Sandhoff disease in two siblings of a Malaysian family: Description of novel beta hexosaminidase mutations, magnetic resonance imaging, and spectroscopic findings

Sir,

Sandhoff disease (OMIM#268800) is a rare, severe, autosomal recessive lysosomal storage disorder, which is caused by a mutation in the beta subunit of the hexosaminidase A and B enzymes, resulting in an accumulation of glycosphingolipids and oligosaccharides in the brain. This leads to progressive destruction of neurons in the brain and spinal cord causing developmental regression and death.[1] Bilateral thalamic involvement has been suggested as a diagnostic marker of this disease along with involvement of the cerebral white matter, basal ganglia, and cerebellum.[2] Here, we present a patient, who along with his sibling, was affected by Sandhoff disease. He demonstrated changes in the basal ganglia, diffuse asymmetric hypomyelination–dysmyelination syndrome, and cerebral hemiatrophy.

A one-year-old boy, born of nonconsanguineous parents, presented with a 6-month history of psychomotor regression, exaggerated startle reaction to sound, and myoclonic seizures. Neurological examination revealed hypertonia, absent reflexes, and a weak muscle power. Ophthalmological examination showed the presence of bilateral “cherry red spots” in the retina. His eldest sister presented at 8 months of age with hand tremors, unsteady gait, uprolling of eyes, and twitching of the mouth. She had regression of her milestones and generalized convulsions; her ophthalmological examination also revealed “cherry red spots.” She died at 17 months of age. His three other sisters were well.

Enzyme studies showed a low total beta-hexosaminidase activity of 3 nmol/min/mg protein (normal: 10–50) and a reduced beta-hexosaminidase of 2.2 nmol/min/mg protein (normal: 3.0–20.0), indicating the diagnosis of Sandhoff disease. Mutation analysis of the beta-hexosaminidase gene showed the presence of compound heterozygote mutations of c.1262_1266delGTTGAA (p.Val,Glu421_422del) and c.1645G>A (p.Gly549Arg), which were predicted to be the probable causative deleterious mutations; both these mutations have not been previously described. Targeted testing of the parents showed that the father and mother were carriers for the mutations c.1262_1266delGTTGAA and c.1645G>A, respectively. The sister’s diagnosis was confirmed by enzymatic analysis.

Magnetic resonance imaging (MRI) of the brain (3T General Electric, USA) revealed left cerebral hemiatrophy, with diffuse hypointense signal abnormalities in bilateral thalami and corticospinal tracts of the substantia nigra on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images [Figure 1]. The right caudate nucleus and putamen were hyperintense and swollen. There was delayed myelination of the right frontoparietal white matter and the right splenium of corpus callosum. The brainstem, cerebellum, left superior central left parietal lobe, and rest of the corpus callosum showed age-appropriate myelination. The caudate nucleus, globus pallidus, and brainstem were normal. Using magnetic resonance spectroscopy (MRS) in single voxel stimulated echo acquisition mode, acquisition of bilateral basal ganglia revealed diminished N-acetylaspartate metabolite peaks (TR: 1960, TE: 98.8) suggestive of neuroaxonal dysfunction and an abnormal peak configuration of amino acids around 2.07 ppm [Figure 2]. Unfortunately, the child passed away at 31 months of age.

Sandhoff disease is caused by mutation in the beta-subunit of the hexosaminidase gene on chromosome 5q13, which is critical for the synthesis of lysosomal enzymes beta-hexosaminidase A and B. The mutations identified in this family suggest that the compound heterozygote mutations of c.1262_1266delGTTGAA (p.Val,Glu421_422del) and c.1645G>A (p.Gly549Arg) are associated with severe clinical presentations of Sandhoff disease, indicating that these mutations are likely responsible for the clinical phenotype observed in this family.
Letters to Editor

There are three subtypes of GM2 gangliosidosis, i.e., classic infantile, juvenile, and adult late-onset. On the basis of the clinical presentation and severity of symptoms, our siblings had the classic infantile subtype of the disease. There is no treatment for Sandhoff disease, and the infantile form leads to death by the age of 3 years. Genetic counselling and supportive therapy are the current management options.\(^\text{[1]}\)

MRI of GM2 gangliosidosis typically demonstrates hypointensity on T2-weighted images of the thalamus.\(^\text{[2,3]}\) There was variable involvement of the caudate nucleus, putamen, globus pallidus, brainstem, and cerebellar white matter.\(^\text{[2,3]}\) Other studies have also reported T2 signal hyperintensities in the caudate nucleus, globus pallidus, and putamen.\(^\text{[2,3]}\) Patchy or homogenous hyperintensities in the cerebral white matter suggest a combination of abnormal myelination or myelin loss. However, in all affected patients, the corpus callosum was intact and myelinated.\(^\text{[2]}\) Our patient’s MRI demonstrated signal abnormalities within the thalami, cerebral white matter, and substantia nigra. However, the caudate nucleus, globus pallidus, and brainstem were spared.

Figure 2: Magnetic resonance spectroscopy single voxel stimulated echo acquisition (TR/TE = 1960/98.8 ms) of the right (a) and left (b) lentiform nuclei demonstrating unusual peak configuration near 2.07 ppm (c and d).

Our patient was also noted to have diffuse T2-weighted cerebral white matter hypointensities. These are late occurring and are thought to be due to secondary demyelination caused by neuroaxonal dysfunction.\(^\text{[2]}\) Other studies have proposed a combination process of delayed myelination and dysmyelination.\(^\text{[2]}\) Apart from Sandhoff disease, bilateral thalamic T2 hypointensities are also seen in other lysosomal diseases, as well as in ceruloplasmin deficiency with hemosiderosis and neuronal ceroid lipofuscinosis.\(^\text{[2]}\)

A recently published study by Lowe et al., showed a new 2.07 resonance on MRS of the brain of a Sandhoff mouse.\(^\text{[6]}\) Wilken et al., reported similar findings on the MRS of a child with Sandhoff disease.\(^\text{[7]}\) Elevated N-acetylhexosamine in the white matter and thalamus corresponded to accumulation of hexosamine-containing oligosaccharides, which appear to be a specific marker for Sandhoff disease. MRS of the white matter, gray matter, and basal ganglia also showed a reduction of total N-acetylaspartate, which is a marker for intact neuroaxonal tissue, and markedly elevated inositol, which is a glial marker found in astrocytes. The MRS picture was a validation of the presence of neuroaxonal damage and gliosis.\(^\text{[7]}\) However, it was shown that there was no correlation between the levels of oligosaccharides and disease severity.\(^\text{[7]}\) Our patient’s MRS also demonstrated an abnormal peak close to the N-acetylaspartate consistent with elevated N-acetylhexosamine in both basal ganglia associated with reduced N-acetylaspartate. Human data have shown this metabolite to be most evident in the white matter and thalamus, and to a lesser degree, within the paramedian parietal gray matter; though this was not seen within the basal ganglia.\(^\text{[7]}\) Interestingly, our patient’s MRS showed elevated N-acetylhexosamine within the basal ganglia region. However, this N-acetylhexosamine resonance was more prominent in the white matter.

The recognition of N-acetyl moiety of N-acetylhexosaminase resonance as a specific finding in Sandhoff disease promotes the use of MRS as a noninvasive modality in the diagnosis and monitoring of disease progression in Sandhoff disease. We suggest that brain MRS be performed in all infants with a suspected neurodegenerative disease and delayed development, especially in those who have been found to be having bilateral thalamic abnormalities on computed tomography and MRI.

We report two new disease-causing mutations: 1262_1266delGTTGAA and c. 1645G>A. These novel findings contribute towards enhancing our understanding of genotype–phenotype correlation, particularly with regard to the neuroimaging findings.\(^\text{[7]}\) There is evidence of intrafamilial variability in the phenotype, as our patient had a delayed onset of symptoms, a variable presentation and a longer period of survival, despite having an identical genotype with the sibling. Hence, there was only moderate genotype–phenotype correlation in this family. Further MRI spectroscopy and molecular studies of Sandhoff disease in Asian children will be vital.

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Conflicts of interest
There are no conflicts of interest.

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