Neonatal Cholestasis as Initial Manifestation of Type 2 Gaucher Disease: A Continuum in the Spectrum of Early Onset Gaucher Disease

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Abstract Gaucher disease type 2 [OMIM #230800] is a rare lysosomal storage disorder with usual onset between 3 and 6 months of age leading to progressive neurodegeneration and death within the first 2 years of life. Rarely it may lack the characteristic symptom-free period and initially manifest prenatally or in the neonatal period. The early course of neonatal onset classic type 2 variants is not well known, and reports of early histological changes in the liver of type 2 Gaucher disease patients are scarce. We describe a patient who presented in the immediate postnatal period with cholestasis without hepatomegaly associated with hepatocellular giant-cell transformation on liver biopsy, thrombocytopenia, and failure to thrive. This was initially thought to represent neonatal giant-cell hepatitis and the correct diagnosis was not made until the age of 6 months. Hepatocellular giant transformation has not been described in the classic acute neuronopathic form of GD. However, it has been reported in congenital GD with nonimmune hydrops and neonatal hepatitis, an example of perinatal lethal Gaucher disease (PLGD), which sometimes is regarded as an entity separate from GD type 2. Our case illustrates that neonatal cholestasis may be part of a spectrum of manifestations which spans a continuum between the PLGD and classic type 2 GD. Giant cells are a nonspecific finding but may reflect the

presence of a systemic inflammatory process that recently has been implicated in the brain stem degeneration associated with acute neuronopathic GD.

Introduction

Three major phenotypes of Gaucher disease (OMIM #230800) have been described based on the absence (type 1) or presence (types 2 and 3) of central nervous system involvement. Type 2, also known as acute neuronopathic form, is rare, with an estimated frequency of 1/150,000 (Sidransky 1997). It typically presents between 3 and 6 months after birth with rapidly progressing neurological degeneration and visceral signs resulting in death prior to age 2 years (Grabowski and Beutler 2006). The early course of classic type 2 variants with neonatal onset is not well known. Here, we report the case of neonatal cholestasis associated with nonspecific giant-cell transformation on liver biopsy as initial manifestation of acute neuronopathic Gaucher disease.

Case History

The male infant was born at an outside hospital (OSH) to nonconsanguineous, African-American parents at 39 weeks gestation via C-section for breech presentation after an otherwise unremarkable pregnancy. His birth weight was 3,500 g. Postnatally, he developed jaundice with a conjugated bilirubin level of 8 mg/dl [136.8 μ mol/l] on the first day of life reaching maximum levels of conjugated bilirubin of 15.5 mg/dl [265 μ mol/l] and total bilirubin of 17.8 mg/dl [304.38 μ mol/l]. Liver transaminases showed maximal elevation for aspartate aminotransferase (AST) to 670 U/l and for alanine aminotransferase (ALT) to 330 U/l. Thrombocytopenia

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nia with platelets of $45,000/\text{mm}^3$ was treated with platelet transfusion within the first week of life while anemia was monitored reaching a hemoglobin level of 9.8 mg/dl within the first month. The report of a liver biopsy performed at 3½ weeks of life noted multinucleated hepatocytes (giant cells), a minimal intralobular inflammatory infiltrate and mild peripheral bile duct proliferation with cholestasis. Hepatic architecture was preserved and hepatocellular necrosis absent. Genetic evaluation during the newborn period at the outside hospital (OSH) was inconclusive yielding essentially normal results for plasma alpha-1 antitrypsin, plasma amino acids, urine organic acids, total and free carnitine, acylcarnitine profile, bile acids, GALT, very long chain fatty acids, and karyotype. At 6 months of age, the child was seen at the OSH for persistent failure to thrive. His weight was 4.79 kg (50th percentile for 6 weeks old), length 59 cm (50th percentile for 2 months old), head circumference 39.8 cm (50th percentile for 3 months old). A comparative genomic hybridization array, and a brain MRI were unremarkable.

Two weeks later, the infant was admitted to our service after a prolonged apnea episode. He had significant developmental delay. Neurological examination showed axial and appendicular hypertonicity and retroflexion of the neck with opisthotonus. Bulbar signs included ophthalmoplegia as well as dysphagia. The recurrent apnea episodes were not associated with stridor and suspected to be a manifestation of brain stem dysfunction in the absence of seizure activity in the EEG. His abdomen was protuberant with severe hepatosplenomegaly. A large, nonincarcerated umbilical hernia was present. Initial laboratory studies were significant for anemia, mild thrombocytopenia, and elevated liver transaminases, but the hyperbilirubinemia had completely resolved. The combination of central nervous system involvement, psychomotor retardation, hepatosplenomegaly and thrombocytopenia suggested the possibility of a lysosomal storage disease. Furthermore, the pattern of neurological impairment with markedly increased tonus and prominent bulbar signs pointed to the neuronopathic form of Gaucher disease as a primary differential diagnosis. A bone marrow aspirate did not contain the typical lipid-laden macrophages with fibrillary structures (Gaucher cells). However, a repeat liver biopsy now showed numerous enlarged histiocytes with cytological features typical of Gaucher cells and the giant-cell transformation seen in the earlier biopsy specimen was no longer apparent (Fig. 1a). The β -glucosylceramidase activity measured in the patient's leukocytes on two different blood specimens was 0.6 and 0.3 nmol/h/mg, respectively (reference range: 4–9 nmol/h/mg). The results indicated a profoundly reduced β -glucosylceramidase activity and confirmed the clinically suspected diagnosis of Gaucher disease. Sequence analysis of GBA, the gene encoding β -glucosylceramidase revealed a compound heterozygous genotype: one missense allele p.D409H

Fig. 1 CD68 stains with inserts of representative hematoxylin and eosin (H&E) stained histiocytes of liver biopsy specimen from the patient. **(a)**, Liver biopsy specimen at 6 months of age when child initially presented to our service. Distortion of normal hepatocellular plate pattern was noted and numerous enlarged histiocytes with cytologic features typical of Gaucher cells are apparent. **(b)**, Liver biopsy at 3½ weeks performed at the outside hospital. Paraffin blocks were obtained and stained in our pathology department. The pathology report from the OSH noted the presence of multinucleated hepatocytes (giant cells) and mild cholestasis with general preservation of the hepatic architecture. We used an antibody to CD68 to stain hepatic macrophages. This revealed more numerous and widespread enlarged sinusoidal histiocytes than are typically present in neonatal cholestasis, but these did not have the typical appearance of Gaucher cells (H&E insert)

(c.1342G>C) in exon 9; the other allele harbored three variants in *cis*, p.L444P (c.1448T>C), p.A456P (c.1483G>C), and p.V460V (1497G>C). In the following months, there was a progressive decline of the child's neurological status with the development of marasmus. Death occurred at the age of 14 months after a short course of pneumonia.

Case Discussion

We describe a rare course of neonatal Gaucher disease in a patient who presented in the immediate postnatal period

with cholestasis without hepatomegaly associated with nonspecific liver histology, thrombocytopenia, and severe failure to thrive. This was initially thought to represent neonatal giant-cell hepatitis. The correct diagnosis was not made until the age of 6 months, at what time he displayed the full spectrum of neurologic and visceral involvement associated with type 2 GD.

Rarely GD type 2 may lack the characteristic symptom-free period and initially manifest prenatally or in the neonatal period. A distinct phenotype termed perinatal lethal Gaucher disease (PLGD) has emerged (Mignot et al. 2003). In PLGD, clinical signs are present at birth and include arthrogryposis, ichthyosis, and facial dysmorphism. Nonimmune hydrops fetalis or *in utero* demise may be prominent features (Orvisky et al. 2002). Some authors regard PLGD as an entity separate from Gaucher disease type 2 based on the presence or absence of clinical signs at birth as well as the clinical spectrum of manifestation (Mignot et al. 2006).

In contrast to PLGD, there is a scarcity of information about the course of neonatal onset classic type 2 variants. As our case illustrates, atypical presentation during the early neonatal period can make an early diagnosis difficult. Predominant features at birth in this patient were direct hyperbilirubinemia, elevation of transaminases and thrombocytopenia in the absence of clinically detectable hepatosplenomegaly. Cholestasis was transient and associated with nonspecific histological changes on liver biopsy (Jevon and Dimmick 1998), which included hepatocellular giant cells.

We identified two previous case reports of early onset Gaucher disease with neonatal cholestasis and hepatomegaly and subsequent development of neurological signs consistent with the acute neuronopathic form (type 2) (Barbier et al. 2002; Schwartz et al. 2009). Details of a liver biopsy performed within the first month of life were available only for one report and, in contrast to our case, did not reveal giant-cell transformation (Barbier et al. 2002).

Three cases of neonatal cholestasis associated with severe courses of perinatal Gaucher disease reminiscent of PLGD were previously reported. The patients had facial dysmorphism, but no neurologic involvement. (Ben Turkia et al. 2009). One case presented with severe thrombocytopenia requiring platelet transfusions, but only mild direct hyperbilirubinemia peaking at 5.4 mg/dl and a normal neurological exam at 5 months of age (Roth et al. 2005).

These cases illustrate that neonatal cholestasis may be part of a spectrum of manifestations, which spans a continuum between the distinct phenotypes of PLGD and classic type 2 Gaucher disease. Detailed descriptions of early histological changes in the liver of type 2 GD patients are scarce (Abrahamov et al. 1995). Hepatocellular giant transformation observed in the initial liver biopsy from our case has not been described in the classic acute

neuronopathic form of Gaucher disease, but has been reported in congenital Gaucher disease with nonimmune hydrops and neonatal hepatitis (Spear et al. 2007) and is a known feature of other lysosomal storage diseases such as Niemann–Pick Type C (Jevon and Dimmick 1998). It is a frequent component of neonatal hepatitis occurring in all cholestatic conditions of infancy and as such is a nonspecific finding consistent with some degree of inflammation (Crawford 2006). Review of the initial liver pathology using an antibody to CD68 expressed in macrophages revealed more numerous and widespread enlarged sinusoidal histiocytes than are typically present in neonatal cholestasis, but these did not have the typical appearance of Gaucher cells (Fig. 1b). These findings suggest that inflammatory processes may be important in early pathogenesis and that the clinical phenotype is due to an effect of macrophage storage beyond the physical presence of the Gaucher cells (Cox 2001). Various proinflammatory cytokines have been implicated in the pathogenesis of Gaucher disease including IL-1 (Gery et al. 1981), TNF-alpha, IL-6, and IL-10 (Michelakakis et al. 1996; Allen et al. 1997). In the Gaucher mouse model, accumulation of glucocerebroside appears to mediate brain inflammation via proinflammatory cytokines (Hong et al. 2006). This raises the possibility that the initial nonspecific clinical and histological features could be manifestations of a systemic inflammatory response (SIR) and as such harbinger of an inflammatory process ultimately resulting in the brain stem degeneration associated with the acute neuronopathic course of GD.

Almost 300 mutations and several polymorphisms have been reported in the GBA gene, but the specific genotypes do not correlate well with the phenotype (Hruska et al. 2008; Sidransky 2004). Most mutations are rare and rarely found in the homozygous form. A recombinant allele containing the three point mutations as identified in our patient — two that introduce the amino acid substitutions L444P and A456P, and one silent mutation, V460V, in exon 10 — was first reported in 1990 and named RecNciI (Eyal 1990; Latham 1990). Recombinant alleles are essentially null alleles and despite being found in all three types of GD are associated with more severe disease manifestations (Tayebi et al. 2003; Cormand et al. 1998).

In summary, neonatal cholestasis presenting with nonspecific histological findings on liver biopsy can be a rare initial manifestation of acute neuronopathic GD. In the absence of typical neurological or visceral findings, a high index of suspicion is needed to make the diagnosis by measuring β -glucosylceramidase activity in lymphocytes or fibroblasts. Lack of Gaucher cells in liver or bone marrow specimen does not exclude GD. Molecular genetic analysis of the genotype may be of prognostic value and help with clinicopathological correlation in certain cases.

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