Clinicopathological Conference Report—PM 27096

A 12-year-old Girl with Massive Hepatosplenomegaly

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This case (PM 27096) was discussed on 3-2-2016, as a staff clinicopathological exercise at PGIMER, Chandigarh, India.

Clinical details and Case analysis – Renu Suthar (Department of Pediatrics, PGIMER, Chandigarh, India)

CLINICAL DETAILS
A 12-year-old girl presented with a history of progressive abdominal distention noticed from infancy. Abdominal distention was insidious, progressive, and predominantly involving upper abdomen and there were no complaints of abdominal pain, constipation, vomiting, or breathing difficulty. History of mild periorbital puffiness was noticed from 11 years of age. She was also noted to have poor linear growth. There was no history of jaundice, bleeding manifestations, blood transfusion, pedal edema, anasarca, diurnal fluctuations in periorbital puffiness, seizures, paresthesia, diminished vision, coarsening of facial features, and previous hospitalization.

She was born to a nonconsanguineously married couple and her birth and development history was normal. She has a similarly affected younger brother who was also noticed to have progressive abdominal distention form infancy. Both the siblings were developmentally normal and attending regular school.

EXAMINATION
On examination, her weight was 26 kg (<3rd centile), height was 129 cm (<3rd centile), and head circumference was 51 cm [(between mean and –2 standard deviation (SD)]. Her blood pressure (BP) records were >99th centile (BP 130/90 mm Hg). She had mild periorbital puffiness, thickened skin, absence of subcutaneous fat and subtle facial dysmorphism. She had prominent forehead, receding hairline, long philtrum, and thin upper lip. Massive firm hepatomegaly (span 16 cm) and splenomegaly (span 21 cm) was present. Cardiovascular examination showed short systolic murmur at cardiac apex. Other systemic examination was normal.

INVESTIGATIONS
- Biochemistry: Na: 137 mEq/l, K: 4.7 mEq/l, Cl: 107 mEq/l, Urea: 16 mg/dl, Cr: 0.2 mg/dl, TSP: 7.1 gms/dl, Alb 4.2 gms/dl. AST: 56 U/l, ALT: 67 U/l, ALP: 151 U/l, Uric acid: 2.8 mg/dl, Serum amylase: 445 U/l, Coagulogram: PT: 18 seconds, aPTT = 43 seconds, PTI: 72%, INR: 1.35, RBS: 192 mg/dl, Lipid profile: Cholesterol: 187 mg/dl, low-density lipoprotein (LDL): 121 mg/dl, high-density lipoprotein (HDL): Very low, Triglycerides: 243 mg/dl, Urine routine: normal.
- Radiology: Chest X-ray – normal (Fig. 1A). X-ray spine was normal, and there was no evidence of skeletal dysplasia or dysostosis multiplex.
- Ultrasonography (USG): Abdomen showed hepatomegaly (size 21 cm, normal echo texture), gallbladder was distended and splenomegaly (size 22 cm and

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normal echo texture). Right kidney measured 9.8 cm and left kidney 9.9 cm; both were normal in size and shape. Portal vein was normal in size.

- Electrocardiogram was normal.
- Echocardiogram showed mitral valve prolapse with moderate mitral regurgitation and normal left ventricular ejection fraction.
- Upper gastrointestinal (UGI) endoscopy showed normal esophagus and nodularity of antral mucosa. Duodenum showed thickened mucosal folds with nodularity (Fig. 1B). Duodenal biopsy showed normal epithelial lining. Histopathology showed lymphoplasmacytic infiltrates in lamina propria, and collection of large foamy cells with finely vacuolated cytoplasm.

**Investigations in Sibling of Index Patient**

Younger brother of the index child also had progressive abdominal distention noticed from infancy. He was admitted in pediatric emergency with acute severe headache and seizures. Anthropometry was suggestive of short stature and normal head size. He also had massive hepatosplenomegaly and hypertensive BP records (BP 218/135 mm Hg). He was managed in pediatric intensive care unit for hypertensive emergency. Subsequently, he had worsening respiratory distress and required intubation and mechanical ventilation.

Investigations showed anemia (Hb 9.7 gm/dl), leukopenia (TLC 3900/µl), and thrombocytopenia (29,000/µl). Biochemistry showed elevated urea: 130 mg/dl and creatinine: 0.76 mg/dl. Total serum protein was 7.2 gms/dl, serum albumin was 2.2 gms/dl, total serum bilirubin was 2.2 mg/dl, and conjugated fraction was 1.1 mg/dl. Aspartate aminotransferase (AST) was 113 U/l, alanine aminotransferase (ALT) was 59 U/l, alkaline phosphatase (ALP) was 71 U/l. Lipid profile showed 171 mg/dl total cholesterol, 281 mg/dl triglycerides, 60 mg/dl, LDL cholesterol, and 5 mg/dl HDL cholesterol.

Bone marrow biopsy showed normocellular marrow with abundant large periodic acid–Schiff (PAS) negative foamy histiocytes suggestive of a storage disorder. Further investigation showed negative urinary glycosaminoglycans (GAGs), normal levels of enzyme acid sphingomyelinase (ASM) assay, and enzyme beta-glucosidase. He had worsening respiratory distress and required high-frequency ventilation. He showed features of restrictive interstitial lung disease and died with respiratory failure.

**Course and Management**

She was admitted in pediatric gastroenterology and she underwent UGI endoscopy. Subsequently, after few hours, she started having intractable vomiting. Blood pressure (BP: 160/140 mm Hg) was high and soon she became encephalopathic. She was started on intravenous labetolol infusion for hypertensive crisis. Blood pressure was controlled and her encephalopathy and irritability improved for few hours. Within 6 hours of infusion, she had precipitous fall in BP, infusion was stopped, fluid boluses were given, and dopamine infusion was started. She became pale, unresponsive, and her BP was not recordable. She required intubation; however, she had bradycardia and cardiac arrest.

**Unit Final Diagnosis**

Lysosomal storage disorder ? Niemann–Picks Disease (NPD) type B ??Glycogen storage disorder ??? Mucopolysaccharidoses

**Cause of Death**

The cause of death was accelerated hypertension with possible cardiac event/intracranial/major internal hemorrhage.
Case Analysis: Dr Renu Suthar

We have a 12-year-old, developmentally normal girl born to nonconsanguineous parents with insidious onset and gradually progressive abdominal distention form infancy. She had a similarly affected 9-year-old younger brother. Both the siblings had subtle facial dysmorphism, short stature, peri-orbital puffiness, thickened skin, and massive hepatosplenomegaly. Clinical course was similar; both presented with malignant hypertension at the same time and died due to hypertensive emergency.

Causes of massive hepatosplenomegaly include infections, malignancy, hemolytic anemia, and lysosomal storage disorders. These two siblings had an autosomal recessively inherited familial condition, possibly a lysosomal storage disorder. Other causes like infections, malignancy, and hemolytic anemia were less likely because of an inherited familial disorder and there was no history of fever, jaundice, recurrent blood transfusion, and bleeding manifestations. Intellectually, these siblings were normal and had a normal head circumference, so a non-neuronal lysosomal storage disorder was more likely. Absence of significant facial dysmorphism, coarse facial features, and skeletal dysostosis was against the diagnosis of mucopolysaccharidoses. Glycogen storage disorders present with recurrent episodes of hypoglycemia and hepatomegaly.

Investigations in both the siblings were suggestive of bone marrow infiltration (anemia, leukopenia, and thrombocytopenia), hepatic dysfunction (mild transaminits, conjugated hyperbilirubinemia, and coagulopathy), and infiltration of various organs and tissues with lipid-laden foamy histiocytes (bone marrow, mucosa of stomach and duodenum, liver and spleen, lungs). Lipid profile was suggestive of markedly reduced levels of serum HDL and elevation of triglycerides.

Non-neuronal lysosomal storage disorders, such as Gaucher Disease type 1 and NPD type B were strongly considered as differential diagnosis in these siblings. Another group of disorders related to cholesterol metabolism and transport, including cholesterol ester storage disorder (CESD), Niemann–Pick (NP) type C, and Tangiers disease were also considered as differential diagnosis.

Children with Gaucher disease type 1 can have massive hepatosplenomegaly, thrombocytopenia, anemia, leukopenia, poor linear growth, mitral valve prolapse, and renal involvement. However, significantly abnormal lipid profile and accelerated hypertension remained unexplained with Gaucher disease. Further bone marrow biopsy showed PAS-negative storage cells with vacuolated cytoplasm and a characteristic “sea blue histiocytes” morphology. Storage cells in Gaucher disease are PAS positive and have “crumpled paper” appearance.

Niemann–Pick disease is a lysosomal storage disorder due to deficiency of enzyme ASM. Niemann–Pick type B is non-neuronopathic storage disorder with variable age of onset and variable clinical presentation. Most common clinical features are massive hepatosplenomegaly, anemia, thrombocytopenia, leukopenia, pulmonary infiltration with storage cells, transaminitis, and growth failure. Niemann–Pick disease type B is also reported to have lipid abnormalities characterized by low HDL, normal or elevated triglycerides, and total cholesterol. These patients have a higher tendency to have atherosclerotic changes in major blood vessels because of atherogenic lipid profile. Diagnosis of NPD type B in index child was also supported by PAS-negative “sea blue histiocytes” in bone marrow of the sibling. Enzyme analysis for ASM in younger sibling showed normal enzyme activity. In NP type B, ASM enzymes levels can be normal if an artificial substrate has been used for assays; in, such situation, diagnosis is based on bone marrow examination and Sphingomyelinase Phosphodiesterase (SMPD) gene analysis. Malignant hypertension could be either secondary to renal involvement or progressive atherosclerosis and vasculopathy involving renal vessels.

Cholesterol storage disorder, such as Wolman’s disease classically has early infantile onset, manifests with massive hepatosplenomegaly, failure to thrive, diarrhea, and bilateral adrenal calcifications; this disease is invariably fatal and affected children who die by 1 year of age. It is an autosomal recessively inherited metabolic disorder caused by lysosomal acid lipase (LAL) enzyme deficiency and characterized by accumulation of cholesterol esters and triglycerides within foamy histiocytes. Cholesterol ester storage disorder is less severe variant caused by partial deficiency of enzyme LAL and clinical features include hepatosplenomegaly, lipid abnormalities, premature atherosclerosis, and infiltration of various organs by foamy histiocytes. Hepatic involvement varies from isolated fatty liver with steatohepatitis to micronodular cirrhosis and portal hypertension. Adrenal calcification is seen in <10% of individuals with CESD; lipid abnormalities include low HDL (<20 mg/dl) and elevated total cholesterol and triglycerides.

Niemann–Pick type C was also kept as a differential diagnosis because of hepatosplenomegaly and lipid abnormalities. However, NP type C has gaze abnormality and severe neurological impairment.

Both the siblings had significantly low HDL cholesterol levels. Chronic therapy with steroids, fibrates, and malignancy can cause reduction in HDL cholesterol. Genetic disorders, such as deficiency of Apo A1, Apo A2, Tangiers disease, and lecithin cholesterol acyl transferase (LCAT) deficiency can have severely low HDL levels.
Tangier disease is a rare, autosomal recessive disorder caused by mutations in the ABCA1 gene and is characterized by near absence of plasma HDL cholesterol, accumulation of cholesterol in multiple tissues, peripheral neuropathy, and accelerated atherosclerosis. Clinically, these patients have orange colored tonsils, anemia, hepatosplenomegaly, and painful peripheral neuropathy. Bone marrow shows collection of foamy histiocytes. In view of massive hepatosplenomegaly, interstitial lung involvement, tissue infiltration with foamy histiocytes, and very low HDL levels, NPD type B is the most likely diagnosis in the index case. However, mitral valve prolapse, renal involvement, and malignant hypertension were unique in this patient.

In a single case report of a 14-year-old girl with an intermediate form of NPD, renal involvement was reported. She had neurovisceral involvement and was found to have elevated serum creatinine levels. Renal biopsy showed focal and global glomerulosclerosis and glomeruli, tubules, and interstitium showed infiltration with foamy storage cells and vessels showed arterial and arteriolar sclerosis. So, my final diagnosis is that these two siblings have NPD type B. Cause of death in index child could be secondary to malignant hypertension with possible major internal hemorrhage or a cardiac event.

Open House Discussion

Dr SC Varma
The clinical protocol is open for discussion.

Dr Sadhana Lal
In view of massive hepatosplenomegaly, Neiman–Pick disease type B is a possibility, but in view of very low HDL levels retrospectively, Tangiers disease can be considered as a diagnostic possibility. In a few adult cases, Tangiers disease with massive splenomegaly has been reported, but, such a degree of hepatosplenomegaly in pediatric age is rare. Other disease, such as CESD can present similarly, but these patients have fatty liver. Absence of fatty liver and orange colored tonsils in index patient does not support a diagnosis of CSED. Elevated amylase levels could be salivary in origin and secondary to UGI endoscopy. Terminal event could be cardiac in this patient.

Unit Senior Resident
Cholesterol ester storage disorder presents with a fatty liver, extensive liver fibrosis, and portal hypertension. Because of very low HDL levels, other cholesterol metabolic defects that come in the differential diagnosis are Tangiers disease and LCAT deficiency.

Dr Jayshree
Brother of the index child was admitted in pediatric intensive care with hypertensive crisis. Presence of massive hepatosplenomegaly in two siblings suggests a genetic storage disorder, possibly NPD-type B. But the malignant hypertension remained unexplained and second issue was cause of respiratory involvement in the brother. Although his X-ray chest was normal, ventilation was difficult and showed features of restrictive lung disease; bronchoscopy showed presence of nodular infiltration of bronchial mucosa similar to upper GI endoscopy. So, keeping everything together, a storage disorder with massive hepatosplenomegaly and airway infiltration, that is, NPD type B is most likely.

Dr Meenu Singh
Chest X-ray done shows bronchoalveolar infiltrate and this suggests possibility of lung involvement and these kind of deposits are most commonly seen in NPD Type B.

Dr Sanjay Jain
Adrenal involvement in index child could be possible because of presence of hypertension and lipid abnormalities. Enzymatic defect of steroid biosynthesis could be possible.

Dr Inusha
Enzyme analysis may not be very reliable in diagnosis of NPD, hence, skin fibroblast enzyme analysis or Deoxyribonucleic Acid (DNA) analysis for genetic diagnosis is recommended. We have sent the DNA of brother for SMPD1 gene analysis and results are awaited. Hyperlipidemia is reported in NPD type B, in view of massive hepatosplenomegaly and lung involvement, NPD type B is most likely.

Dr SC Varma
With this clinical presentation, NPD type B is the most likely possibility. However, hypertension remained unexplainable here. Possible involvement of autonomic nervous system could be responsible for that.

Autopsy Findings – PM27096 –
Prof Nandita Kakkar
A complete autopsy was performed on this 12-year-old female child. She was a short statured child. The pericardial and pleural cavities were within normal limits. The abdomen yielded 50 ml of blood and large blood clots were present adherent to the intestine, kidney, ureter, and urinary bladder. The bone marrow (Figs 2A and B) showed plenty of characteristic NP cells, which are large lipid laden, foamy
histiocytes, 40 to 75 µm in size, having an eccentric nucleus. These cells contained innumerable small vacuoles of uniform size, which are the distended lysosomes containing sphingomyelin, cholesterol, glycolipid, and acylglycerophosphorylcholine. The liver (Figs 2C and D) weighed 2600 gm. It was pale and no focal lesion was identified. The portal vein and the biliary system were within normal limits. Microscopic examination revealed expansion of the portal tracts and porto-portal and portocentral bridging fibrosis (Stage 4) with occasional nodule formation (Figs 3A and B). The fibrosis was highlighted on reticulin and Massons trichrome stains. The sinusoids were dilated and packed with the characteristic NP cells (Figs 3C and D), forming nodules in areas. These are the kupffer cells, wherein the lysosomal accumulation of sphingomyelin, cholesterol, glycolipid, and acylglycerophosphorylcholine has imparted the characteristic foaminess. No cholestasis was noted. The hepatocytes also exhibit a foamy cytoplasm indicating lipid accumulation. But the NP cells stood out remarkably from the foamy hepatocytes. The spleen weighed 1500 gm (Fig. 4A). The cut section showed diffuse enlargement with no focal lesion. Microscopic examination showed sheets of characteristic NP cells in the red pulp (Fig. 4B). The white pulp was compressed and also showed presence of these cells. The lymph nodes (mesenteric, peripancreatic, aortic, carinal, hilar) were minimally enlarged and showed total replacement by NP cells (Figs 4C and D). A few follicles could be seen pushed toward the capsule. The lungs (Figs 5A and B) were heavy and on cut section showed hemorrhages. Microscopic examination confirmed the hemorrhage. The alveoli were distended and packed with the characteristic NP cells. Overall features were those of lipid pneumonia. No infection was however seen. The heart weighed 112 gm. The right ventricular wall measured 0.5 cm indicating hypertrophy. The posterior leaflet of the mitral valve showed hooding and this leaflet was enlarged, redundant, thick, and rubbery. Microscopy (Figs 5C and D) revealed thickening of the spongiosa layer with deposition of myxomatous material. Amidst the myxomatous degeneration were seen clusters of large foamy macrophages with morphology consistent with NP cells. Hence, mitral valve does show features of prolapse with presence of NP cells amidst the myxomatous degeneration. Right coronary artery and left circumflex artery were within normal limits, but the LAD (Fig. 6A) showed atherosclerotic narrowing (40%). The aorta also showed atherosclerosis (Fig. 6B).
Figs 3A to D: (A) Photomicrograph of the liver showing porto-porto and porto-central bridging fibrosis forming a nodule, (B) reticulin stain highlights the fibrosis, (C) liver showing the characteristic foamy Niemann–Pick cells in the sinusoids, and (D) the foamy NP cell are better appreciated in the Massons trichrome stain.

Figs 4A to D: (A) Coronal slices of the massively enlarged spleen, (B) photomicrograph of the spleen showing sheets of NP cells, (C) photomicrograph from the lymph node showing total replacement by NP cells. Few follicles can be seen, and (D) lymph node showing characteristic NP cells with a vacuolated cytoplasm.
Stomach on gross examination showed nodularity and on microscopy revealed NP cells in the lamina propria (Fig. 6C). The small intestine also showed nodularity and NP cells in the lamina and in the villi clogging and distending them (Figs 6D and 7A). The colon however did not show any NP cells. The ganglion cells also revealed foaminess, indicating deposition of lipid. The serosal aspect of some portions of the small intestine, rectum, and posterior aspect of the urinary bladder revealed hemorrhage and blood clots. However, the site of the bleed could not be identified. The kidneys were normal grossly, but on microscopic examination showed the presence of classical NP cells in the glomeruli (Fig. 7B). Pancreas showed congestion on cut section and microscopic examination revealed foaminess of the acinar cells indicating deposition of lipid. The brain (Fig. 7C) weighed 1270 gm and was normal grossly and on microscopic examination. Electron microscopy (Fig. 7D) from the liver and spleen showed large cells packed with distended lysosomes. These distended lysosomes contain membranous cytoplasmic bodies resembling concentric lamellated myelin figures known as Zebra bodies.

There was death of one sibling, 9 years male, 6 days after the demise of the index case. This child had presented with similar clinical features and bone marrow done was consistent with a diagnosis of NPD.

Final Autopsy Diagnosis 12 years Female
- Niemann–Pick disease (nonneuronopathic) – Type B – Bone marrow, liver, spleen, lymph nodes, lungs, stomach, small intestine, mitral valve, kidney, and pancreas
- Lipoid pneumonia, pulmonary hemorrhage
- Mitral valve prolapse
- Intra-abdominal bleed ? site
- Atherosclerosis – Aorta: Grade 1; LAD: 40% occlusion

Open House Discussion

Dr SC Varma

Both clinical and pathology protocols are now open for discussion.

Molecular diagnosis is awaited in index child, but cause of hypertension still remains an enigma. It may be essential hypertension and so it would be interesting to know the BP records of the parents. Terminal event in the index child also remains unclear, that is, because of sudden hypotension and pallor, a bleed was considered. What was the source of intra-abdominal bleed in this patient?

Dr Sanjay Jain

Presence of, such a low HDL in the index patient would predispose to atherosclerosis. What was the source of
Figs 6A to D: (A) Left anterior descending artery showing atherosclerosis, (B) aorta showing atherosclerosis, (C) NP cells in the villi of the small intestine, and (D) NP cells in the lamina propria of the stomach.

Figs 7A to D: (A) NP cells in the lamina propria of the small intestine, (B) NP cell in the mesangium of the glomeruli (arrow), (C) electron microscopy showing lysosomes with lamellated structures, that is, the Zebra bodies, and (D) coronal slice of the normal brain.
bleed here and does the vessels showed atherosclerosis and inflammatory cells?

**Dr Meenu Singh**

Could this bleed be secondary to complication of upper GI endoscopy?

**Dr Sadhana Lal**

It is less likely to have an intra-abdominal bleed following a UGI endoscopy.

**Dr Nandita**

Renal vessels did not show any atherosclerotic changes. It was an intra-abdominal bleed with staining of outer aspects of lower GI tract and urinary bladder along with attached blood clots. The source of bleeding could not be identified in the index patient.

**Dr Thapa**

Bleeding following upper GI endoscopy can occur rarely.

**Dr SC Varma**

Presence of thrombocytopenia can explain hemorrhage in lungs and abdomen, but the platelet count was >50,000. There could be a coagulopathy due to platelet function defect.

**Highlights in Index Patient**

This 12-year-old girl presented with progressive abdominal distention from infancy. On examination, she was short stunted, and had facial dysmorphism, massive hepatosplenomegaly, mitral valve prolapse, and hypertensive BP record. Investigations revealed anemia, leukopenia, thrombocytopenia, transaminits, and very low HDL. Clinically, a diagnosis of lysosomal storage disorder, that is, NPD type B was considered. Autopsy showed infiltration of almost all organs with the characteristic NP cells.

**Cardiac Involvement**

 Clinically, this patient had a cardiac murmur at apex, and echocardiography (ECHO) showed presence of mitral valve prolapse. X-ray chest showed mild left ventricular prominence. Cardiac involvement is rarely reported in NPD type B. Autopsy revealed right ventricular hypertrophy and mitral valve prolapse. The mitral valve showed thickening of the spongiosa layer with deposition of myxomatous material along with NP cells.

**Atherosclerosis**

 Various authors have reported reduced HDL cholesterol in about 56 to 88% patients with NPD-type B. Both of these children had very low HDL cholesterol. Although it has been suggested that an increased risk for atherosclerotic disease exists in these patients, symptomatic cardiovascular disease is rare. The pathophysiology is incompletely understood, but there is evidence that the presence of high concentrations of sphingomyelin in nascent lipoprotein particles inhibits the formation of mature HDL-particles. Autopsy showed presence of atherosclerosis in aorta and left anterior descending coronary artery in index child.

**Hepatic Fibrosis**

 Microscopic examination of the liver in the index case revealed expansion of the portal tracts and portoportal and portocentral bridging fibrosis (stage 4) with occasional nodule formation. Liver biopsies from a cohort of 17 adult patients with NPD type B revealed some degree of fibrosis ranging from minimal to frank cirrhosis. Studies in the mouse model of NPD have shown that inactivation of ASM leads to overexpression of cathepsin B, which promotes liver fibrosis.

**Renal Involvement**

 Renal size and function was normal. At autopsy, glomeruli showed presence of clusters of NP cells in the mesangium. Could this be the cause of hypertension, is a speculation. Sibling of the index patient showed abnormal urea and creatinine levels. The terminal event in the index case was an abdominal bleed, the source of which could not be ascertained.

**Niemann–Pick Disease**

 Niemann–Pick disease due to ASM deficiency is a rare autosomal recessive lysosomal storage disorder caused by mutations in the sphingomyelin phosphodiesterase 1 (SMPD1) gene. The deficiency of ASM causes accumulation of sphingomyelin in the lysosomes of macrophages and other cell types, with secondary changes in cholesterol metabolism. Accumulation of
lipid-engorged macrophages, i.e., NP cells, is predominantly seen in the spleen, liver, lung, and brain. The clinical picture is dominated by variable neurological signs, hepatosplenomegaly, and cytopenia.

Classically, the disease is divided into two main subtypes: NPD type A and B. Type A disease is the most severe form, with early onset of central nervous system disease characterized by progressive psychomotor retardation, cherry red spots, variable hepatosplenomegaly, and death by the age of 2–3 years. Type A disease has a predilection for Ashkenazi Jewish population. Type B disease is panethenic and has more variable manifestations. Onset can be late with variable degrees of hepatosplenomegaly, cytopenia, in particular thrombocytopenia, and pulmonary disease. Rarely, skeletal symptoms and arthralgia can occur in some cases. A highly atherogenic lipid profile has been suggested to result in increased cardiovascular complications. Very mild phenotypes do exist and diagnosis is sometimes made in middle-aged patients also. Recent reports have described the existence of an intermediate form with onset in childhood and presence of neurological symptoms, which are much milder and distinct from those seen in type A. Majority of patients with NPD type B have characteristic laboratory abnormalities, such as low HDL cholesterol levels and increased plasma chitotriosidase activities. A diagnosis can be made by establishing deficient activity of ASM in leukocytes or fibroblasts. More than 100 mutations have been found in the SMPD1 gene and some important genotype–phenotype correlations have been established. Heterozygous mutation in deltaR608 gene is associated with nonneuronopathic disease. Enzyme replacement therapy (ERT) with recombinant ASM is currently studied as a potential treatment for NPD-B patients.

Patients with NPD type B can develop significant life-threatening complications, including liver failure, hemorrhage, oxygen dependency, pulmonary infections, and splenic rupture. Few can develop coronary artery or valvular heart disease. The most common causes of disease-related morbidity and mortality are respiratory and liver failure. Almost 20% of children with NPD type B died during the course of a longitudinal natural history study, suggesting that NPD type B is a serious, life-threatening pediatric disease.

REFERENCES
