CASE REPORT

Niemann-Pick disease type C or Gaucher's disease type 3? A clinical conundrum

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SUMMARY

We describe a patient who presented with a neurovisceral syndrome characterised by ataxia, bulbar dysfunction, supranuclear gaze palsy, splenomegaly and foamy histiocytes in the bone marrow. This presentation was suggestive of a lysosomal storage disorder such as Niemann-Pick disease type C or Gaucher's disease type 3. We review the presentation of these disorders, with a focus on the neurological features. In addition, we briefly discuss the disease-modifying therapeutic options which have recently become available.

BACKGROUND

Gaucher's disease (GD) and Niemann-Pick disease (NPD) are rare autosomal recessive lysosomal storage disorders (LSD). GD is the most common LSD, with an estimated incidence of 1 in 40 000 live births, and results from the deficiency of the enzyme β -glucosidase.¹ NP type A and B result due to deficiency of the enzyme sphingomyelinase.² In contrast, NPD type C (NP-C) occurs due to abnormalities in the intracellular trafficking of lipids, particularly cholesterol.² NP-C is seen among all ethnic groups and has an estimated incidence of 1 in 120 000 live births.³

Being rare illnesses, most clinicians are unfamiliar with the clinical presentation of both these disorders, leading to underdiagnosis. The advent of disease-modifying therapies has made it increasingly important to improve awareness regarding these disorders. In this case report, we present a patient with a neurovisceral syndrome compatible with a diagnosis of either NP-C or GD type 3. Through this report we would also like to highlight the difficulties in diagnosing and treating these patients, especially in resource poor settings.

CASE PRESENTATION

A 25-year-old woman presented to us with insidious onset, gradually progressive symptoms in the form of imbalance, and a tendency to fall while walking of 2 years duration. In addition, she had noticed slurring of her speech for the past 1 year, and difficulty in swallowing since the past 6 months. She had no history of cognitive decline, behaviour abnormality, seizures, involuntary movements, parkinsonism, motor weakness, sensory symptoms or autonomic dysfunction. She had no significant medical history, and no history to suggest similar illness in other family members.

On general examination she was found to have pallor and mild splenomegaly. Neurological examination was positive for restriction of gaze both in

the horizontal and vertical directions with preserved movements elicited using the oculocephalic manoeuvre, slow saccades, mixed dysarthria having both cerebellar and pseudobulbar features, decreased palatal movements, Babinski sign bilaterally and gait ataxia with minimal limb ataxia.

INVESTIGATIONS

Complete blood counts showed a haemoglobin level of 8.6 g/dL, TC of 7300/mm³ and a platelet count of 163 000/mm³. Erythrocyte sedimentation rate was 16 mm/h. Peripheral smear revealed a microcytic hypochromic anaemia. Blood sugar, renal, liver and thyroid functions were normal. Serum lactate, copper and ceruloplasmin assays were within the normal range. Ultrasound abdomen confirmed splenomegaly, where as the rest of the study was normal. In view of the clinical findings, we performed an MRI of the brain specifically looking for abnormalities in the brainstem and cerebellum in view of the clinical presentation; however this was found to be normal. A T1 axial MRI image of the patient at the level of the mid-brain is shown in [figure 1](#). Nerve conduction studies were normal. Cardiac evaluation with ECG and echocardiogram was normal. Bone marrow aspiration and trephine biopsy showed scattered foamy histiocytes in a background of normal hematopoietic cells, as shown in [figure 2A,B](#). Sphingomyelinase enzyme assay was within normal limits.

DIFFERENTIAL DIAGNOSIS

- Niemann-Pick disease type C
- Gaucher's disease type 3

DISCUSSION

Our patient's clinical presentation comprising supranuclear gaze palsy, ataxia, pseudobulbar features and mild splenomegaly is compatible with both NP-C and GD type 3. We discuss the clinical features of these two disorders below and finish by discussing the pathophysiology, diagnostic confirmation and treatment of NP-C.

NPD presents in three different forms: type A is characterised by fatal infantile neurological deterioration with visceromegaly, whereas type B has visceral involvement only. NP-C is a neurovisceral syndrome that manifests in early life, but may rarely be seen in the elderly.^{2 4} The clinical presentation varies depending on the age of onset and can be classified as pre/perinatal (<3 months), early infantile (3 months to 2 years) late infantile (2–6 years), juvenile (6–15 years) and adult onset.^{2 4} The pre/perinatal

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Figure 1 Normal T1 axial MRI of the brain at the level of the midbrain with no evidence of atrophy.

type has a predominant visceral presentation with prolonged cholestatic jaundice, fetal ascites, hepatosplenomegaly and occasionally hepatic failure.²⁻⁴ In the early infantile and late infantile types,

Figure 2 (A) H&E stain showing foamy histiocytes (arrow) in the background of normal haematopoietic cells. (B) Foamy histiocyte shown in higher magnification.

neurological features are seen more often, and are characterised by delayed motor milestone, hypotonia, gait ataxia, dysarthria, dysphagia, hearing loss, cataplexy and seizures.²⁻⁴ Visceral attributes such as hepatosplenomegaly continue to be a marked feature of the disease. However, this becomes less obvious with later onset. In juvenile and adult onset varieties, behavioural problems, learning disability, psychosis and depression are increasingly seen.²⁻⁴ Abnormal saccadic eye movement is a key clinical feature suggesting the diagnosis of NP-C. It is often the earliest sign, and can be seen even in the early infantile period, but may be difficult to recognise at such a young age.²⁻⁴ The eye movement abnormality initially involves vertical gaze and is typified by delayed initiation and slowness of saccadic movement with preserved pursuits.²⁻⁴ This progresses to restricted degree of movement, and later on in the disease involves the horizontal direction.²⁻⁴

GD is also a neurovisceral syndrome with a varied presentation. GD type 1 which is the most frequent type, accounting for 95% of cases, was initially considered a non-neuropathic disease characterised by hepatosplenomegaly, cytopenia and bone disease.¹ However, recently an association between GD and Parkinson's disease (PD) has been found.⁵ In fact heterozygous mutation in the glucocerebrosidase gene (GBA), which is the gene implicated in GD, has been demonstrated to be the strongest genetic risk factor for PD.⁶ GD type 2 affects infants with an acute neuropathic presentation and visceromegaly; it is rapidly fatal.¹ GD type 3 may have systemic features, but usually presents with neurological features in the form of ataxia, seizures, horizontal supranuclear gaze palsy and dementia.¹

Our patient's clinical presentation, comprising supranuclear gaze palsy, ataxia and pseudobulbar features, is compatible with both NP-C and GD type 3. Supranuclear gaze palsy is an important neurological finding in both the disorders. In NP-C this typically involves vertical gaze initially, whereas it involves horizontal gaze in GD type 3. The preservation of oculocephalic reflex points to the supranuclear origin of gaze difficulty. In contrast to the description of adult onset NP-C in the literature, psychiatric symptoms, cognitive decline, seizures, myoclonus and cataplexy²⁻⁴ were not present in our patient. Additionally, splenomegaly is only seen rarely in adult onset cases. We were able to detect splenomegaly using ultrasound examination. For GD type 3, the absence of systemic features could be a pointer against the diagnosis. However, patients with mild systemic manifestations and severe neurological disease have been described.⁷ In terms of imaging, MRI of the brain in patients with NP-C can be normal in the early course of the disease.⁸ Later, the radiological abnormality correlates with the predominant clinical manifestation.⁸ Patients with predominant psychiatric and cognitive symptoms have cortical atrophy, whereas patients with gait difficulty and movement disorders, as seen in our patient, have brainstem and cerebellar atrophy.⁸ In addition, white matter changes and corpus callosum atrophy have been described using both routine MRI imaging and diffusion imaging.⁹ In our patient no white matter changes were seen. The corpus callosum appeared normal; however, sagittal images, the ideal sequence to comment on the corpus callosum, were not obtained. In patients with GD type 3, MRI of the brain can be normal or demonstrate mild cerebral atrophy.¹⁰ Sphingomyelinase levels were normal; this is an expected finding in patients with suspected NP-C, as the defect involves intracellular trafficking of lipids rather than an enzyme deficiency. An additional relevant finding seen in our patient was the presence of foamy histiocytes in the bone marrow. Foamy histiocytes are macrophages containing empty vacuoles, filled with soluble non-oxidised lipids and non-soluble oxidised lipids.

They are an indicator of either increased production of lipids, such as in myelodysplastic syndromes where there is an increased cellular turnover in the marrow, or conditions where there is a failure of catabolism of lipids such as in NP-C.¹¹ On staining with Giemsa solutions, the oxidised lipid granules stain with a characteristic blue colour and are called sea blue histiocytes.¹¹ These have also been described in GD, although the characteristic description is that of a wrinkled paper appearance. Although bone marrow findings may be suggestive, confirmation of the diagnosis should be based on enzyme assays in GD and in NPD types A and B. The diagnosis of NP-C is discussed in detail below. Unfortunately, we were unable to make an accurate diagnosis in our patient because of a lack of sufficient resources at our centre to perform confirmatory testing.

NP-C results due to abnormal intracellular processing and transport of cholesterol, glycosphingolipids and sphingosine, resulting in an accumulation of these lipids in late endosomes/lysosomes of the liver, spleen and brain.²⁻⁴ The underlying aetiology in NP-C is a mutation in either the NPC1 (95% of cases) or the NPC2 (4% of cases) gene.²⁻⁴ In the rest, a mutation has not yet been identified. Diagnosis of NP-C is based on special biochemical tests which demonstrate the abnormal intracellular processing of cholesterol in living cells. Currently, the filipin test is the most sensitive and specific biochemical test for the diagnosis of NP-C.²⁻⁴ In this test, skin fibroblasts are cultured in a low-density lipoprotein enriched medium, and later fixed and stained with filipin. In classical NP-C, fluorescence microscopy will reveal fluorescent perinuclear vesicles filled with cholesterol. In a subset of patients this test may be inconclusive. NP-C is confirmed by identifying a known pathogenic mutation in either the NPC1 or NPC2 gene.²⁻⁴ Ideally NP-C is diagnosed by performing the filipin test followed by confirmation with genetic testing. Pharmacological therapy for NP-C, till recently, consisted primarily of medications to improve the symptoms of the disease. The introduction of a novel drug called miglustat has provided a disease-modifying therapeutic option, which can potentially stabilise the disease, and may help in reversing some of the neurological manifestations.²⁻⁴ The safety, efficacy and tolerability of miglustat at a dose of 200 mg three times a day has been well demonstrated in several trials, and it is the only agent which has shown efficacy and has been approved for the treatment of NP-C.²⁻⁴ Miglustat is an iminosugar compound, first used for the treatment of Gaucher's disease. It acts as a competitive inhibitor of the enzyme glucosylceramide synthase, which is the first committed step in glycosphingolipid synthesis, thereby reducing the accumulation of toxic gangliosides. Overall miglustat has been found to be well tolerated, with common adverse effects noted being diarrhoea, flatulence, weight loss and tremor.⁴

Current therapeutic options for GD include enzyme replacement therapy or substrate reduction therapy with drugs like miglustat.¹ They have not been clearly shown to be beneficial for the neurological manifestations but are very useful for the systemic features.¹² Although miglustat has shown efficacy in NP-C,⁴ to our knowledge, it is not available in our country. As

such the diagnosis and management of patients with such rare and devastating disorders is further complicated in resource poor settings by financial constraints, lack of expertise and non-availability of the appropriate drug.

Learning points

- ▶ Gaucher's disease (GD) and Niemann-Pick disease (NPD) results from a deficiency of the enzyme glucosidase and sphingomyelinase, respectively. However, in NPD type C (NP-C) there is no enzyme deficiency and the defect is in intracellular lipid transport.
- ▶ Systemic features, such as splenomegaly, should alert the clinician to the possibility of NP-C and GD type 3. However, systemic features may not be obvious in all patients.
- ▶ Supranuclear gaze palsy especially in a young patient should raise the suspicion of NP-C (vertical gaze is involved initially) and GD type 3 (horizontal gaze is affected initially).
- ▶ Disease-modifying therapies such as enzyme replacement therapy and substrate reduction therapy with miglustat should be considered in these disorders.

Competing interests None.

Patient consent Obtained.

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