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Case report

Perinatal-lethal Gaucher disease can be the underlying cause of congenital ichthyosis

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Abstract

In this paper, we present an infant born with congenital ichthyosis who was also diagnosed with a perinatal-lethal form of type 2 Gaucher disease (GD). GD is a glycolipid storage disease leading to widely variable phenotypes such as hydrops fetalis, congenital ichthyosis, hepatosplenomegaly, thrombocytopenia, anemia, muscular hypotonia, seizures, and respiratory failure. Our patient died due to respiratory failure at 78 days of postnatal age. Molecular genetic tests showed homozygous mutation c.[1505G>A];[1505G>A] of the β-glucocerebrosidase gene. We would like to focus the attention on the fact that perinatal-lethal GD can be the underlying cause of congenital ichthyosis.

Keywords

Gaucher disease, congenital ichthyosis, β-glucocerebrosidase.

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Introduction

Congenital ichthyosis is an abnormal skin disorder resulting in shiny, almost cellophane-like skin. The term collodion baby is used for "babies with cellophane-like skin". The syndromes which have been reported as being associated with collodion membranes include: Sjögren-Larsson syndrome, Conradi-Hunermann syndrome, trichothiodystrophy, ichthyosis vulgaris, epidermolytic ichthyosis, neutral lipid storage disease, keratitis-ichthyosis-deafness syndrome, holocarboxylase synthetase syndrome, Gaucher disease (GD), hypohidrotic ectodermal dysplasia, and congenital hypothyroidism [1].

GD is an autosomal recessive lysosomal storage disorder (LSD) caused by a deficiency of the enzyme glucocerebrosidase. It is the most common of the more than 50 known LSDs and is traditionally divided into three distinct types based on the presence and progression of neurological signs [2]: type 1 (non-neuronopathic), type 2 (acute neuronopathic), and type 3 (subacute neuronopathic). Most patients suffer from type 1 disease with extensive clinical heterogeneity. Only 1% of Gaucher patients suffer from type 2 disease which presents with neurological involvement (such as myoclonus, seizures, choreoathetosis, and spasticity) within the first months of life and progresses rapidly, culminating in severe degeneration and death in the first 2 years of life. Widely variable phenotypes such as hydrops fetalis, congenital ichthyosis, hepatosplenomegaly, thrombocytopenia, anemia, and respiratory failure can also be seen in this type. A variant of type 2 GD which presents in the neonatal period was named as perinatal-lethal GD [3]. Herein, we report an infant with perinatal-lethal GD presenting with collodion membrane and hydrops fetalis beyond thrombocytopenia, hepatosplenomegaly, respiratory failure, and hypotonia.

Case report

A male infant was born to a gravida 4 para 4 36-year-old mother by caesarean section because of meconium-stained ruptures of membranes and hydrops fetalis. He was born at 35 weeks' gestation with a birth weight of 2,400 grams (50^{th}-75^{th} p) and an Apgar score of 4/6 in the 1^{st} and 5^{th} minutes, respectively. The baby was transferred to our neonatal intensive care unit because of non-immune hydrops fetalis and respiratory distress. The parents were third degree cousins. In the family history, we learned that one of his siblings was diagnosed as a collodion baby, transferred to a neonatal intensive care unit, and died at 30 days of postnatal age.

On admission, the physical examination of the newborn revealed skin edema, tachypnea, respiratory distress, hypotonia, and the collodion baby phenotype. Initially he did not have organomegaly. Because of respiratory failure he was intubated and mechanical ventilation support was started. His chest X-ray supported respiratory distress syndrome, so surfactant and systemic antibiotic treatments were begun. The results of the initial hematologic tests revealed: hematocrit 53.2%, hemoglobin 17.1 g/dL, WBC 14,090/μL, platelets 45,000/μL. Seizures started at the first days of life. Seizures were controlled with phenobarbital and levetiracetam. Cranial ultrasonography and magnetic resonance imaging were performed and revealed nearly a 5 mm size hemorrhagic nodular lesion near the left lateral ventricle anterior horn. For skin treatment retinoic acid and lubricants were used. In the days that followed, persistent thrombocytopenia and slightly elevated liver enzymes were noted. Retinoic acid treatment was stopped because of elevated liver enzymes and good skin condition. At 48 days of postnatal age, hepatosplenomegaly became progressively prominent. He also still required assisted ventilation. Bone marrow aspiration was done for storage disorders by the Pediatric Hematology Department at 50 days of postnatal age and revealed non-diagnostic changes. Intravenous immunoglobulin treatment was started but thrombocytopenia was persistent. Because of respiratory insufficiency, progressive hepatosplenomegaly and refractory seizures, LSD was investigated. Tandem MS tests were normal but β-glucocerebrosidase activity was found to be decreased (0.1 umol/L/h; cut-off value > 2.5 umol/L/h).

Molecular analysis confirmed a homozygous mutation c.[1505G>A];[1505G>A] (p.[Arg502His];[Arg502His]) of the β-glucocerebrosidase gene. He died due to respiratory failure at 78 days of postnatal age. Genetic counseling was provided for the family.

Discussion

GD is an autosomal recessive LSD caused by a deficiency of the enzyme glucocerebrosidase. It is chronic and progressive in its clinical presentation

and affects 1 in 60,000-100,000 births worldwide. Although pan-ethnic in distribution, it occurs with increased prevalence among the Jewish people of Eastern and Central European descent (Ashkenazi Jews) with an 8.9% carrier rate.

GD was initially described by Philippe Charles Ernest Gaucher, in his doctoral thesis in 1882, when he hypothesized that abnormal histiocyte infiltration of a spleen represented a "neoplasm" [4]. The biochemical basis for GD was elaborated in 1965 by Roscoe O. Brady's group at the National Institutes of Health and GD was shown as an inherited deficiency of lysosomal glucocerebrosidase [5]. The molecular basis of the disease was clarified in the 1980s, when the glucocerebrosidase gene mutations were identified.

The glucocerebrosidase gene is encoded by the human *GBA 1* gene. The *GBA 1* gene is located on chromosome 1 q2. There are over 300 known mutations that can cause GD, and the most common are c.1226A>G (N370S), 84GG, IVS2+1, and the c.1448T>C (L444P) mutations. The L444P mutation homozygous state has a very high association with neuropathic variants of GD [6]. The association between collodion babies and type 2 GD was first reported by Lui et al. [7]. They reported two siblings with generalized thick collodion-like skin at birth. While one of the patients had recurrent laryngospasms, convulsions and thrombocytopenia, his brother had hepatosplenomegaly, respiratory failure, and generalized joint contractures. Both patients had neurological problems and died early (3 months and 11 days, respectively). There are many cases of neonatal GD with congenital ichthyosis in literature [8-20]. One of them was very similar to our case. A neonate with type 2 GD was reported because of severe clinical findings including congenital ichthyosis, hepatosplenomegaly, muscular hypotonia, myoclonus, and respiratory failure. Like our patient, the baby died from respiratory failure without positive neurological progress. Similar to our patient, molecular analysis identified a homozygous null mutation, c.1505G→A of the β-glucocerebrosidase gene [17].

A variant of type 2 GD which presents in the neonatal period was named as perinatal-lethal GD. The most frequent finding of perinatal-lethal GD was non-immune hydrops fetalis. Less frequent signs of the disease were including hepatosplenomegaly, ichthyosis and arthrogryposis [3]. Our patient was clinicaly compatible with this variant of type 2 GD according to the combination of hydrops fetalis, ichthyosis, and hepatosplenomegaly.

In 1992, the first mouse knockout model of GD was generated by homologous recombination with a null glucocerebrosidase allele [21]. Mice homozygous for this null mutation had no detectable glucocerebrosidase activity and died a few hours after birth. These affected mice had dry-ichthyotic skin. Further analyses of these mice showed hyperkeratosis and disruption of the lamellar structure of the stratum corneum. This shows the importance of glucosylceramides for maintenance of the epidermal permeability barrier.

There are different options for treatment. Lubricants, fluids and retinoic acid can be used for skin abnormalities. Enzyme replacement therapy, substrate reduction therapy, gene therapy, bone marrow transplantation and molecular chaperones are other treatments for disease [22].

Conclusion

We would like to especially mention that if a collodion baby has neurologic and hematologic symptoms, rare metabolic diseases must be considered as differential diagnoses. Some storage 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 [23]. Perinatal-lethal GD should be considered in infants presenting with congenital ichthyosis, hydrops fetalis, visceromegaly, neurological symptoms, and thrombocytopenia.

Declaration of interest

The Authors declare that there is no conflict of interest.

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