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SHORT REPORT

Type II Gaucher disease manifesting as haemophagocytic lymphohistiocytosis

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Summary Haemophagocytic lymphohistiocytosis (HLH) is a rare and rapidly progressive disease which, untreated, invariably leads to death. Gaucher disease is a rare lysosomal storage disorder. The acute neuronopathic variant; type II, is also rapidly progressive. We report an infant with Gaucher disease type II manifesting as HLH. Immunoblot revealed a deficiency of Munc 13-4, an intracellular protein responsible for docking of secretory lysosomes. This, and other possible pathogenetic mechanisms to explain the link are discussed.

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Abbreviations

FHL	familial HLH
GD	Gaucher disease
HLH	haemophagocytic lymphohistiocytosis
HSCT	haematopoietic stem cell transplantation

Introduction

Haemophagocytic lymphohistiocytosis (HLH) comprises familial and secondary forms. They can both be triggered by viral infections and both are clinically characterized by fever, hepatosplenomegaly, and pancytopenia, with associated raised ferritin and triglycerides. Central nervous system involvement, consisting of irritability and convulsions, is common (Haddad et al 1997).

The hallmark of the condition is immune dysregulation. On the one hand, there is a massive outpouring of cytokines from cytotoxic T lymphocytes and histiocytes. Despite this, the killing ability of these cells is defective, with impaired natural killer cell and cytotoxic T cell activity, which results in accumulation of T lymphocytes and activated macrophages, some of which may be phagocytes (Janka and zur Statdt 2005).

Familial HLH (FHL) comprises primary and secondary forms. Four genetic loci have been identified to be affected in patients with primary FHL. Affected genes have been identified in three out of these four loci—PRF1 (coding for perforin) (Stepp et al 1999), UNC13D (coding for Munc 13-4) (Feldmann et al 2003), and STX11 (coding for syntaxin 11) (zur Stadt et al 2005).

In the United Kingdom, HLH is treated with a combination of chemotherapy and immunotherapy

followed by haematopoietic stem cell transplant (HSCT). In secondary HLH, treatment of the cause of immune activation may be curative. The median survival was 1–2 months in the 1980s (Janka 1983), but in 2002 the estimated 3-year probability of survival was 51% (Filipovich 2005; Henter et al 2002).

Gaucher disease (GD) is a lysosomal storage disorder. It results from the deficiency of beta-glucosidase, resulting in the accumulation of its natural substrate, glucocerebroside. A small number of patients have the acute neuronopathic form, characterized by onset of neurological signs and symptoms in the first few months of life and death usually before the age of 2 years (Beutler and Grabowski 2001).

We report a case of a female infant diagnosed with severe HLH and who was found to have an absent Munc 13-4 protein on immunoblot. She was eventually found to have an underlying diagnosis of GD and died at 78 days of age. This case illustrates the diagnostic difficulties that can be encountered in both conditions, and also prompts further investigation into possible relationships between the two conditions.

Case report

A female infant was born at 36 weeks' gestational age. She developed respiratory distress at one hour of age and was transferred to the neonatal unit. She had petechiae, purpura, hepatomegaly, and massive splenomegaly.

Investigations revealed cytopenia. The blood film showed multiple nucleated cells and Heinz Jolly bodies. There was coagulopathy. The HLH screen revealed raised ferritin and normal triglycerides.

Bone marrow aspirate showed only one example of erythrophagocytosis noted in trails. Although there was no florid haemophagocytosis, this did appear on subsequent aspirates, along with occasional pseudo-Gaucher cells. The liver biopsy showed non-specific neonatal hepatitis, with no evidence of phagocytosis or a storage disorder.

Her clinical condition gradually worsened. Further investigations for HLH revealed that she had absent Munc 13-4 expression by Western blot; perforin expression was normal. In view of her absent Munc protein and clinical condition, she was commenced on treatment for HLH (Henter et al 2007). However, the response was poor. Hepatosplenomegaly, pancytopaenia with persistent transfusion requirement, and raised liver transaminases all persisted.

She also developed markedly increased tone with scissoring and opisthotonic posturing. MRI showed mild generalized cortical sulcal and ventricular prominence with no focal abnormality. The findings suggested a non-specific leukoencephalopathy and some cerebral swelling.

She continued to deteriorate over the next few weeks, with significant respiratory distress, acute renal failure, and tumour lysis syndrome. At this time, in view of her poor response, it was decided to proceed with HSCT.

Just before the HSCT was due, the cultured fibroblast enzyme assay revealed a glucocerebrosidase activity of 9 nmol/h per mg protein (normal range 35–191), confirming a diagnosis of GD. Peripheral blood could not be used for the assay as she had been recently transfused. It was decided to proceed with HSCT and this was therefore performed. However, over the next week she developed a severe pneumonitis, requiring intubation and ventilation. Despite maximal ventilatory support she continued to deteriorate and died aged 78 days.

Postmortem examination revealed PAS-positive diastase-resistant macrophages in the liver, spleen, and lungs. However, they did not have the typical morphology of Gaucher cells. The brain was entirely normal.

Discussion

The finding of features of HLH in an infant with proven GD prompted us to look for a possible connection between the two conditions.

Our patient had immunological features of HLH-cytokine excess as well as defective cytolytic activity. Cytokine excess is a also well-known feature of GD. The defective cytotoxicity may have resulted from Munc 13-4 deficiency. In the absence of a proven genetic cause of HLH (analysis of Munc 13-4 gene failed to identify a mutation), we assume this was secondary to GD. Secondary HLH is most usually attributed to viral infections. It is associated with immune deficiencies such as Chediak–Higashi syndrome, Griscelli and X-linked lymphoproliferative syndromes, rheumatological disease (macrophage activation syndrome), and malignancies. It is also associated with inborn errors of metabolism such as lysinuric protein intolerance and multiple sulfatase deficiency. It has, however, been described only anecdotally in association with GD (Mignot et al 2006).

The French GD2 study group published a retrospective study of 15 patients including a literature review (Mignot et al 2006). They found that 60% of those 15 patients showed signs of GD2 in the first few

days of life. The neurological manifestations were homogeneous, severe, and progressive. They included opisthotonus as well as apnoea. Pulmonary disease is the most severe non-neurological feature of GD2. As well as being due partly to consolidation, fibrosis, and arterio-venous shunting in hepatic disease, it may be secondary to interstitial infiltration by Gaucher cells (with associated inflammation) as they found in some specimens at autopsy, although this was not specifically looked for in our case. Features of GD2 that they found, which are common to HLH, include unexplained fevers and cytopenias,; both of which are explainable by the inflammation mediated by macrophages. Interestingly, they found erythrophagocytosis in the bone marrow of one of their patients (Mignot et al 2006).

The paucity of Gaucher cells in our patient was striking; the reason for this was unclear. It may be that very little storage is required to trigger erythrophagocytosis. The overwhelming underlying process of disease in GD appears to be inflammation as established by research groups across the world. Mizukami and colleagues recently developed mice carrying the GD point mutation L444P in the glucocerebrosidase gene(Mizukami et al 2002). These mice exhibited a partial enzyme deficiency and had multisystem inflammation including B-cell hyperproliferation. Hong and colleagues found that the fetal brains of Gaucher mice had very high levels of pro-inflammatory cytokines, nitric oxide, and reactive oxygen species (Hong et al 2006). They therefore hypothesized that accumulated glucocerebroside and glucosylsphingosine might mediate cerebral inflammation.

This infant presented a diagnostic dilemma. She satisfied 5 or more of the 8 clinical/laboratory criteria in addition to having a known genetic defect (absence of Munc 13-4, although subsequent gene analysis failed to find a defect) for a diagnosis of HLH (Ravelli et al 2005) (see Table 1). However, in retrospect there were some atypical features. Her disease was refractory to treatment for HLH. The neurological disease was atypical; opisthotonus is not typical, and the MRI did not show the typical appearance seen in HLH (though this is not always the case). Once the diagnosis of GD was confirmed, it all fell into place.

Munc 13-4 is an intracellular protein responsible for priming of the secretory vesicles. The reason for its absence in this patient is unclear. Possible explanations include downregulation of the UNC-13D gene, proximity of the accumulated glucocerebroside to the secretory lysosomes, or alternatively retention of mutated beta-glucosidase protein in the endoplasmic reticulum. The last mechanism has, in fact, been demonstrated by Horowitz and colleagues (Ron and Horowitz 2005). Further studies of the exocytic machinery in GD may help to unravel this problem.

Table 1 Diagnostic criteria for HLH[a]

1. *Familial disease/known genetic defect*
2. *Clinical and laboratory criteria* (5/8 criteria)
   - Fever
   - Splenomegaly
   - Cytopenia ≥ 2 cell lines (haemoglobin < 90 g/L (below 4 weeks < 120 g/L), neutrophils < 1×10^9 /L)
   - Hypertriglyceridaemia and/or hypofibrinogenaemia (fasting triglycerides ≥ 3 mmol/L fibrinogen < 1.5 g/L)
   - Ferritin ≥ 500 μg/L
   - sCD25 ≥ 2400 U/mL
   - Decreased or absent NK-cell activity
   - Haemophagocytosis in bone marrow, CSF or lymph nodes

Supportive evidence includes cerebral symptoms with moderate pleocytosis and/or elevated protein, elevated transaminases and bilirubin, LDH > 1000 U/L

[a] Ravelli et al (2005).

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