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Case Report

Miglustat therapy in a case of early-infantile Niemann-Pick type C

Miho Usui [a], Akihiko Miyauchi [a], Yuko Nakano [b,a], Sachie Nakamura [a], Eriko Jimbo [a], Shinji Itamura [c], Kaori Adachi [d], Eiji Nanba [d], Aya Narita [e], Takanori Yamagata [a], Hitoshi Osaka [a,*]

[a] *Department of Pediatrics, Jichi Medical University, Tochigi, Japan*
[b] *Department of Pediatrics, Ashikaganomori Ashikaga Hospital, Ashikaga, Japan*
[c] *Department of Child Neurology, Hiroshima City Hospital, Hiroshima, Japan*
[d] *Division of Functional Genomics, Research Center for Bioscience and Technology, Tottori University, Yonago, Japan*
[e] *Department of Child Neurology, Tottori University, Faculty of Medicine, Yonago, Japan*

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Abstract

Niemann-Pick disease type C (NPC) is a rare, progressive autosomal recessive disease. It is caused by mutations in either the *NPC1* or *NPC2* genes, resulting in defective regulation of intracellular lipid trafficking. Miglustat, which reversibly inhibits glucosylceramide synthase, reportedly has beneficial effects on the progressive neurological symptoms of NPC and was approved in Japan in 2012. Some reports suggested that miglustat therapy delayed the onset or progression of NPC when treatment was initiated before the onset of neurological manifestation or at an early stage. We report here a patient with the early-infantile form of NPC who started on miglustat at 4 months of ages. To our knowledge, this patient is the youngest reported patient with NPC in which miglustat therapy was initiated. Our patient, who had hypotonia and developmental delay before treatment, remained stable and showed no new neurological symptoms. In addition, pulmonary involvement was improved during miglustat therapy. Our case and previous reports underscore the importance of early initiation of miglustat therapy for NPC.

Keywords: NPC; Early infantile; Miglustat; Lung involvement

1. Introduction

Niemann-Pick disease type C (NPC) is a rare, progressive autosomal recessive disease. It is caused by mutations in either the *NPC1* or *NPC2* gene (OMIM #607623, 601015), resulting in intracellular lipid trafficking regulation defects. Mutations in *NPC1* are more common than those in *NPC2*, and are detected in ~90% of patients with NPC. The estimated birth incidence of NPC is 1 case in 100,000–120,000 newborns in Europe. There are five clinical phenotypes based on the age at onset of neurological manifestations: the perinatal, early-infantile form (<2 years), late-infantile form (3–5 years), juvenile form (5–16 years), and adult forms (>16 years). Manifestations are typically more severe in cases with earlier onset and the prognosis is worse. In patients with the early-infantile form, hepatosplenomegaly is often detected within the age of first month of age. Hypotonia and psychomotor delay appear by the age of 1–2 years. The prognosis of the patients with early-infantile form is poor; they

* Corresponding author at: Department of Pediatrics, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke-city, Tochigi, Japan. Fax: +81 285 44 8329.
E-mail address: hosaka@jichi.ac.jp (H. Osaka).

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often die within 5 years old due to neurological progression [1].

Miglustat, which reversibly inhibits glucosylceramide synthase, reportedly has beneficial effects on the progressive neurological symptoms of NPC and is approved in 45 countries. The beneficial effects of miglustat were limited in patients with the early-infantile form in advanced stages, suggesting the importance of early diagnosis and initiation of therapy [2]. However, there are few reports regarding the use of miglustat therapy in the early stage of NPC.

Here, we report one early-infantile case diagnosed with NPC at 3 months of age in whom miglustat therapy was initiated at 4 months of age.

2. Case report

The patient was a 2-year-old boy born to non-consanguineous parents. There was no family history of neurological or metabolic disease. He was born via normal delivery at 39 weeks gestation and weighted 2,945 g. He received phototherapy and a partial blood exchange because he was diagnosed with hyperbilirubinemia at 2-days-old (T-Bil 15.5 mg/dL; D-Bil 2.2 mg/dL). He exhibited tachypnea and hypoxia ($SpO_2 < 90\%$) at 6-days-old and oxygen therapy was started (0.5 L/min). At the age of 2 months, he displayed hypotonia, poor sucking, and hepatosplenomegaly. Biochemical analysis showed liver dysfunction (AST 291 U/L, ALT 80 U/L) and hyperbilirubinemia (T-Bil 5.7 mg/dL; D-Bil 4.5 mg/dL). Cholescintigraphy showed no abnormalities. Chest computed tomography (CT) showed frosted-glass formed low-attenuation areas in the bilateral dorsal lung. Interstitial pneumonia with thickening of the lung lobule interval wall was revealed by thin-section CT. He was referred to a previous doctor for checkup of biliary atresia. However, hepatosplenomegaly, hypotonia and prolonged jaundice indicated storage disorders, including lysosomal diseases. Lysosomal enzyme activities and filipin fluorescence staining from skin fibroblasts were ordered, but he was referred to our hospital before getting results.

At the age of 3 months, when he was admitted to our hospital for detailed examination, his body weight was 4970 g (−1.8 standard deviation [SD]) and his height was 59.3 cm (−1.0 SD). He was tachypneic (respiratory rate, 32 breaths/min) and needed oxygen therapy via nasal cannula (0.5 L/min). He showed hypotonia with normal deep tendon reflexes and developmental delay with poor head control at 4 months. Hepatomegaly and splenomegaly were observed: both the liver and spleen were enlarged (9 cm below the costal margin). Lysosomal enzyme activities and plasma amino acid analysis revealed no abnormalities. Brain magnetic resonance imaging (MRI) showed no structural abnormalities and no delay of myelination. A bone marrow smear stained by the Wright–Giemsa method revealed foam cells, which auto-fluoresced when stained with filipin. Massive accumulation of intracellular free cholesterol was also found in skin fibroblasts by filipin fluorescence staining. From these examinations, NPC was suspected. The DNA sequence from his peripheral white blood cells showed compound heterozygous point mutations in *NPC1* (exon 1–25); c.2783 A > C, p (Q928P) in the exon 18, which was reported previously, and a novel point mutation of c.3008 T > G, p(L1003R) in the exon 20. L1003 is highly conserved amino acid and this variant was neither found in ExAC nor 1000G. PolyPhen-2 predicted that the latter mutation was probably damaging (a score of 1.000); MutationTaster predicted that it was a disease-causing mutation (probability 1.0). Sequencing of the parent's DNA showed that the Q928P mutation was inherited from the mother; the L1003R mutation arose de novo (Fig. 1).

At the age of 4 months, 100 mg/day miglustat was initiated. He had diarrhea at during the initial 2 weeks of therapy, which was controlled with diastase, disaccharide restriction, and avoidance of meals 2 h before and after taking miglustat. He learned to roll over at age 5 months, to sit up at age 11 months, and to walk alone at age 24 months. Brain MRI showed appropriate myelination progress for his age. His developmental quotient, as determined using the Kinder Infant Developmental Scale (KIDS), was 83 before starting therapy, 85 after 7 months of therapy, and 78 after 14 months of therapy. The hepatomegaly and splenomegaly improved; the length from the inferior edge to the costal margin decreased to 2 cm for the liver and 6 cm for the spleen after 8 months of therapy. After 15 months of therapy, the liver was not palpable. The hyperbilirubinemia disappeared within a month after starting therapy. Liver dysfunction had decreased gradually from that observed at the age 3 months. The chest CT findings and the KL-6 value improved after starting therapy (Fig. 2A–D): 1767 U/mL at 2 months, 338 U/mL at 6 months. His oxygen therapy level gradually decreased and was stopped during daytime hours.

3. Discussion

Here we reported on a patient with the early-infantile form of NPC who started miglustat therapy at the age of 4 months and showed subsequent clinical improvement. Previous reports demonstrated that miglustat therapy was effective at slowing the progression of neurological symptoms in pediatric and adult patients with NPC, including swallowing, ambulation, and horizontal saccadic eye movements [2]. However, patients in the advanced stages of the early-infantile form of NPC had a poor response to miglustat therapy [2,3]. Therefore, miglustat therapy may be most beneficial if it is