Novel Insights from Clinical Practice

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Congenital Ichthyosis in Severe Type II Gaucher Disease with a Homozygous Null Mutation

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Established Facts

- Type II Gaucher disease (acute neuronopathic form) is a rare neonatal disease with poor prognosis.
- β-Glucocerebrosidase is important to ensure the epidermal barrier function.

Novel Insights

- The homozygous c.1505G→A (R463H) mutation described in this patient leads to destruction of the donor splice site between exons 10 and 11 resulting in a functional knockout of the whole enzyme; this mutation will thus induce the clinically severest presentation of type II Gaucher disease.
- Electron microscopy is helpful for an early diagnosis because it can demonstrate characteristic remnants of a disturbed metabolism of the epidermal lipid barrier.

Key Words
Gaucher disease · Collodion baby · Glucocerebrosidase · Null mutation

Abstract
This paper describes a neonate with type II Gaucher disease. The phenotype was unusually severe with congenital ichthyosis, hepatosplenomegaly, muscular hypotonia, myoclonus and respiratory failure. Electron microscopy of the skin revealed lamellar body contents in the stratum corneum interstices, appearances considered to be typical of type II Gaucher disease. The baby died from respiratory failure 1 month postpartum having made no neurological progress. Molecular analysis identified a previously not reported homozygous null mutation, c.1505G→A of the β-glucocerebrosidase gene.

Introduction

Gaucher disease is a glycolipid storage disease caused by glucosylceramide accumulation in macrophages and monocytes. It can be divided into 3 phenotypes: type I (nonneuronopathic), type II (acute neuronopathic) and

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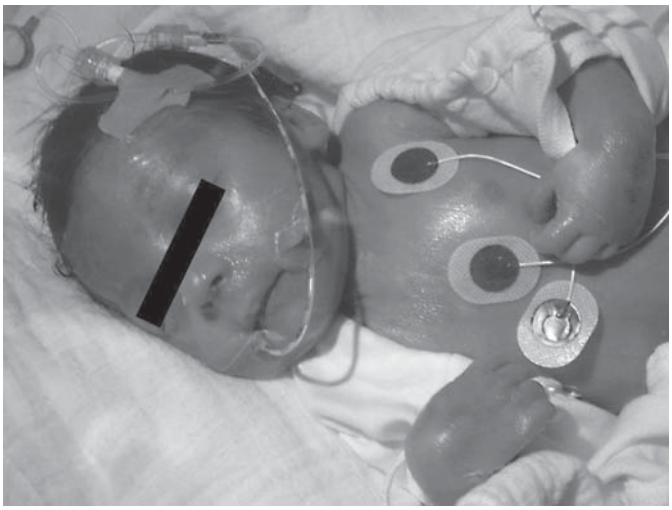

Fig. 1. Patient with collodion baby appearance and contraction of both elbows and wrists.

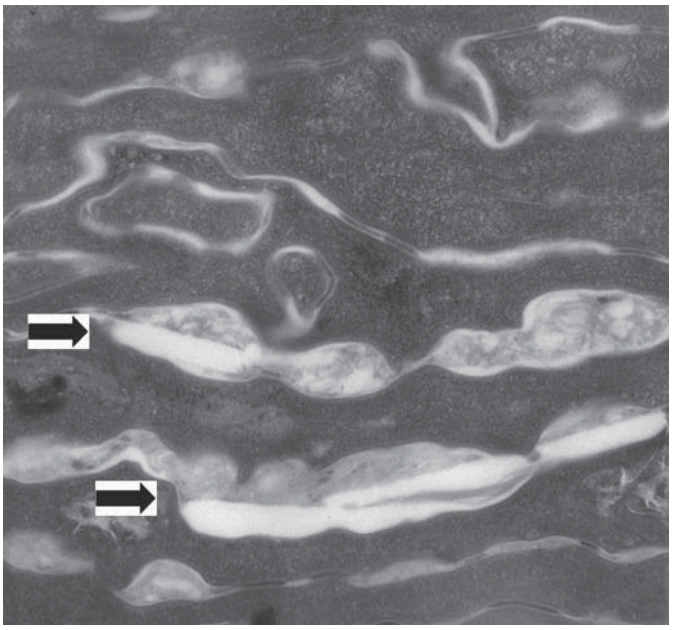

Fig. 2. Interlamellar deposits in the horny layer considered to be irregularly processed contents of lamellar bodies with lamellar, granular and crystalline (arrows) appearances. The crystals are putative remnants of cholesterin crystals, further signs for a disturbed metabolism of the epidermal lipid barrier. Electron microscopy ×15,200.

type III (subacute neuronopathic). 95% of the patients suffer from type I disease. Only 1% of Gaucher patients are affected by type II disease, characterized by failure to thrive, hepatosplenomegaly, joint contractures, respiratory failure and neurological complications such as myoclonus, seizures, choreoathetosis and spasticity. Affected patients die within the first 2 years of life. Some of these neonates present with a collodion baby phenotype at birth. Other storage diseases such as multiple sulfatase deficiency, early infantile galactosialidosis, Hurler disease and type I gangliosidosis can also lead to skin abnormalities, ranging from dry skin to ichthyosis, skin hypopigmentation, telangiectatic skin changes and extended Mongolian spots [1].

Clinical Description

Our patient was the first child of consanguineous Lebanese parents. Apgar scores were 4/8/8 and the baby's weight, length and head circumference were within normal limits (25th–50th/10th–25th/25th percentiles). Clinical examination revealed lamellar dermal desquamation resembling the collodion baby phenotype with joint contractures and hepatosplenomegaly (fig. 1).

Thrombocytopenia (104,000/μl), slightly elevated liver enzymes, an elevated lactate dehydrogenase along with a highly elevated ferritin level were noted. Plasma chitotriosidase activity was grossly elevated (2,376 nmol/h/ml; normal <80). Light microscopy of the skin biopsy revealed an acanthotic, mostly flat epidermis with a thin stratum granulosum and corneum. Electron microscopy demonstrated incompletely processed lamellar bodies in the stratum corneum interstices typical of type II Gaucher disease (fig. 2). Gaucher disease was confirmed by a decreased β-glucocerebrosidase activity in lymphocytes (1.39 nmol/h/mg protein, control 10.2).

During the following weeks hepatosplenomegaly rapidly progressed. Muscular hypotonia was profound and there was no neurological progress. Recurrent unexplained fever and respiratory insufficiency occurred, and a chest X-ray showed diffuse shadowing of both lungs. At the age of 1 month, the baby died from respiratory failure; mechanical ventilation was however not initiated. Parental consent was not granted for postmortem examination.

Molecular analysis confirmed a homozygous mutation c.1505G→A (R463H) in the glucocerebrosidase gene. Both parents were heterozygous for this mutation.

Discussion

Lui et al. [2] first reported the association between ichthyotic lamellar desquamation of the newborn ('collodion baby') and type II Gaucher disease. They presented 2 siblings with tight collodion skin at birth. The first boy

developed recurrent laryngospasms, convulsions and thrombocytopenia. A brother was dependent on assisted ventilation from birth and had hepatosplenomegaly as well as generalized joint contractures. Both patients were characterized by a lack of any normal neurological reactivity and early death (3 months/11 days). Diagnosis was confirmed by a decreased glucocerebrosidase activity in leukocytes. In addition, Gaucher cells were discovered in different organs by postmortem examination in patient 2.

Ichthyosis in Gaucher type II patients demonstrates the importance of β-glucocerebrosidase for ceramide production and supports the assumption that ichthyosis based on other molecular defects may be caused by a decreased ceramide content due to secondary β-glucocerebrosidase deficiency. Lamellar bodies contain glucosylceramides and phospholipids that are cleaved by glucocerebrosidase and sphingomyelinase to ceramides and free fatty acids. They form intercellular lamellar membranes between the corneocytes in the stratum corneum. Ceramides are a major component of the stratum corneum and make up to 40% of the total lipids [3]. β-Glucocerebrosidase metabolizes ceramide from glucosylceramide. The pH gradient in the stratum corneum (pH from 7.4 to 5.0) is essential for the enzymatic activity of β-glucocerebrosidase [4]. A disturbance of the epidermal barrier in disorders like ichthyosis vulgaris leads to increased pH and induces impaired β-glucocerebrosidase function.

In ultrastructural and functional studies in type II Gaucher disease null allele mice [5], β-glucocerebrosidase was shown to be necessary to ensure the epidermal barrier function. Sidransky et al. [6] examined skin biopsies of all 3 types of Gaucher patients and type II Gaucher mice to find out whether epidermal abnormalities are unique to this disease entity. Only patients with type II disease had an increased ratio of epidermal glucosylceramide to ceramide and ultrastructural abnormalities, such as incompletely processed lamellar body-derived contents throughout the stratum corneum intersitices. These human findings were comparable to those found in type II mice and were therefore considered to be characteristic of type II Gaucher disease.

Like other Gaucher patients, type II patients with congenital ichthyosis demonstrate a genotypic diversity [7]. On the other hand, there is a large phenotypic variability among patients with the same mutations [8]. The c.1505G→A (R463H) mutation described in this patient leads to destruction of the donor splice site between exons 10 and 11. In a patient described by Ohshima et al. [9], an alternative donor splice site is used resulting in a 12-bp insertion and the generation of a premature stop codon following codon 463 and deleting the terminal 34 amino acids with a complete loss of activity. This patient was compound heterogeneous for the c.1505G→A mutation but carried a second mutation leading to Gaucher disease type III. In a series of 6 patients with 5 new mutations, Beutler et al. [10] described a Gaucher type I patient carrying another mutation in the same splice donor site [c.1505, IVS10(+2)], but this patient's second mutation was only a mild one (c.1604G→A). In contrast, our patient was homozygous for the splice donor site mutation, resulting in a functional knockout of the whole enzyme. The residual activity of β-glucocerebrosidase measured in our patient was determined with an artificial 4 MU substrate and is no indication of genuine residual activity.

An animal model was established by Tybulewicz et al. [11] from targeted disruption of the mouse glucocerebrosidase gene. Comparable to our patient, these mice typically show ichthyosiform skin and they rapidly deteriorate with decreased movements, reduced respiratory drive along with feeding difficulties leading to death within 24 h of birth. The induced genetic defect in these mice resulted in a complete functional knockout of the β-glucocerebrosidase gene like the homozygous splice site mutation found in our patient.

In summary, our patient not only revealed the previously described collodion baby phenotype and characteristic horny layer deposits, seen at the ultrastructural level but also carried a homozygous functional knockout mutation leading to an extremely severe and early lethal form of Gaucher type II disease. Comparable to knockout mice, leading clinical signs were a collodion-baby-like appearance with hepatosplenomegaly and lack of neurological progress. Although Gaucher disease is and in this case was ultimately confirmed by reduced β-glucocerebrosidase activity and a mutation in its gene, skin biopsy contributed to the early diagnosis. Management included limitation to supportive care.

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Laboratories

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Disclosure Statement

No conflict of interest.

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