Perinatology
pISSN 2508-4887 • eISSN 2508-4895

Case report
Perinatology Vol. 32, No. 4, December, 2021
https://doi.org/10.14734/PN.2021.32.4.208

Neonatal Type 2 Gaucher Disease with Congenital Ichthyosis: A Case Report

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Gaucher disease (GD) is a rare autosomal recessive genetic disease. The symptoms and age of onset vary depending on the subtype. Type 2 GD is potentially lethal, and the mean lifespan is less than 2 years. Due to rapid disease progression, early diagnosis of type 2 GD is important. Here, we present an infant with congenital ichthyosis and rigidity with joint contracture, who later presented with bulbar involvement. Feeding difficulty, apnea, hepatosplenomegaly, and thrombocytopenia were also evident. She was diagnosed with type 2 GD via whole-exome sequencing, which showed 2 pathogenic variants in *GBA* as a compound heterozygote: Arg296Gln (c.887G>A) and Pro24His (c.719C>A). Congenital ichthyosis with progressive respiratory and neurologic impairment may be key clinical findings for the early diagnosis of type 2 GD.

Key Words: Gaucher disease, Ichthyosis, Infant, Whole exome sequencing, Case reports

Introduction

Gaucher disease (GD) is a rare autosomal recessive genetic disease caused by glucocerebrosidase deficiency. Glucocerebrosidase is a type of lysosomal enzyme. Its deficiency leads to the accumulation of glucosylceramide in macrophages and affects multiple organs, including the liver, spleen, lung, bone marrow, brain, and skin.[1] The *GBA* gene, located on chromosome 1q21–q22 is responsible for encoding beta-glucosidase. The gene involves 11 exons, and more than 400 mutations have been reported.[2] Type 1, the most common form of GD, has an ethnic predominance for Ashkenazi Jewish. The typical clinical manifestations of visceral involvement begin soon after childhood.[3] Types 2 and 3 are characterized by central nervous system involvement with rapid progression compared to type 1. Type 2 GD manifests early in infancy and has lethal clinical courses with a lifespan of less than 2 years. In contrast, the lifespan of type 3 GD is longer (2 to 60 years).[1]

The incidence of GD is reported to be 0.39 to 5.8 per 100,000. Type 2 GD accounts for less than 5% of all GD cases.[4] Type 2 GD is challenging to diagnose in infants because of its low incidence and the lack of experience regarding this condition among physicians.

Here, we present an infant with type 2 GD who had congenital ichthyosis at birth, which was the significant clue that led to the diagnosis of type 2 GD.

Case

A female neonate weighing 2,920 g was born at 39 weeks of gestation by emergency cesarean section due to variable decelerations and maternal premature rupture of the membrane before delivery. She was conceived through *in vitro* fertilization and had no history of antenatal abnormalities, except for a suspicious left renal duplication. At the delivery room, the neonate showed respiratory failure requiring endotracheal intubation and an Apgar score of

Received: 29 September 2021
Accepted: 18 October 2021

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5, 6, and 8 in the 1st, 5th, and 10th minutes, respectively. She was transferred to the neonatal intensive care unit. The initial physical examination revealed collodion skin, a yellow and shiny film-like covering, of the whole body. Rigidity with contracture in both the upper and lower limbs was profound (Fig. 1). She had ectropion with lagophthalmos and no definite organomegaly on palpation. Initial laboratory tests were as follows: white blood cell, 10,980/μL; hematocrit, 45.5%; hemoglobin, 15.3 g/dL; platelets, 84,000/μL; and C-reactive protein, negative. The platelet counts recovered to the normal range after 10 days without transfusion. The serologic study of TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes) revealed negative results. Chest radiography excluded any pulmonary disease. Abdominal ultrasonography showed mild splenomegaly (7.1 cm) and a bifid renal pelvis in the left kidney.

Suspecting congenital ichthyosis, a daily petroleum impregnated gauze dressing was applied, and the neonate was kept in a highly humidified incubator for several weeks. We assumed that rigidity with joint contracture was due to restricted movements by the collodion skin. But while collodion skin began to peel off and resolve, contracture remained. Next-generation sequencing (NGS) for skin disorders was used to determine the etiology of congenital ichthyosis.

She was extubated 48 hours after birth. However, repeated apneas with bradycardias requiring tactile stimulation were started on the 8th day of life. To exclude central causes, the neonate underwent brain magnetic resonance imaging and electroencephalogram, which were normal with no ictal waves. At the same time, the neonate's swallowing difficulty with upper airway stridor progressed. She had to be fed via a nasogastric tube. The patient was discharged from the neonatal intensive care unit at 2 months of age, after 5 apnea-free days, following parental training for tube feeding, respiratory monitoring, and resuscitation.

The neonate returned to the emergency room with worsened apnea and rigidity with irritability on the 4th day after discharge. She was admitted to the pediatric intensive care unit for respiratory care. Two weeks after admission, anemia and thrombocytopenia became prominent, and multiple transfusions were required. A follow-up ultrasound study showed hepatosplenome-

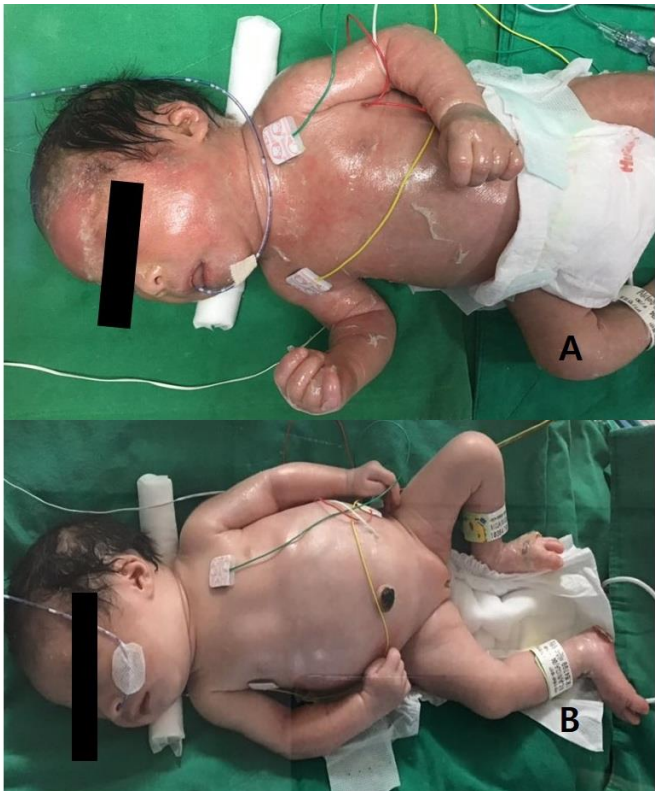

Fig. 1. (A) Patient's clinical phenotype of collodion skin and contracture at 48 hours after birth. (B) While collodion skin peeled off and resolved 13 days after birth, her contracture of joint still remained.

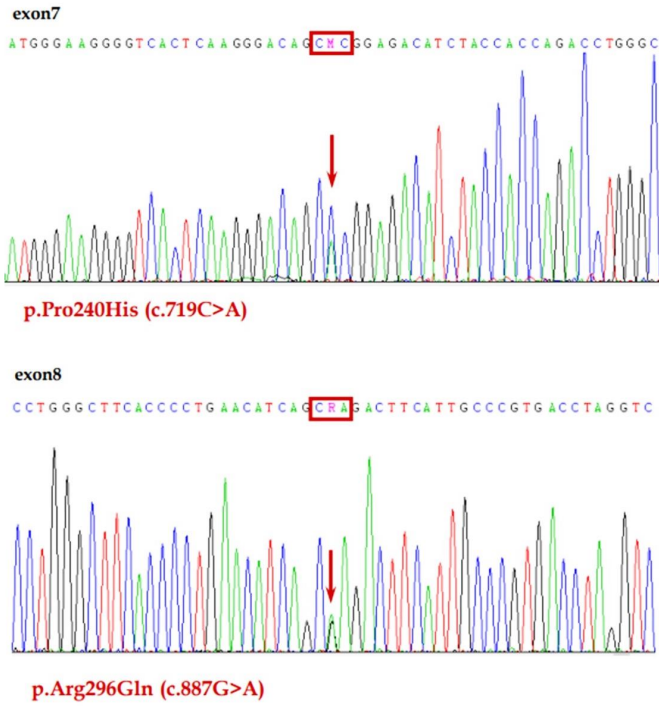

Fig. 2. Patient's DNA sequencing of the glucosylceramide beta gene. Arrows show heterozygous single-nucleotide polymorphisms, with c.719C>A and c.887G>A.

galy, which was much more profound than in the initial study. The whole-exome sequencing result revealed 2 pathogenic variants in *GBA*; Arg296Gln (c.887G>A) and Pro24His (c.719C>A) (Fig. 2), and his parents were identified as asymptomatic carriers of each variant by Sanger sequencing. Dried blood spot analysis for lysosomal enzyme showed decreased β-glucocerebrosidase activity (0.2 μmol/hr/L; reference, >1.88 μmol/hr/L) (Fig. 2). The patient subsequently developed pneumonia and multiple organ failure. She died after decision to withdraw life-sustaining treatment at the age of 5 months.

This study was approved for exemption of subject consent by Severance Institutional Review Board (approval number: 4-2021-1470).

Discussion

Congenital ichthyosis, an abnormal skin disorder, also called the collodion-baby phenotype, may be observed in newborn type 2 GD patients. This shiny, cellophane-like skin is thought to result from altered ratios of ceramides to glucosylceramides in the outermost layers of the skin. Harlequin ichthyosis or congenital ichthyosiform erythroderma is considered the usual presentation of the collodion-baby. However, ichthyosis is also a typical clinical manifestation in type 2 GD patients. When diagnosing congenital ichthyosis, physicians must consider the different types, from common ichthyosis to syndromic ichthyosis. Moreover, syndromic causes should be seriously considered if non-cutaneous symptoms are also present.[5]

Type 2 GD, the most severe and progressive form of GD, generally manifests prenatally or in the first month of life. Hydrops fetalis and ichthyosis are visible immediately after birth. Provoked asphyxia episodes and prolonged spontaneous apneas are prominent features of GD. Hepatosplenomegaly and thrombocytopenia are common remarkable nonspecific features.

Dysmorphic facial features often accompany ichthyosis. Dysmorphia may result from the presence of a thick membranous layer and decreased skin elasticity *in utero*. The most common neurological signs include a hyperextended neck, spontaneous apnea, progressive spasticity, poor sucking and swallowing reflexes, and rapidly progressive brainstem degeneration.[6] Abnormal auditory brainstem response may also be a clue for early diagnosis. Previous studies have reported abnormal auditory brainstem response as an initial manifestation of type 2 GD, before neurological symptoms develop.[7]

It is difficult to diagnose type 2 GD because of its rarity. GD has an incidence of approximately 1 in 60,000 to 100,000 births worldwide.[4] In Korea, there are less than 100 diagnosed patients.[8] Of these, only 5% of GD patients are type 2. Previous studies have revealed that epidermal abnormalities distinguish type 2 GD from type 1 and 3.6 Hepatosplenomegaly, pancytopenia, and ichthyosis are associated with the perinatal-lethal form of GD.[7] Patients presenting with ichthyosis as the first sign of type 2 GD usually survive for less than 1 year.[9-11] In addition, other metabolic diseases, such as multiple sulfatase deficiency, early infantile galactosialidosis, Hurler disease, and type 1 gangliosidosis can also lead to skin abnormalities, ranging from dry skin to ichthyosis. Early diagnosis with NGS in patients with congenital ichthyosis is beneficial for differentiating various devastating diseases and predicting prognosis.

In summary, this case highlights the importance of early evaluation of neonates born with congenital ichthyosis with suspicion of type 2 GD, especially in patients with progressive respiratory or neurological impairment.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Authors' Contributions

Conceptualization: JES, JO; Data curation: HL, JH, JP, SHB; Formal analysis: MJL, RY; Investigation: all authors; Methodology: JES, JO, MJL, HSE, MSP; Project administration: JES; Visualization: HL; Writing–original draft: HL; Writing–review & editing: all authors.

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