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Gaucher Disease in the Neonate: A Distinct Gaucher Phenotype Is Analogous to a Mouse Model Created by Targeted Disruption of the Glucocerebrosidase Gene

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ABSTRACT. A group of neonates with Gaucher disease with a particularly devastating clinical course is described. The phenotype of these infants is analogous to that of a Gaucher mouse, which was created by targeted disruption of the mouse glucocerebroside gene. Similar to the homozygous mutant mice with glucocerebrosidase deficiency, these infants present at or shortly after birth, have rapidly progressing fulminant disease, and many have associated ichthyotic skin and/or hydrops fetalis. This transgenetic mouse model of Gaucher disease has helped us to appreciate a distinct Gaucher phenotype. Potentially, as this technology is applied to create other animal models of metabolic diseases, it may enable the recognition of other, as yet unappreciated presentations of inherited disorders. (*Pediatr Res* 32: 494–498, 1992)

A group of neonates having a uniquely devastating course as a consequence of Gaucher disease is described. The association of this phenotype with Gaucher disease was emphasized after observation of the phenotype of a glucocerebrosidase-deficient strain of transgenic mice created by targeted disruption of the mouse glucocerebrosidase gene.

Gaucher disease, the inherited deficiency of the lysosomal enzyme glucocerebrosidase (EC 3.2.1.45, β-D-glucosyl-N-acylsphingosine glucohydrolase) presents with diverse clinical manifestations (1, 2). To better understand the pathogenesis of this disease, a mouse model of glucocerebrosidase deficiency recently was generated by targeted disruption of the mouse gene (3, 4). This mouse line carries a null allele created by disrupting the presumptive active site of the glucocerebrosidase gene (2). The glucocerebrosidase activity in homozygous mutant mice was less than 4% of control, and the mice display a particularly devastating phenotype that is autosomal recessively inherited (4). Over 100 of these affected newborn animals have been studied. On electron microscopy, they demonstrate lipid storage in macrophages in liver, spleen, bone marrow, and brain. The homozygous mutant mice are readily identified by their mothers and are ejected from the nest. Compared to their unaffected littermates, they are cyanotic, lethargic, and exhibit poor turgor (Fig. 1). Their skin shows abnormal prominent rugation, and light microscopic evaluation reveals hyperkeratosis (Fig. 2*A* and *B*). These mice have weak, irregular respirations, do not feed, and all die within 24 h of birth. With the observation of this striking mouse phenotype, we reviewed cases of Gaucher disease at our institutions and in the literature and have identified a subset of neonates diagnosed with severe type 2 Gaucher disease paralleling the clinical course observed in the glucocerebrosidase-deficient mouse.

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CASE REPORT 1

This infant was born at term by elective cesarean section to a 37-y-old gravida 2 para 1 Greek mother who had previously delivered a stillborn infant with unknown congenital malformations. On routine physical examination, he was found to have hepatosplenomegaly and was admitted to the neonatal intensive care unit for further investigation. At a few days of life, he developed hypertonia, hyperreflexia, and hyperextension of the neck (Fig. 3). His neurologic status progressively deteriorated; he demonstrated poor suck and swallow reflexes. Death occurred at 2 mo of age. His β-glucosidase level was 0.81 nmol/mg protein/h. On Western analysis of fibroblast extracts, no glucocerebrosidase protein was detected.

CASE REPORT 2

A 1935-g male infant was born by cesarean section at 34 wk gestation to a 22-y-old gravida 2 para 1 black mother. The early

Fig. 1. Normal and homozygous mutant newborn mice. The six animals shown are littermates. The three affected mice (*left*) are cyanotic, smaller, and have absent spontaneous movements and rugated skin. The normal littermates (*right*) are more active, demonstrate milk in their stomachs, and have good color and respirations.

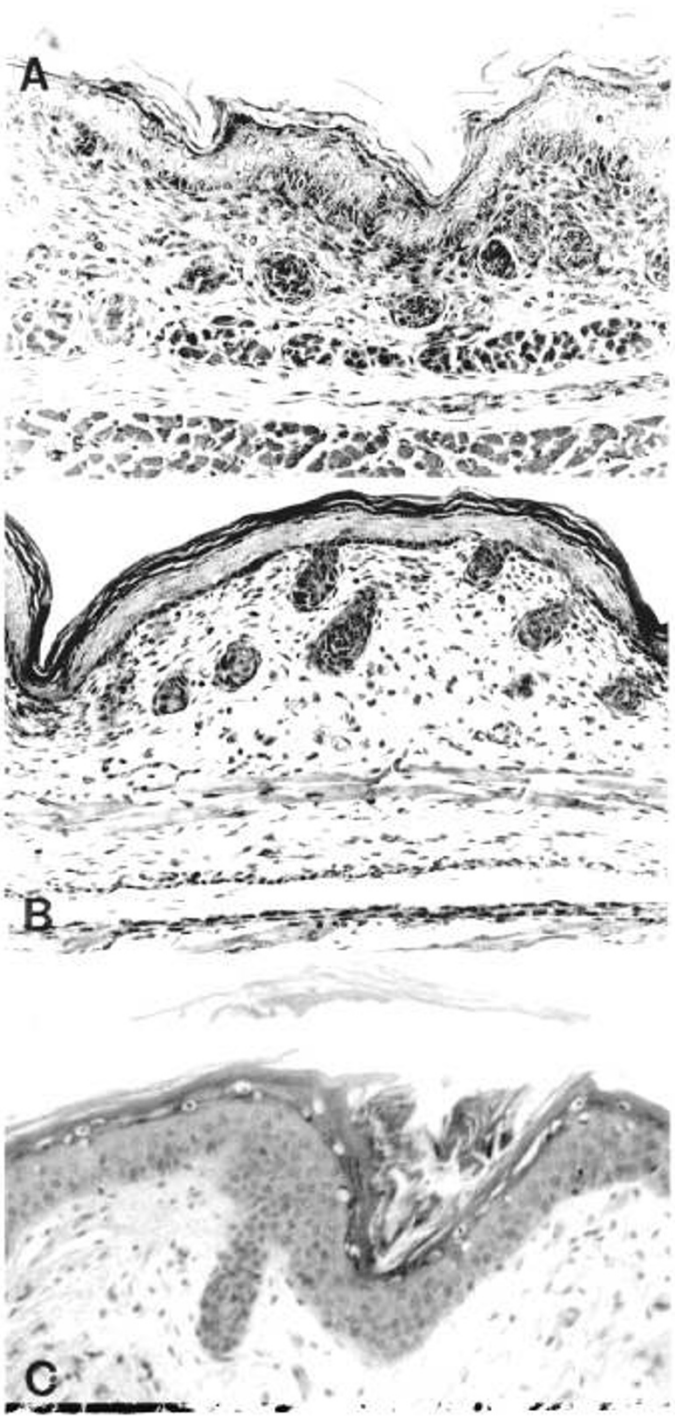

Fig. 2. Histologic appearance of skin (20× power, hematoxylin and eosin stain). *A*, Skin from a normal newborn mouse; *B*, skin from a homozygous mutant mouse (littermate of *A*); and *C*, skin from an infant with Gaucher disease and a collodion baby phenotype (case report 2).

portion of her pregnancy and sonograms at 14 and 22 wk were normal. However, 2 wk before delivery her uterus was noted to be large for dates, and a sonographic examination revealed massive polyhydramnios, absent fetal movements, thickened skin, and fetal facial features with a flattened nose, proptosis, and a continuously open mouth. The baby was born, with Apgar scores of 2, 2, and 2 at 1, 5, and 10 min, respectively, and did not breathe spontaneously. He was noted to have stiff, thick, shiny collodion skin, flexed extremities, and open eyes and mouth (Fig. 4). Skin biopsy revealed lamellar exfoliative ichthyosis with normal epidermis and dermis but a thickened overlying keratin layer and follicular plugging with keratin (Fig. 2*C*). Mechanical ventilation was continued for 7 d, but the infant had no spontaneous movements or respiratory effort. He also had absent auditory evoked potentials and an abnormal EEG with low-amplitude voltage. Life support was discontinued with parental consent and death immediately followed. On postmortem examination, large macrophages with lipid storage (Gaucher cells) were found in the spleen, liver, thymus, lymph nodes, adrenals, bone marrow, and throughout the CNS (5).

Fig. 3. Clinical photograph. Infant with Gaucher disease (case report 1) diagnosed in the newborn period with hepatosplenomegaly and neurologic disease.

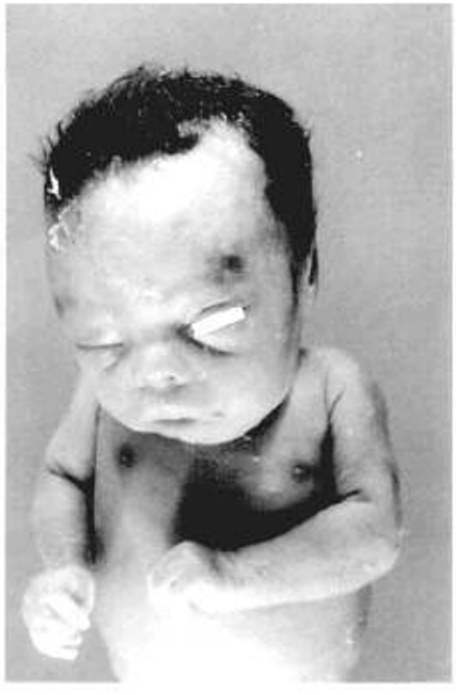

Fig. 4. Clinical photograph. Infant with Gaucher disease and congenital ichthyosis with restrictive dermopathy (case report 2).

REVIEW OF LITERATURE

Examination of the literature (5–15) identified a group of 15 additional patients from 11 unrelated families in which Gaucher disease was eventually diagnosed because of symptoms presenting during the neonatal period (Table 1). In each of the cases, death ensued within days or months. There was no sex or ethnic predilection for this phenotype. Some of these infants were born at term and others were delivered at 32–36 wk gestation.

Table 1. *Gaucher patients presenting in neonatal period*

Patient no.	Associated diagnosis	Year/ reference	Ethnic origin	Sex	Gestation	Onset	Age at death	Miscellaneous
1	Ichthyosis	1988/6	Lebanese	M	38 wk	Birth	3 mo	Ichthyotic skin, apathy, hepatosplenomegaly, respiratory death
2	Collodion baby	1988/6	Lebanese sibling of case 1	M	40 wk	Birth	11 d	Collodion skin, hepatosplenomegaly, apathy, convulsions
3	Collodion baby	1990/7	Australian		32 wk	Birth	3 wk	Mild collodion baby phenotype, hepatosplenomegaly, thrombocytopenia, apnea
4	Collodion baby	Present report and/5	Black	M	34 wk	Recognized prenatally	7 d	Collodion skin, absent movement, no spontaneous respirations
5	Ichthyosis	1984/8		M	Term	Birth	13 wk	Jittery from birth, congenital lamellar ichthyosis, trismis, hepatosplenomegaly, hyperextension of neck, dysconjugate gaze
6	Ichthyosis	1962/9		M	Term	Birth	3 mo	Cellophane skin, petechial rash, hepatosplenomegaly, opisthonus, respiratory death
7	Ichthyosis and hydrops	1954/10	German	F		Birth	16 h	Congenital ichthyosis, hepatosplenomegaly, apnea, erythroblastosis, aortic calcification
8	Hydrops	1954/10	German sibling of case 7	F		Birth	2 h	Congenital hydrops, hepatosplenomegaly
9	Hydrops	1984/11	Black	M	38 wk	Birth	7½ h	Generalized edema, hydrops fetalis, widespread petechie, marked hepatosplenomegaly
10	Hydrops	1973/12	Caucasian		34 wk	Stillborn		Macrated stillborn, generalized edema
11	Hydrops	1973/12	Caucasian sibling of case 10	M	36 wk	Birth	20 min	Hepatosplenomegaly, edema, hydrops fetalis, pleural effusions, and ascites
12	Possible hydrops	1970/13	Sephardic Jewish	F	32 wk	Birth	48 h	Edema, hepatosplenomegaly, apnea, purpura, ? hydrops, four previous miscarriages
13		1938/14	Caucasian American	F		1 wk	4.5 mo	Opisthotonus, neck rigidity, strabismis, poor feeding, hepatosplenomegaly
14		1974/15	Spanish	F	32 wk	Less than 2 wk	3 mo	Generalized spasticity, hepatosplenomegaly, apnea, poor feeding
15		1974/15	Spanish sibling of case 14	M		Stillborn		
16		1974/15	Spanish sibling of case 14	F			45 d	
17		Present report	Greek	M	Term	Birth	2 mo	Hepatosplenomegaly, hypertonia, hyperreflexia, hyperextension of neck
18		Present report	Greek sibling of case 17			Stillborn		Unknown congenital malformations

Noteworthy were associated dermatologic manifestations. In seven of the case reports, the infants were described as either "collodion babies" or as having congenital ichthyosis or "cellophane-like" skin (5–10). In the earlier reports, this finding was not emphasized but was described as an incidental observation. However, more recently Lui *et al.* (6) and Lipson *et al.* (7) reported the association and commented that the ichthyosis might be related to abnormal lipid composition of the skin or, alternatively, that the hyperkeratosis and glucocerebrosidase deficiency may be the result of contiguous gene disorders. Interestingly, there was no mention of Gaucher disease in large reviews of collodion babies (16, 17).

Another observation is the association of Gaucher disease and hydrops fetalis. Six infants in four unrelated families were described with Coombs negative hydrops and Gaucher disease with CNS involvement (10–13). These patients all succumbed within the first 24 h of life. In one family (10), two infants were described who most probably had nonimmune erythroblastosis and Gaucher disease. The second of these children also had shiny, reflective, thin "cellophane paper-like" skin with hemorrhagic rugation.

DISCUSSION

Type 2 or acute neuronopathic Gaucher disease is generally thought to be fairly stereotypic in its presentation (1, 9, 13). The child is usually born at term after an uneventful pregnancy and appears normal at birth. Several months pass before the first diagnostic signs appear, which may manifest as failure to thrive, hepatosplenomegaly, or difficulty in feeding or swallowing. Once the neurologic symptoms begin they progress rapidly, and there is loss of developmental milestones. Classically, the affected infants develop hyperextension of the neck, strabismus, trismus, and hypertonia with hyperreflexia. Death generally occurs between age 9 and 18 mo (1, 9, 13). The infants with type 2 Gaucher disease described in this report clearly had a different and more severe phenotype. In the subset of patients described here, signs and symptoms presented prenatally or at birth, and death frequently ensued within hours to days, or at the most 2–3 mo. In these infants there was an association with congenital ichthyosis and/or hydrops fetalis.

Although the initial cases of perinatal Gaucher disease were reported more than 50 y ago (13), this more severe presentation has not been recognized as a distinct entity. Most of the cases were only identified serendipidously, often after other siblings had died undiagnosed. Thus, it is important that physicians, particularly neonatologists and dermatologists, recognize these cases to appreciate the full spectrum of manifestations of Gaucher disease.

The use of transgenic technology to create animal models of human disease is still in its infancy (18). There is the possibility that mutations introduced into an animal gene could result in either a phenotype that is not analogous to that seen in the human disorder (19) or a lethal phenotype. The targeted disruption of the mouse glucocerebrosidase gene to produce a null allele has resulted in an homozygous mouse who was affected, in this instance severely, with Gaucher disease. We now have examined, by Southern analysis, more than 100 homozygous-mutant mice, all of whom died in the first 24 h of life. Specific clinical manifestations of this mouse, particularly its ichthyotic skin and early demise, have aided us in recognizing and beginning to emphasize a distinct human phenotype of Gaucher disease. The generation of other, less severely affected mouse lines should provide insight into other aspects of the human disease.

The association of Gaucher disease with congenital ichthyosis in both the human and the mouse is particularly noteworthy. The skin abnormality observed in the Gaucher mouse generated by targeted disruption of the glucocerebrosidase gene suggests that the association in the human is not due to contiguous genes (6, 7). The enzyme deficiency with resultant abnormal glucocerebroside degradation appears directly responsible for the abnormal skin of these infants. Glucosylceramide and ceramide are components of the intercellular bilayers in the stratum corneum of normal skin (20, 21). Recently, sphingolipids have been demonstrated to play an important role in skin permeability barrier homeostasis (22). The absence of glucocerebrosidase may consequently affect functional skin integrity. Histologically, the thickened overlying keratin layer was found in skin of both the homozygous mutant mice and an affected human neonate. Thus, Gaucher disease should be considered in the differential diagnosis of the "collodion baby" or congenital ichthyotic skin phenotype. Early diagnosis of type 2 Gaucher disease is essential for genetic counseling and assigning prognosis.

Although the association of Gaucher disease and hydrops fetalis has been reported, the pathophysiology of the phenomena still remains obscure. Fetal pathology of Gaucher disease has been studied (23, 24), and there is documentation of advanced pathologic alterations in fetal tissues. There was an increase in perinatal deaths and spontaneous abortions among the families reviewed here, but Gaucher disease often was only recognized when a second child was affected. The observation of this fetal loss associated with Gaucher disease has been reported in the past (25). Further systematic study of the incidence of perinatal deaths among Gaucher families should prove helpful. Perhaps Gaucher disease has been underdiagnosed in the neonatal period.

Gaucher disease exhibits a large degree of phenotypic heterogeneity, and it is not surprising that subsets of type 2 patients exist with different clinical courses. Among type 2 patients studied, multiple genotypes have been identified and many individuals have alleles that have not yet been defined (2, 26–28). However, the finding that the infant described in case report 1 was similar to the glucocerebrosidase-deficient mouse in that it had almost no enzyme activity and no detectable enzyme on Western analysis is unusual. Generally, no unique DNA mutation or particular range of residual glucocerebrosidase activity (29) is specifically found in type 2 patients. A total absence of cross-reactive material on Western analysis is not usually seen in Gaucher patients (2), although one other case has been reported (30). Thus, even type 2 patients may prove less homogeneous than previously thought.

The glucocerebrosidase-deficient mouse is the first animal model of an inborn error of metabolism with an appropriate phenotype created by gene targeting. This initial transgenic model of Gaucher disease having a null allele has provided us with valuable insight into the human disease. It may also aid in the investigation of the role of specific lipids in skin. Potentially, as this transgenic technology is applied to create other animal models of metabolic diseases, it may enable us to recognize other, as yet unappreciated presentations of inherited disorders.

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