc. Incidence is 1 in 3,84,000 to 1 in 4,20,200. No gender predilection has been reported. The prevalence of GM2 gangliosidosis in India is not known. These cases might have been misdiagnosed as cerebral palsy. It was reported that the *HEXB* variant [c.850C>T (p.Arg284)] was observed in the Indian population.[4]

Subacute Juvenile Sandhoff Disease

These children are normal at birth and have attained all milestones at their respective stages. Then, the developmental progress is slowed down between 2 and 5 years of age, followed by regression

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and neurologic impairment, resulting in a decline in previously acquired functional as well as cognitive skills.

Clinical Features

The regressive changes in SJSD are noticeably manifested in speech and motor skills, subsequently resulting in abnormal gait, spasticity, seizures, and dysphagia in later stages. Subsequent neuropathy and dysautonomia result in serious complications and eventual death.[3] The disease-related functional limitations in gross and fine motor functions, balance, etc., are observed progressively in these children. Gross motor functional difficulties result from muscle weakness, which might progress into an inability to walk without assistance, get up from a seated position, and climb stairs. These children experience frequent falls, resulting in traumatic injuries.[5]

Limited mobility and increased risk of falling hamper the daily activities of these children. They lose hand coordination and the ability to grip due to the loss of fine motor functions, leading them to drop items more frequently. Muscle weakness, clumsy gait, fatigue, falling, and difficulty in climbing stairs are frequent findings. Slurred speech and other types of speech difficulties are frequently found in these children. With the presence of physical and speech difficulties, these children tend to show constant fear, frustration, and embarrassment. The progressive physical and functional limitations lead to a lack of independence, which impacts the self-esteem of the growing child. The cumulative effect of the degenerative changes negatively impacts long-term emotional and social behavior, jeopardizing the child's quality of life.[5]

Progressive weakness, intellectual disability, impaired hearing and vision, exaggerated startled response, increased myotonic reflexes, seizures, and eventual death are reported in severe cases.[6]

Molecular Genetics

Gangliosides are sciatic acid-containing glycosphingolipids, which are highly important molecules in immunology. They are present on cell plasma membranes, as well as on nuclear membranes of visceral tissues, body fluids, and predominantly in the nervous system. Gangliosides are involved in neural functions such as neuronal transmission and the structural maintenance of the nervous system. They have specific determinants in cellular recognition and cell-to-cell communication. They play an important role in modulating intracellular and intranuclear calcium homeostasis, which is crucial in cellular functions.[7]

These gangliosides are metabolized and regulated by the enzyme β-hexosaminidase. Any disturbance in the enzymatic activity reduces the ability of the cell to catabolize GM2 gangliosides, leading to the accumulation of GM2 and related glycolipids in visceral and neural cells. The progressive increase in cellular gangliosides leads to cellular apoptosis and loss of myelin and axons in the cortical neurons, resulting in neurodegeneration.[1]

The subunits α and β of the enzyme β-hexosaminidase A are encoded by *HEXA* and *HEXB* genes. Any mutations in either of the genes result in the accumulation of GM2 gangliosides in specific tissues, and *HEXB* mutation causes SD.[6] Loss of function of *HEXB* variety reduces the activity of *HEXB*,[3] which is located on 5q13, containing 14 coding exons, spanning an mRNA of 2 kb, and encoding 556 amino acids.[3,8]

Investigations

Electroencephalogram (EEG), magnetic resonance imaging (MRI) of the brain, serum testing of enzymatic activity, genetic tests, etc., are essential for diagnosis. Neuroimaging findings: MRI of the brain shows hypomyelination or delayed myelination, supratemporal brain atrophy, cerebral and cerebellar atrophy, involvement of the superior vermis, etc.[1,2]

Diagnosis is established by enzymatic testing showing abnormally low activity of *HEXB*.[3] Comprehensive genetic testing and whole exome sequencing (WES) are helpful to identify biallelic pathogenic variants in *HEXB* on molecular testing, and this test also confirms the diagnosis of the phenotype.[2,3]

Differential Diagnosis

Subacute juvenile Sandhoff disease has to be differentiated from Tay–Sachs disease (deficiency of hexosaminidase A) and other GM2 gangliosidoses based on the time of onset, molecular pathogenesis, deficiency of specific enzymatic activity, and genetic analysis using the WES test.[3] Acquired disorders like heavy metal poisoning (e.g., lead), postinfectious meningoencephalitis, and neurological manifestations of other systemic diseases should also be differentiated based on etiology and other characteristics.[3]

Case Description

A 10-year-old female child reported right lower tooth pain. She was noncoherent, and a staggering gait was observed. Family history revealed a first-degree consanguineous marriage. A full-term pregnancy and breech delivery were reported, and early infancy and childhood were uneventful. All milestones were achieved at the appropriate age, and the child showed normal interaction with peers in preschool. Gross motor skills were developed normally, and the child could dress and feed herself.

But the parents started observing regressive changes around 4.5 and 5 years of age. She became progressively slow and unsteady, stopped running and hopping, and couldn't walk down the stairs (Fig. 1). She was not able to dress herself or eat on her own. Her speech was affected, and she started secluding herself without showing any interest in social interaction. Slowly, she lost orientation to time, place, and people. Drooling of saliva and inappropriate laughter were noticed (Fig. 2).

Magnetic resonance imaging of the brain showed sulcal prominence with mild atrophy of the bilateral parieto-occipital

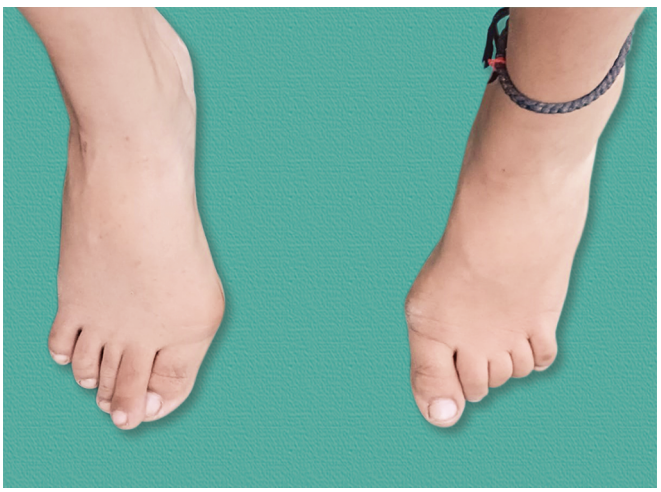

Fig. 1: Hallus valgus, deformity of the joint connecting the big toe to the foot

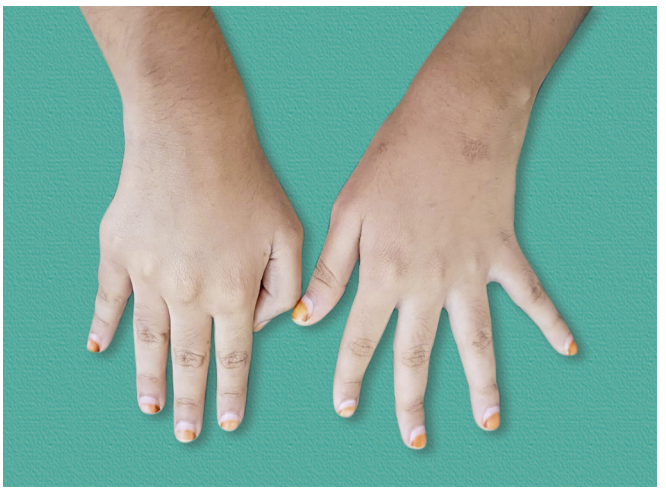

Fig. 2: Hands

lobes. The WES test suggested the diagnosis of a homozygous variety of uncertain significance. This autosomal recessive inheritance was reported to have resulted from a new mutation, c.875C>T (p.Pro292Leu), which has not yet been reported in the clinical database for SD. Biochemical genetic investigation showed decreased activity for total hexosaminidase A and B at 44.2 nmol/hour/mL (normal: 800–1600 nmol/hour/mL) and normal activity for arylsulfatase at 8.61 nmol/hour/mL (normal: >7 nmol/hour/mL). These results suggest the diagnosis of SD.

Treatment

Early genotyping during the presymptomatic phase and diagnosis are crucial for controlling disease progression. Treatment with n-butyldeoxynojirimycin (NB-DNJ) showed effective results when therapy is given before the onset of symptoms. Supportive care is advocated to maximize motor function and speech and to aid in normal activities required for daily living and communication. To provide adequate nutrition and hydration, prevent infection, control seizures, and prevent deformities are other modalities advised in these cases as per the requirement.

Subacute juvenile Sandhoff disease needs multidisciplinary involvement, including a physiotherapist, speech therapist, psychiatrist, etc., to regularly monitor the prognosis as well as diagnose future manifestations requiring supportive care and to provide adequate functioning and activity of daily living.[3] As the treatment objective is to prevent progression, periodic evaluation with MRI of the brain, EEG, assessment of motor, adaptive, cognitive regression, and speech evaluation are mandatory for a comprehensive treatment plan.

Recent Advances in Managing Subacute Juvenile Sandhoff Disease

Administration of N-acetyl-L-leucine, oral venglustat, a combination therapy using miglustat, and the ketogenic diet, etc., are in various stages of investigation in the treatment of SJSD.[3]

Added Care to be Taken while Treating Subacute Juvenile Sandhoff Disease

Avoid positioning with risk of aspiration, extended periods of immobility that might cause contracture or pressure sores, circumstances with increased fall risk, like walking on uneven or unstable surfaces, and higher doses of antiepileptic drugs causing drowsiness.[3]

Prognosis

Not much literature is published to shed light on how SJSD impacts daily lives and function. However, the functional limitations resulting from neurodegeneration might adversely impact daily activities. Lack of independence and self-esteem in the growing child may result in long-term emotional and social effects that negatively impact the patient's quality of life. Hence, regular follow-up is required for periodic assessment of neurologic decline, seizures, speech, etc. In severe cases of SJSD, the rapid course of the disease results in serious complications and eventual death.[3]

Genetic Counseling

As SJSD is inherited in an autosomal recessive manner, the parents are presumed to be heterozygous for a *HEXB* pathogenic variant. Hence, molecular genetic testing is recommended to allow future risk assessment. The risk of recurrence in the family should be explained, and carrier testing for at-risk relatives should be advised.[3] Prenatal testing and preimplantation genetic testing are recommended in affected families for confirmation of the risk assessment. Expanded carrier screening (using next-generation sequencing for variant detection of serious recessive disorders) is advised for couples without an existing family history of a genetic condition.[9]

Discussion

Subacute juvenile Sandhoff disease is an autosomal recessive lysosomal storage disorder that results in a reduction in the ability of cells to catabolize GM2 gangliosides. This leads to the gradual accumulation of GM2 gangliosides within visceral cells and neurons, subsequently resulting in cell death. The ganglioside GM2 content of the brain increases to 100–300 times the normal amount, and similar abnormal amounts are seen in visceral organs. Gangliosides play an important role in modulating intracellular and intranuclear calcium homeostasis, thus ensuring cellular functions.[7] Accumulation of calcium associated with the collection of GM2 ganglioside leads to gliosis and loss of myelin and axons in the cortical neurons.[1] This GM2 accumulation might result in progressive motor and sensory dysfunctions and deterioration in spatial learning and memory with age.[7] Symptoms of neurodegenerative disorders manifest in abnormal gait, ataxia, spinocerebellar and motor neuron dysfunction, increased myotonic reflexes, and motor deterioration.[8] These children develop normally and attain all milestones at appropriate ages, and degeneration starts between the ages of 2 and 5 years.

Genetic analysis revealed the mutation in the lysosomal enzyme *HEXB*.[5,10] Defects in lysosomal glycosidase or specific coactivators result in the accumulation of substrates like glycosphingolipids, including gangliosides.[11] Ganglioside deficiency due to its improper catabolism might result in enhanced cell apoptosis, axonal degeneration, and disturbances in axon-glia interactions in the cerebral cortex. Absence or deficiency of gangliosides is detected in the pathology of many diseases.[7]

The progressive neurodegeneration impairs limb coordination, causes abnormal gait, fatigue, and other functional limitations. Over time, SJSD shows progressive weakness, intellectual disability,

impaired hearing and vision, exaggerated startled response, seizures, and death at an earlier age.[6]

Depending on the symptoms and severity, SJSD can be subdivided into four stages: the presymptomatic phase, the early symptomatic phase showing tremors but with muscle strength and coordination not yet affected, the late symptomatic phase with progressive muscle wasting resulting in loss of muscle coordination, and the terminal phase.[12]

Clinical variability can be observed among families with the SJ phenotype. Individuals with one null variant (non-expressing) and one missense variant develop SJSD.[3] Serum testing for enzyme activity of *HEXA* and *HEXB* confirms the diagnosis. Comprehensive genome testing and genome sequencing confirm the diagnosis of the phenotype.[1,3] Once the diagnosis has been established, the clinical management of the child depends on the age of presentation, site involved in the brain, and severity of neuroregressive changes. Periodic evaluation with MRI of the brain, assessing motor, adaptive, cognitive development, and speech evaluation, is mandatory for a comprehensive treatment plan.

Conclusion

Subacute juvenile Sandhoff disease is one of the genetic disorders characterized by the accumulation of ganglioside GM2, which is evidenced by a defect in acetyl hexosaminidase activity. Until now, no correlation has been observed between the genotype and phenotype in SJSD. The recently acquired knowledge about mutations will facilitate genetic counseling and prenatal diagnosis in affected families. More research is required to disclose the consequences and impact of this disease and to analyze the effects of novel treatments from the patient's perspective. Early genotyping and diagnosis during the presymptomatic phase are crucial for controlling disease progression. Further insights are required into measures to increase life expectancy in children.

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