CASE REPORT

Niemann-Pick type B in adulthood

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SUMMARY

Niemann-Pick disease (NPD) is a rare group of autosomal recessive disorders associated with intracellular deposition of sphingomyelin. NPD type B is a milder form, generally later in onset, with a good prognosis for survival into adulthood and usually with no neurological abnormalities. The authors describe the case of a 52-year-old man who presented with unexplained pancytopenia and splenomegaly. He was admitted to emergency splenectomy due to pathological splenic rupture. The histological findings showed diffuse histiocytosis, suggesting lysosomal storage disease. The NPD was confirmed when residual activity of acid sphingomyelinase in peripheral blood leucocytes and cultured skin fibroblasts was detected. Besides lipid abnormalities, the patient also had lipid interstitial pneumonia. There is no treatment for NPD. Management is based on surveillance and supportive care. The patient has reached the sixth decade of life with no symptoms and, despite the pneumonia and splenectomy, he still has a fairly healthy life.

BACKGROUND

Niemann-Pick disease (NPD) is a rare group of autosomal recessive disorders associated with intracellular deposition of sphingomyelin. There are three main forms: NPD type A is the acute neuro-pathic form, appearing during early childhood with a rapidly progressive neurodegenerative course that leads to death by the age of 2–3 years. NPD type B is a milder form, generally later in onset, with a good prognosis for survival into adulthood and usually with no neurological abnormalities. NPD type C has a highly variable age of onset, with systemic involvement of the liver, spleen and lung preceding the development of neurological symptoms, which can be very incapacitating.

There are some differences in the physiopathology as well as in the genetics between the different types of NPD. NPD types A and B are allelic disorders caused by mutations in the sphingomyelin phosphodiesterase-1 gene (SMPD1), and characterised by a primary deficiency of acid sphingomyelinase (ASM) activity, whereas NPD type C is caused by mutations of the NPC1 and NPC2 genes, has a smaller number of cases and results in impaired cellular processing and transport of low-density lipoprotein cholesterol.

The authors present a case of adult-onset NPD type B, with pulmonary involvement. As a rare disease, most clinicians are unaware of the presenting forms, probably leaving some patients undiagnosed. As there is progressively more evidence of new disease modifying therapies that can actually change the prognosis of these disorders, this report

aims to illustrate one of the forms of presentation of NPD type B, the way to diagnose it and the most important features to keep in mind.

CASE PRESENTATION

A previously healthy 52-year-old man was sent to the Internal Medicine outpatient clinic to investigate an accidentally discovered pancytopenia. The patient had been reporting of asthenia, anorexia and non-quantified weight loss for some time. The initial workup revealed an unexplained splenomegaly and only the thrombocytopenia persisted. He was diagnosed with a dyslipidaemia. Liver function was completely normal and viral serologies were negative (cytomegalovirus, Epstein-Barr virus, hepatitis C and B, HIV and parvovirus). Antinuclear antibodies were also negative and serum protein electrophoresis, immunophenotyping and β -2-microglobulin were normal. The splenomegaly was heterogeneous with some hypo-dense nodules. CT of the lungs showed a generalised interstitial pattern and pulmonary function tests revealed low diffusing capacity of carbon monoxide (DLCO) and hypoxaemia.

While the patient was waiting for a bone marrow aspiration and biopsy, he was admitted in the emergency department with an acute, sharp, left flank abdominal pain, accompanied by syncope. His haemoglobin was 7.9 g/dL and the CT scan showed a splenic rupture. The patient was submitted to emergency splenectomy and the histological findings were consistent with diffuse histiocytosis, suggesting lysosomal storage disease.

INVESTIGATIONS

The patient finally had a bone marrow biopsy, which revealed sea-blue histiocytosis, a sign of a storage disease. The NPD was confirmed when residual activity of ASM in peripheral blood leucocytes and cultured skin fibroblasts of less than 10% of that of controls was detected (sphingomyelinase activity 0.0 nmol/h/mg with a normal range between 0.84 and 3.36 in peripheral blood and 3 nmol/h/mg with a normal range between 18 and 300 in cultivated fibroblasts of the skin). All the typical clinical features of NPD type B were present: splenomegaly with thrombocytopenia, interstitial lung disease and lipid abnormalities. Finally, the molecular study showed homozygosity for the SMPD1 mutation c.1829_31delGCC (p. R610del), described as causing NPD type B.

DIFFERENTIAL DIAGNOSIS

- Gaucher disease
- NPD type B

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TREATMENT

There is no specific treatment for NPD. Management is based on surveillance and supportive care.

The patient maintained regular visits to the Internal Medicine outpatient clinic and was also sent to the Genetic outpatient clinic.

Lowering lipid treatment (simvastatin) was started and regular pulmonary evaluation was performed.

OUTCOME AND FOLLOW-UP

For the last year, the patient has been reporting of worsening dyspnoea on exertion and wheezing. At lung auscultation, faint crackles were apparent in both lung bases. The last chest CT scan showed ground glass opacity with basal predominance, possibly related to lipid interstitial pneumonia, worse in comparison to previous examinations. The pulmonary function tests showed preserved flow rates and lung volumes with a decreased DLCO and hypoxaemia. The patient was sent for pneumology evaluation and was started on bronchodilators. For the moment there is no need for supplementary oxygen but the patient will be re-evaluated periodically.

DISCUSSION

NPD, also called sphingomyelin-cholesterol lipidosis, is a lysosomal storage disease caused by deficient activity of ASM and the accumulation of sphingomyelin within cells of the monocyte-macrophage system.¹ This typical accumulation of sphingomyelin may result from a variety of biochemical derangements, including enzyme deficiency and altered intracellular cholesterol processing, which are associated with the accumulation of 'foam cells'. Although the diagnosis is usually established in childhood, the disease may rarely be first recognised in adolescence or adulthood, as this case illustrates.² There are several types of NPD, mainly types A, B and C, differing from each other in age of onset, neurological manifestations and type of substrate accumulation. The overall prevalence of ASM deficiency (types A and B combined) is estimated to be 1:250 000.³

NPD type B is pan-ethnic, generally later in onset and less severe, with a good prognosis for survival into adulthood.⁴ It is characterised by hepatosplenomegaly with progressive hyperesplenism, worsening atherogenic lipid profile, gradual deterioration in pulmonary function and stable liver dysfunction.⁴

Diagnostic suspicion is the main path to diagnosis. The combination of signs and symptoms, which can be similar to many other diseases, may raise the hypothesis and lead to the diagnosis. The diagnosis of ASM is confirmed when residual ASM activity in peripheral blood leucocytes or cultured skin fibroblasts is less than 10% of that of controls.^{4 5}

Bone marrow examination reveals sea-blue histiocytes and lipid-laden macrophages. Molecular genetic testing can also confirm the diagnosis of ASM deficiency if it identifies both disease-causing alleles, but such testing should only be used after biochemical testing for ASM activity.⁴

There is no treatment for NPD that has been proven to modify the onset or neurological progression of the disease or

to prolong lifespan.⁴ Therefore, the management of these patients is based on surveillance and supportive care. Patients with NPD type B should be evaluated at least yearly for: history (growth and weight (in children), fatigue, bleeding, dyspnoea, abdominal pain, headaches, extremity pain, any change in social, domestic, school-related or work-related activities), physical examination (including neurological functions), blood tests (including liver enzymes, platelet count and fasting lipid profile), pulmonary function testing and chest radiograph, skeletal assessment, and nutrition assessment. Individuals who have splenomegaly should avoid contact sports.⁴ Genetic counselling and prenatal testing should be offered.

The presented case describes a patient whose first disease manifestations were cytopenias and splenomegaly. The diagnosis was hastened by pathological splenic rupture, which is the most feared acute complication of this disease. However, the patient has survived until the sixth decade of life with no symptoms and even now, despite the lung involvement and splenectomy, he continues to have a fairly healthy life. It is known that his neurological functions may also become affected and his pulmonary function may deteriorate even more. Nonetheless, survival until this age with such a good quality of life makes this case worth publishing.

Learning points

- ▶ Unexplained cytopenias and organomegalies should raise the possibility of a lysosomal storage disease.
- ▶ There is no specific treatment for Niemann-Pick disease (NPD) and its management is based on surveillance and supportive care.
- ▶ Patients with NPD type B can survive with fairly good health until adulthood and lead a normal life.

Contributors RGS and HM performed diagnosis, treatment and follow-up. The case report was written by RGS and revised and approved by HM.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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