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Case Report

Infantile Sandhoff Disease: Unusual presentation

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ARTICLE INFO

Article history:

Received 22 April 2012

Accepted 16 November 2015

Available online 22 February 2016

Keywords:

GM2 gangliosidosis

Hexosaminidases

Sandhoff disease

Introduction

Sandhoff disease is a rare autosomal recessive disorder of sphingolipid metabolism that results from deficiency of the lysosomal enzymes, β -hexosaminidase A and B.¹ The resultant accumulation of GM₂ ganglioside within both grey matter nuclei and myelin sheaths of the white matter results in eventual severe neuronal dysfunction and neurodegeneration. Disease progression is rapid, resulting in early death. Currently, there is no definitive treatment, with therapy remaining primarily supportive. We report a case of infantile Sandhoff disease with characteristic clinical and imaging features.

Case report

A 22-month-old male patient presented with myoclonic seizures aggravated by loud noise and psychomotor regression.

He had been hospitalized thrice before, twice for uncontrolled seizures and once for pneumonia. He was the second child of unrelated parents, born at term without any remarkable antenatal or natal history. The elder sister and parents were healthy. He had shown normal development until 8 months of age when the mother first observed progressive loss of power for holding his head and moving his limbs. Initially, myoclonic seizures of the face and upper limbs and later generalized seizures usually after a loud noise began to be noticed after 1 year of age. On examination, he had only mild dysmorphic features consisting of a frontal bossing and a high arched palate. The neurological examination revealed psychomotor retardation, bilateral nystagmus, exaggerated startle response, axial hypotonia with muscle weakness and brisk reflexes. He could not follow objects and had neither visual attention nor eye contact. His fundii examination revealed chalk-white macular areas with a “cherry red spot” in the centre of both eyes without optic atrophy. He had hepatosplenomegaly. Other systemic examination was normal.

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0377-1237/© 2016 Published by Elsevier B.V. on behalf of Director General, Armed Forces Medical Services.

Fig. 1 – Axial T2WI MRI scan at the thalamic level showing bilateral diffusely hypointense thalami, hyperintense caudate nucleus, putamen, globus pallidus and prominent ventricles.

His routine investigations revealed a normal hemogram and serum electrolytes. Chromosomal analysis was normal. His electroencephalogram revealed an abnormal pattern suggestive of myoclonic seizures. Chromatography of amino acids in the blood, urine and cerebrospinal fluid was normal and chromatography of organic acids in the urine was also normal. Echocardiogram showed no cardiovascular abnormality. MR imaging was done on a 1.5 T Signa Excite HD, General Electric Company, USA. Multiplanar MR imaging was done using T1 FLAIR, T2 FLAIR and T2W FSE. The study revealed bilateral, diffuse, T1 hyperintense (Fig. 1), T2 hypointense (Fig. 2) thalami. Hyperintensity of the putamen, globus pallidus was noted bilaterally on T2W FSE. Magnetic resonance imaging (MRI) also revealed a delayed myelination pattern for age, with no visible areas of diffusion restriction. There was evidence of cerebral atrophy with mild ventriculomegaly. Computed tomography (CT) revealed bilateral diffuse hyperdense thalami (Fig. 3). Based on these features, a diagnosis of Sandhoff disease was made. Assaying for the enzymatic activity revealed a deficiency of both hexosaminidases A and B confirming the diagnosis of Sandhoff disease. His parents' specimen showed decreased activities of total Hexosaminidases and relative preservation of Hex A, suggesting carrier status of the disease. The patient was on follow-up till 6 months after which he was lost to follow-up.

Discussion

Sandhoff disease is a rare autosomal recessive disorder of sphingolipid metabolism, with a reported incidence of 1 in

Fig. 2 – Axial T1WI MRI scan at the thalamic level showing bilateral diffusely hyperintense thalami.

384,000 live births, related to a genetic deficiency of the enzyme β -hexosaminidase.¹ There are two active forms of this enzyme β -hexosaminidase A, composed of one α and one β subunit, and β -hexosaminidase B, which contains two β subunits.² The gene HEXA encodes the α subunit, and mutations affecting this gene result in a deficiency of β -hexosaminidase A, clinically known as Tay-Sachs disease.^{1,2} In Sandhoff disease, both β -hexosaminidase A and B have been found to be deficient secondary to mutations within the HEXB gene which encodes the common β subunit.^{1,2}

Fig. 3 – Axial non-contrast CT scan at the thalamic level showing a bilateral thalamic hyperdensity.

As per clinical presentation, Sandhoff disease is of three types classical infantile, juvenile/subacute and adult/chronic. The infantile form has an onset between 3 and 9 months of age,³ following initial normal development. Clinical manifestations include regression of milestones, muscular hypotonia, startle response followed by spastic quadriparesis and seizures.^{3,4} Macular cherry red spots are occasionally observed, though this finding is non-specific. There is rapid progression of disease with death occurring by 3–5 years of age. The juvenile/subacute variant is seen between 2 and 5 years of age and the adult/chronic variant is seen in the second or third decade. Both these have a better survival rate.⁴

Bilateral symmetric changes in thalamus are an early finding that is specific to GM₂ gangliosidosis like Sandhoff disease in infants with neurodegenerative disorders.⁵ The thalami are usually homogeneously hyperdense on CT⁶ and T2 hypointense and T1 hyperintense on MRI.⁷ MR findings include T2 hyperintense signals within caudate nucleus, globus pallidus and putamen.^{5,8}

Hypointense T2 signal in thalamus is seen in Tay–Sachs disease, late stages of Canavans disease and Krabbes disease. Canavans will show white matter necrosis resulting in cavitation as well. In Krabbes disease, more cerebral structures show hyperdensity on CT with more extensive white matter disease.^{8,9}

Proton MR spectroscopy may reveal increase in a specific marker N-acetylhexosamine at 2.07 ppm in white matter and thalamus in patients of Sandhoff disease.¹⁰ Management is mainly supportive in infantile Sandhoff disease as there is no definitive cure. However, therapeutic interventions are being attempted in juvenile varieties of Sandhoff disease.^{11,12} Our case highlights the typical imaging features of this extremely rare disorder.

Conflicts of interest

The authors have none to declare.

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