

## TEACHING FILES (GRAND ROUNDS)

### IS IT GAUCHER'S DISEASE OR NIEMANN-PICK'S DISEASE?

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#### Clinical Problem

A three and a half-year-old girl, currently bedridden, presented in 2013 with progressive loss of milestones from two years of age. On examination she showed poor oral hygiene, oral thrush over the hard palate, left cervical lymphadenopathy of size 2x2cm, and hepatomegaly (1cm), splenomegaly (10 cm). In 2011, she was diagnosed with Gaucher's disease and advised regarding enzyme replacement therapy. Bone marrow examination at that time had shown foamy macrophages and a lysosomal enzyme study revealed reduced levels of beta-glucosidase (Patient: 3.7 nmol/m/hr, Control: >13 nmol/m/hr), raised plasma chitotriosidase (4274.8 nmol/m/hr) and normal levels of sphingomyelinase enzyme. She also had pancytopenia. In July 2012, a genetic test for Gaucher's disease was negative. On presentation to us in 2013 in view of neurological involvement, a repeat beta-glucosidase levels were done which was 3 nmol/m/hr (low), chitotriosidase was 2879 nmol/m/hr and sphingomyelinase was 9.3 nmol/m/hr (normal). A further genetic test showed NPC1 gene mutation and a normal NPC2 gene suggestive of Niemann-pick type C 1 disease.

*Is this Gaucher's disease or Niemann Pick disease?*

#### Discussion

Gaucher's disease and Niemann-Pick's (NPC) disease are classified as lysosomal storage disorders with autosomal recessive inheritance. Gaucher's disease (GD) is the most common lysosomal storage disease in India and worldwide and should be considered in any child or adult with unexplained hepatosplenomegaly and cytopenia. (1) It is caused due to deficiency of beta-glucosidase and leads to accumulation of lipid-laden macrophages in various tissues. Type 1 GD is a non-neuronopathic form and type 2 and 3 are neuronopathic (1). Niemann pick disease (NPD) is classified as Type A (Classic infantile neuronopathic form), Type B (Non-neuronopathic visceral) and Type C (juvenile form). (2) Type A and Type B occur due to deficiency of acid sphingomyelinase. Type C occurs due

to defective transport of cholesterol and glycolipid. (3) They ultimately lead to accumulation of sphingomyelin and cholesterol in the monocyte-macrophage system characterized by lipid-laden macrophages or Niemann pick cells (NP cells). (2) Niemann-pick disease type C (NPC) in approximately 95% of patients have a mutation in NPC1 gene which encodes large membrane glycoproteins, and the remainder 5% have mutations in NPC2 gene which encodes a small soluble lysosomal protein with cholesterol binding properties. (4)

Type 1 GD and Type1 NPD have overlapping presentation. They usually present from infancy to late childhood with hepatosplenomegaly, cytopenias, irritability, bone marrow involvement and failure to thrive. NPD additionally also causes loss of early motor skills which was seen in our patient, recurrent infections, and in later stages, loss of intellectual capabilities, rigidity and spasticity. (5,6) Definitive diagnosis for both diseases is made by enzyme assay. Molecular studies for mutation are useful in confirming diagnosis, screening family members, and prognosticating the disease. (1)

Our patient was initially diagnosed with GD due to reduced levels of beta-glucosidase, elevated chitotriosidase, normal levels of sphingomyelinase, and compatible clinical presentation like hepatosplenomegaly and pancytopenia. Low beta-glucosidase activity is observed in both NPD and GD, at least in leukocytes and can lead to false positive testing for GD. Glucocerebroside (GCCase) accumulates within cells deficient in NPC1 protein and this occurs despite the lack of GBA1 mutation. The precursor of glucocerebroside/beta-glucosidase is found at normal levels in NPC fibroblasts, however, the level of the mature protein is reduced. This pattern suggests accelerated breakdown of mature GCCase rather than decrease in production. This is in contrast to GD1 where the GBA1 gene mutation causes a decrease in production of GCCase. (7) A second diagnostic marker like chitotriosidase or TRAP can help in diagnosis. (7) Chitotriosidase (CT) is an enzyme that is selectively activated in tissue macrophages and is markedly elevated in lysosomal storage diseases. A positive chitotriosidase is neither sensitive nor specific and can be useful in screening patients. It can be elevated in GD and NPD. CT levels above 200 nmol/h/ml are predictive for GD, NPD type A, B or C, but levels above 4000 nmol/h/ml are predictive of GD. (7,8) A diagnostic delay can occur in NPC due to overlapping

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features with Gaucher's disease and false positive testing for beta-glucosidase and hence requires a high index of suspicion along with mutation analysis to diagnose correctly.

**Compliance with Ethical Standards**

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**Conflict of Interest:** None

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