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Case Report

Early cardiac involvement in an infantile Sandhoff disease case with novel mutations

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Abstract

Introduction: Hepatosplenomegaly is often present in infantile Sanshoff disease. However, cardiac involvement is extremely uncommon.

Case report: We describe a 14-month-old female baby who exhibited mitral regurgitation and cardiomegaly at the age of 2 months, dilation of the left atrium and left ventricle at age of 6 months, followed by regression of developmental milestones after an episode of minor infection at age of 14 months. Brain magnetic resonance imaging revealed signal changes over the bilateral thalami, bilateral cerebral white matter and left putamen. An examination of the fundus showed presence of cherry-red spots in both macular areas. The lysosomal enzymatic activities showed a marked reduction of β-hexosaminidase B (HEXB) activity. Two novel mutations of HEXB gene were identified. One of the mutations was a c.1538 T > C mutation, which predicted a p.L513P amino acid substitution of leucine to proline; the other was a c.299 + 5 G > A mutation, which was a splice site mutation.

Conclusion: Cardiac involvement might occur prior to neurological symptoms in infantile Sandhoff disease, and it should be included in the differential diagnoses of metabolic cardiomyopathies in the infantile stage.

Keywords: Metabolic cardiomyopathy; Infantile Sandhoff disease; HEXB gene mutation; Cardiac manifestations; Neurological features

1. Introduction

Sandhoff disease (SD) (MIM 268800) is a rare, autosomal recessive lysosomal storage disorder, which is caused by a deficiency of β-N-acetylhexosaminidase (HEX). HEX comprises two subunits, α and β, that dimerize to form separate isozymes of HEXA (αβ) and HEXB (ββ). The HEXB gene located on chromosome 5q13 encodes the β subunit. Mutations in this gene are causative of SD because of loss of both the HEXA and the HEXB enzymes, leading to the neural deposition of GM2 ganglioside, its asialo derivative, and the neural and visceral accumulation of globoside. An excess accumulation of this particular sphingolipid is found primarily in liver, spleen, heart, kidney, and brain [1,2]. SD is characterized by progressive neurodegenera-

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tion. The clinical phenotypes associated with SD have been classified according to the age of onset of symptoms and thus there are three forms of the disease: infantile, juvenile, and adult forms of the disease.

The infantile SD is characterized by early onset of symptoms, which usually occur between the ages of 2–9 months [3,4]. Clinical features of hyperacusis with excessive startle response, developmental delay or regression, together with axial hypotonia and bilateral pyramidal signs, visual deterioration with macular cherry-red spots, and seizures are clinical hallmarks of this disease. This form is usually characterized by stereotypical progression of disease, leading to death before the age of 4 years [3,4]. Unlike Tay-Sachs disease, hepatosplenomegaly is often present in SD. However, cardiac involvement in SD patients is extremely uncommon.

Here we report an infantile SD patient, who exhibited cardiac involvement prior to typical neurological manifestations and was diagnosed with a marked reduction of HEXB enzyme activity and novel HEXB gene mutations.

2. Case report

The female patient was the first child of healthy nonconsanguineous parents. Both the pregnancy and delivery were normal. Family history was unremarkable. According to her mother, she exhibited elevated noise sensitivity and experienced recurrent symptoms of upper respiratory tract infection during infancy. At 2 months of age, a chest radiograph revealed cardiomegaly and echocardiography (ECG) showed mitral regurgitation (MR). She developed normally until the age of 3 months, when loss of head control was observed. At 6 months of age, follow-up ECG showed MR and dilatation of the left atrium (LA) and left ventricle (LV). Developmental delay became evident, which included head lag, fisted hands, use of cooing to express herself, and poor eye contact. She was then entered into a rehabilitation program. At 13 months of age, improvement of developmental milestones was observed after rehabilitation. She could control her head in an upright position and sit with assistance, transfer objects, laugh out loudly, and recognize strangers. At 14 months of age, unfortunately, regression of developmental milestones and seizure-like events developed after an episode of upper respiratory tract infection. She was referred for further evaluation.

Upon admission, physical examinations showed head circumference 49 cm (>97th percentile), body weight 9.5 kg (50th percentile) and body height 73 cm (3–15th percentile). Her skull shape was normal with closed fontanelles and sutures. The child had facial dysmorphism with coarse facial features, frontal bossing, expressionless face, depressed nasal bridge, and an inverted V-shaped lip. Occasional upward gaze was noted. A grade III/VI systolic ejection murmur over the apex was auscultated. Abdominal examination showed the liver was located 2 cm below the right costal margin with soft consistency. Neurological examinations revealed generalized weakness, drowsy consciousness, intact cranial nerves, axial hypotonia with limb spasticity, muscle power 2/5, brisk deep tendon reflexes, and an upward response of plantar reflex. With respect to developmental milestones, she exhibited loss of searching for an

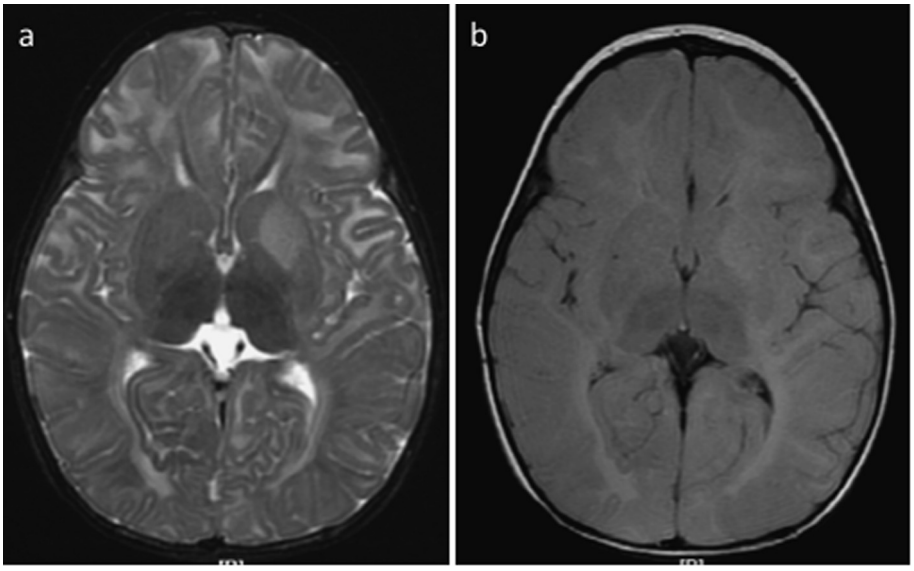

Fig. 1. Brain MRI of the index case. Axial images, T2-weighted image (TE 80 msec, TR 6000 msec) (a) and FLAIR image (TE 84msec, TR 9002 msec) (b), show hyposignal intensity in the bilateral thalami compared to the cerebral cortex, and hypersignal intensity in the cerebral white matter and the left putamen.