Isolated splenomegaly as the presenting feature of Niemann–Pick disease type C

J Imrie, J E Wraith

Abstract

We describe four patients with Niemann–Pick disease type C (NPC), in whom the presentation was isolated splenic enlargement; this remained the only abnormality for a number of years. Diagnosis can be suggested by either finding abnormal storage material in a tissue biopsy specimen or by showing a modest elevation in plasma chitotriosidase activity. In patients with suggestive abnormalities, filipin staining of a skin fibroblast sample should confirm the abnormality in cholesterol trafficking. Formal esterification studies and mutation analysis should also be performed, especially if prenatal testing is to be performed in subsequent pregnancies. If the diagnosis is not considered and established, the family are at risk of having further affected children. Investigation of patients with isolated splenomegaly is not complete until NPC has been excluded.

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Niemann–Pick disease type C (NPC) is an autosomal recessive lipid storage disorder, usually characterised by hepatosplenomegaly and severe progressive neurological dysfunction; it occurs as a result of mutations in the NPC1 gene in the vast majority of patients (95%). The NPC1 gene is known to have sequence homology with known sterol sensing proteins; a relatively common mutation in exon 21 (I1061T) in patients of Western European extraction, correlates with the common juvenile onset of the disease and is associated with the characteristic biochemical abnormality in intracellular low density lipoprotein (LDL) cholesterol processing.¹

A second, rarer complementation group (NPC2) cannot be distinguished by clinical or biochemical criteria, although severe pulmonary involvement may turn out to be a typical complication of mutations in the NPC 2 gene.²

Although the disorder is heterogeneous, three common phenotypes have been described³:

- (1) An early onset, rapidly progressive form associated with severe liver dysfunction and developmental delay in infancy, followed by supranuclear gaze palsy, ataxia, increasing spasticity, seizures, and dementia in those patients who survive the neonatal liver disease.

- (2) A juvenile onset form, correlating with the common NPC1 mutation and characterised by mild learning difficulties in childhood. There is a slowly progressive supranuclear gaze palsy, ataxia, and spasticity. Gelastic seizures, cataplexy, and complex epilepsies often occur and are difficult to control. Dementia usually occurs in teenage years, but survival into adult life is common.

- (3) A late onset variant similar to (2), but presenting for the first time in adolescence or adult life.

In addition, a non-neuronopathic form of the disease has been described.⁴

The pathogenesis of the disorder remains unclear. The NPC1 protein is implicated in the retrograde transport of sterols from lysosomes and has to be located to the lysosomal/endosomal compartment for proper function to occur.⁵

Unfortunately there is no effective treatment for NPC. The use of lipid lowering drugs⁶ and bone marrow transplantation⁷ have been ineffective in preventing the neurological decline in affected patients. Prenatal diagnosis is possible in the majority of families (but not all) if cholesterol processing abnormalities have been clearly shown in the index case.⁸

In some patients the disorder can present with isolated splenomegaly.⁹ Because of the genetic nature of NPC it is important to consider this diagnosis in all patients with splenic enlargement. Most patients will show the characteristic storage cells on bone marrow examination,¹⁰ but in some patients these cells will be difficult to identify and repeat examinations may be necessary.¹¹ In cases where there is doubt, or a high clinical suspicion in the presence of normal bone marrow findings, filipin staining of cultured skin fibroblasts should be performed.¹² To emphasise this point we present the details of four NPC patients whose only abnormal physical sign for a number of years was isolated splenic enlargement.

Patients

CASE 1

This female infant is the first child of healthy, unrelated, white parents. There were no neonatal problems and she was discharged home, well at 3 days of age. Early progress was uneventful until the age of 5 years when she presented to her local paediatrician with recurrent abdominal pain. On examination her spleen was found to be enlarged and palpable 4 cm below the left costal margin. Preliminary investigations including full blood count, blood film, and liver function tests were normal.

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Gaucher disease or Niemann–Pick disease type B were thought to be possible diagnoses, but both β -glucocerebrosidase and sphingomyelinase activity in leucocytes were normal. As part of the routine lysosomal studies in our laboratory, plasma chitotriosidase activity is measured as this enzyme is often increased in lysosomal storage disease. In NPC a modest elevation is typical, and in this patient was 536 $\mu\text{mol/l/h}$ (normal range 4–195 $\mu\text{mol/l/h}$; range in Gaucher disease 2000–70 000; range seen in eight of our NPC patients studied 152–1616 $\mu\text{mol/l/h}$). Filipin staining of cultured skin fibroblasts showed a possible defect of cholesterol esterification that was confirmed on formal studies, suggesting a classical biochemical subtype of NPC (M Vanier, Lyon).

At the age of 7 years the only abnormal physical sign continued to be splenic enlargement (4 cm); this continued until 8 years and 3 months when early signs of supranuclear gaze palsy became evident. No other neurological abnormalities have developed.

CASE 2

This female infant is the first child of healthy, unrelated, white parents. She was born normally at term and weighed 3200 g. There were no neonatal concerns.

At 9 months she presented to her general practitioner with an upper respiratory infection; during the course of the clinical examination, significant splenomegaly was detected (4 cm). No other abnormal clinical signs were detected. Following a referral to the local haematology services a bone marrow aspiration was performed that revealed foam cells. White cell enzyme analysis excluded Niemann–Pick disease types A and B (sphingomyelinase deficiency) and Gaucher disease (glucocerebrosidase deficiency). Filipin staining of a skin fibroblast culture was strongly positive and formal esterification studies were abnormal (A Fensom, London), confirming a diagnosis of NPC.

The patient has been followed up for five years. Considerable splenomegaly (4–6 cm) remains the only abnormal physical sign. The child's developmental progress is completely normal as is a detailed neurological and ophthalmological assessment.

CASE 3

This female patient is the second child of healthy, unrelated, white parents. She was induced at 34 weeks gestation after a pregnancy complicated by poor fetal growth. Her birth weight was 2200 g and she was nursed in the special care baby unit for 10 days before discharge home. There were no subsequent neonatal problems.

At the age of 2 years she presented to her local paediatrician with a history of abdominal pain and lethargy. Her spleen was enlarged (5 cm) but no other abnormalities were detected. Routine investigations including haematological indices, liver function tests, and white cell enzymes were normal. Chitotriosidase activity was 756 $\mu\text{mol/l/h}$; in view of our previous experience a bone marrow examination was

performed and a skin fibroblast culture collected. Foamy macrophages were seen on histological examination of the bone marrow and a defect in cholesterol esterification was confirmed on testing (M Vanier, Lyon).

No other significant abnormalities were reported despite persistence of the splenomegaly (5 cm) until the age of 7 years when an early gaze palsy became evident and gelastic seizures also became apparent. Over the next three years motor difficulties increased; at age 10 she was mainly in a wheelchair and was having regular speech therapy reviews for progressive dysphagia.

CASE 4

This male child is the first child of healthy, unrelated, white parents and was born at 36 weeks gestation by normal delivery. There were no neonatal problems and early health and development were normal. He was referred to his local asthma clinic at age 6 years and was noted to have splenic enlargement (4 cm). A number of investigations were done; results included a mild thrombocytopenia (platelets 115, normal 150–400 000) and an adenovirus titre of greater than 1/320, consistent with recent infection. Eighteen months later his spleen was still enlarged (5–6 cm) and he was referred for haematological assessment. Full blood count and film, routine liver function tests, and white cell enzymes were normal. Chitotriosidase activity was not measured and no further studies were performed as the child appeared so well. He continued to attend the asthma clinic and at the age of 12 years he was referred for metabolic opinion because of persisting splenic enlargement. Although there were no overt abnormal neurological findings there was a suspicion of very early gaze palsy with difficulty in maintaining upward gaze. His spleen was easily palpable 5 cm below the costal margin. Filipin staining of skin fibroblasts were strongly positive and characteristic of NPC. Formal esterification studies are awaited, but mutation analysis shows him to be homozygous for the common I1061T mutation.

Discussion

NPC is a heterogeneous disorder and at any time one may see patients with varying degrees of neurological abnormality. It is important to realise that a number of patients will present with isolated splenomegaly as their only abnormal physical sign. In an otherwise healthy patient there may be reluctance to consider bone marrow aspiration as a diagnostic test. Under these circumstances there will be a chance that the diagnosis will be delayed; in view of the genetic nature of the disease the family will be at risk of further affected children. Plasma chitotriosidase could be a useful additional investigation to consider, and if abnormal, further investigations to exclude a specific lysosomal storage disorder are indicated. If white cell enzyme studies are normal (excluding Gaucher disease and Niemann–Pick A and B), filipin staining of cultured skin fibroblasts should be performed to detect

NPC. If abnormal, formal esterification studies and mutation analysis should be performed. Investigation of the patient with isolated splenomegaly is not complete until NPC has been excluded.

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