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## Infantile Type Sandhoff Disease with Striking Brain MRI Findings and a Novel Mutation

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### Summary

**Background:**

Sandhoff disease is an autosomal recessive disorder caused by  $\beta$ -hexosaminidase deficiency in which the ganglioside GM2 and other glycolipids accumulate intracellularly within lysosomes. This process results in progressive motor neuron manifestations, death from respiratory failure and infections in infants.

**Case Report:**

This report presents a 22-month-old girl with infantile type Sandhoff disease that was hospitalized for generalized seizures and psychomotor retardation. She was diagnosed with a genetically proven novel mutation and by demonstrating its specific imaging findings.

**Conclusions:**

Determination of specific changes in neuroimaging which are initial findings for GM2 gangliosidosis is important from the point of diagnosis and follow-up in infants suspected of having a neurodegenerative disease.

**MeSH Keywords:**

Brain Diseases, Metabolic • Lysosomal Storage Diseases, Nervous System • Magnetic Resonance Imaging • Sandhoff Disease

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### Background

GM2 gangliosidosis is a group of lysosomal enzyme disorders with autosomal recessive transmission in which the ganglioside GM2 and other glycolipids accumulate intracellularly within lysosomes, dominantly within neurons [1,2]. There are 3 main types, i.e. of B, O and AB. These groups are also divided into three subtypes: infantile, juvenile, and adult. Sandhoff disease, also named infantile type O, is characterized by hexosaminidase B subunit deficiency [1]. Here, we present a case report of an infant with Sandhoff disease by demonstrating its specific brain magnetic resonance imaging (MRI) findings with a genetically proven novel mutation.

### Case Report

A 22-month-old girl was hospitalized for generalized seizures and psychomotor retardation. She was born after an

uncomplicated full-term pregnancy by vaginal delivery. The inception of clinical symptoms started at the age of 6 months with diarrhea, recurrent fever and vomiting with elevated liver enzymes. Patient's history revealed that she had been diagnosed as lysosomal and lipid storage disease in two different clinics. The onset of tonic seizures began at the age of one and continued for a minute. The parents had a third-degree consanguinity and two cousins of the father were expired at the age of 18 months because of Sandhoff disease. Physical examination found macrocephaly of 52 cm (>97 percentile). Her weight was 12 kg (25–50 percentile) and height was 87 cm (75–90 percentile). Fundoscopy demonstrated cherry red spots at the maculae. Ichthyosis of the skin, rocker bottom foot, valgus and equinus deformity of the foot (Figure 1), and hepatomegaly were present. Enzyme assay revealed marked reduction of hexosaminidase A and B levels in the serum. We found a homozygous missense mutation in the patient for HEXB gene which is located at 5. chromosome which was not defined in the



**Figure 1.** Rocker bottom foot, valgus and equinus deformity of the foot is demonstrated.

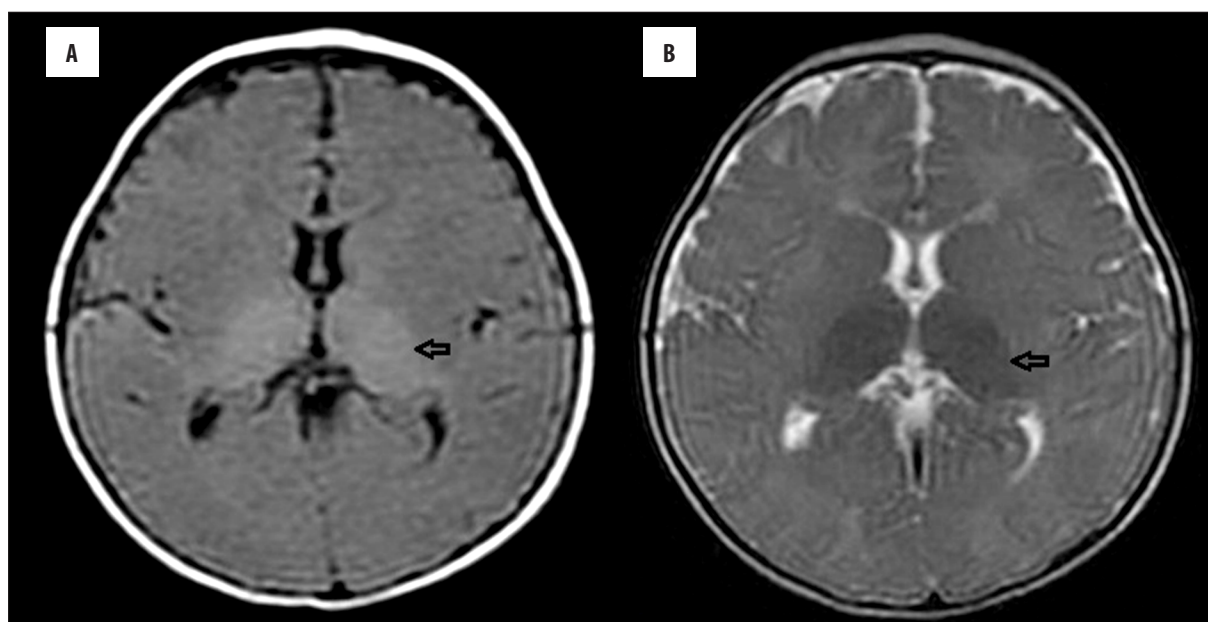
literature before. This mutation for HEXB (1447G→A) was identified in the cDNA and genomic DNA coding for the  $\beta$ -hexosaminidase. The patient was homozygous and her parents were both heterozygous for this mutation which should have resulted in a glycine-to-serine substitution at codon 483. Computer-assisted analysis of this amino acid substitution predicted alteration in the secondary structure in the region of a highly conserved sequence. First brain MR imaging without contrast medium injection was performed at the age of 10 months and it showed increased T1 signal of bilateral thalamus and delayed myelination (Figure 2). A follow-up non-contrast MRI was performed at the age of 16 months and it revealed diffuse high-signal intensity in the superficial and deep cerebral

white matter including the external capsule. Corpus callosum was thin but showed no signal abnormality. There was bilateral symmetric increased T1 and decreased T2 signal of the anterior thalamus, and increased T2 signal of the dorsal thalamus. Also, there was high T2 signal intensity of the external capsule, extreme capsule, bilateral putamen, right caudate nucleus and anterior part of pons which includes corticospinal tracts. Slight cortical atrophy and a thin corpus callosum with normal signal intensity were noted (Figure 3). According to these findings the patient was diagnosed as Sandhoff disease.

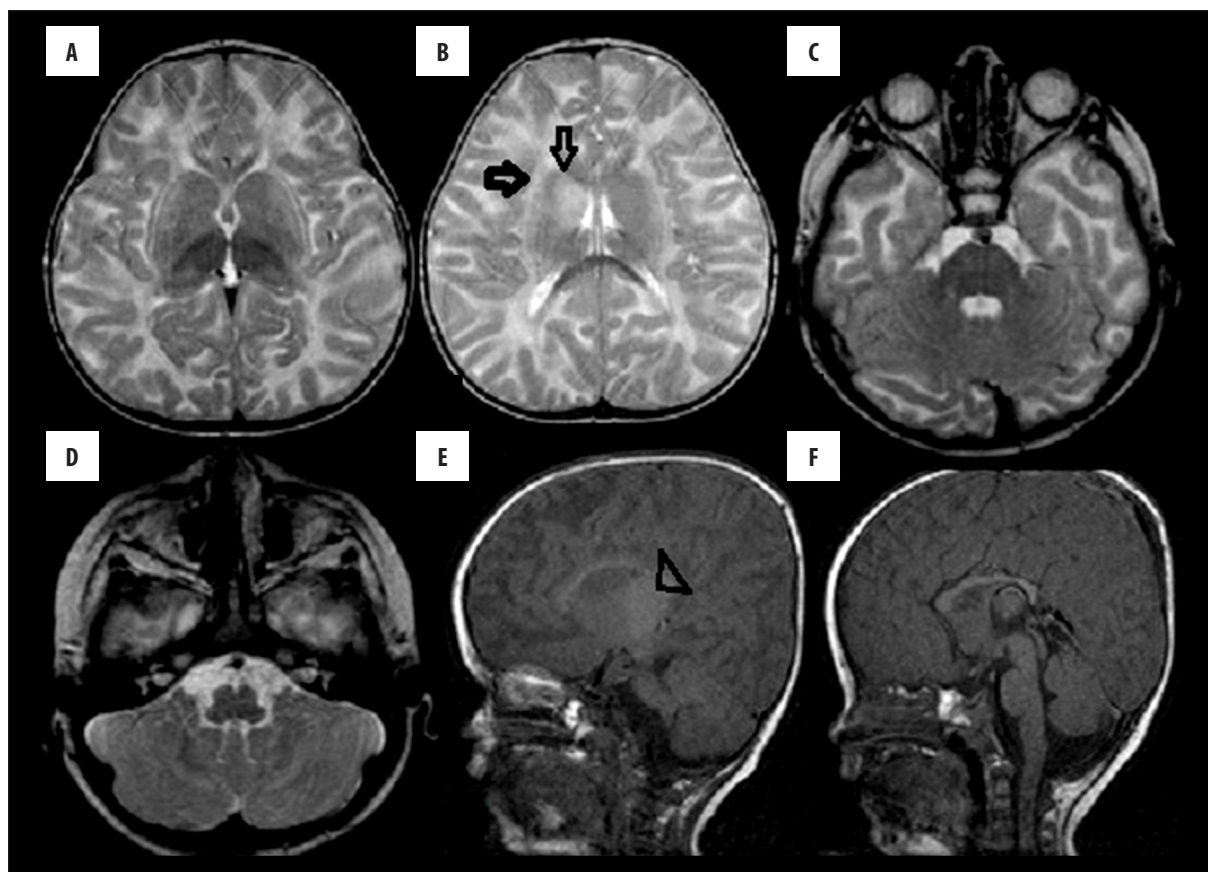
## Discussion

Sandhoff disease is the heavy subtype of GM2 gangliosidosis, which is attributable to a deficiency of b-hexosaminidase B-subunit resulting in progressive motor neuron manifestations and death from respiratory failure and infections in infants [4]. The diagnosis of Sandhoff disease is based on decreased levels of hexosaminidases A and B. Another common form of GM2 gangliosidosis, Tay Sachs disease, is characterized by reduction of the levels of only hexosaminidase A [3]. The enzyme deficiency causes inability to hydrolyze intracellular lysosomal ganglioside GM2, which leads to lysosomal swelling and cellular destruction [4]. This process ends with delayed myelination and myelin breakdown [2]. Clinically, it is classified into infantile, juvenile or adult forms, with the infantile-onset form being a rapidly progressive neurologic dysfunction and usually death by the age of 3 [1].

Specific property of the infantile form of Sandhoff disease is early beginning of symptoms, generally in the first 6 to 18 months of life [3]. Progressive psychomotor retardation, macular red cherry spot, blindness, and hypotonia are the main clinical findings [1]. After 2 years of age, macrocephaly is typical and during the disease process,



**Figure 2.** First MR examination at the age of 10 months demonstrates bilateral symmetric thalamic T1 hyperintensities on image (A) and T2 hypointensities on image (B) (arrows). Also delayed myelination and mild T2 signal increase in frontoparietal white matter are seen on image (B). Corpus callosum is spared.



**Figure 3.** Axial T2-weighted images in (A–C) and d reveal diffuse, symmetrical hyperintensity in the periventricular, deep, and subcortical white matter, dorsal thalami (A), the external (thick arrow) and extreme capsules, and cerebellar white matter Short T2 relaxation time is seen in the ventral thalamic nucleus, resulting in hypointensity. Right caudate nuclei and bilateral putamen appear swollen, and show hyperintense appearance (thin arrow). On image (D, E), hyperintense thalami (arrowhead) and an intact thin corpus callosum can be seen.

spasticity, dystonia, rigidity, choreiform movements, and athetoid posturing are often demonstrated. Seizures usually begin after the first year of life and mostly tonic-clonic or myoclonic [1]. Pathogenic mutations in *HEXB* gene leads to enzyme activity diminution and prevention of normal metabolic cycle of GM2 ganglioside in Sandhoff patients [2]. The only treatment for the disease is supportive therapy.

Studies on magnetic resonance imaging in Sandhoff disease suggested bilateral thalamic hyperdensity on computed tomography and hypointensity on T2-weighted MRI images as the earliest diagnostic markers of Sandhoff disease [5,6]. The calcium accumulation which is linked with the intracellular collection of GM2 ganglioside, loss of axon and myelin in the central cortical neurons, and gliosis were suggest to be the reasons of hypointense thalami and these findings are described as the significant features of the infantile form of Sandhoff disease [1,2,4] There is no correlation between the severity of the central nervous system imaging findings and the clinical presentation [1].

Several other reports in the literature have shown mild cortical atrophy, corpus callosum thinning, and abnormal signal intensities in the cerebral white matter, caudate nucleus, globus pallidum, putamen, cerebellum, and brain stem involvement as the neuroimaging findings of

Sandhoff disease [4]. A hyperdense thalamus on CT scans and hypointense thalamus on T2-weighted MR imaging are also observed in Krabbe's disease but white matter abnormalities extend to larger areas, more homogenous, and include the corpus callosum [7]. The cerebral white matter revealed homogenous or patchy hyperintensity which is in relation with a combination of disturbed and abnormal myelination and myelin loss. In all reported patients the corpus callosum is well myelinated and intact [1]. Infratentorial involvement is regarded as the extension of the primary abnormalities of the supratentorial white matter through the corticospinal tracts. Magnetic resonance spectra obtained from the thalami and basal ganglia show decreased N-acetylaspartate and moderately increased choline and lactate. More prominent neuronal loss is observed in the thalami. These findings in the cerebral white matter are secondary to delayed myelination and demyelination [4]. MRI findings in our case were consistent with the reported features of Sandhoff disease (Figures 1, 2).

## Conclusions

Determination of neuroimaging findings for GM2 gangliosidosis is essential from the point of early diagnosis, therapy and follow-up in infants suspected of having a neurodegenerative disease.

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