A 3 year old girl presented with abdominal distention since birth with developmental delay

Luthfun Nahar, A. S. M. Bazlul Karim, Subir Ananda Biswas, Mohuya Mondal and Bishnu Pada Dey

Article Info

Department of Pediatric Gastroenterology and Nutrition, Faculty of Pediatrics, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, Bangladesh (LN, ASMBK, SAB, MM); Department of Pathology, Faculty of Basic Science and Paraclinical Science, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, Bangladesh (BPD)

For Correspondence:
Luthfun Nahar
dr.mukta27@gmail

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Presentation of Case

Dr. Luthfun Nahar: A 3 year old girl, 3rd issue of consanguineous parents from the Feni District (south part of Bangladesh) immunized as per EPI schedule presented at the outpatient department with the history of progressive abdominal distension and not growing well since birth. She had also the history of developmental delay and recurrent respiratory tract infection. Still she can not stand without the support and unable to make a sentence completely. Her brother died at 5 months of age with abdominal distention with unknown cause. She had no history of jaundice, hematemesis, melena, convulsion and craving for food. For her respiratory problems, she needed hospitalization on two occasions. The mother had no history of fever and rash during pregnancy.

On examination, she was apathetic, anicteric, mildly pale, vitally stable, there was no stigmata of chronic liver disease; lymph nodes were not palpable and BCG mark was present. Anthropometrically she was severely underweight and severely stunted.

On abdominal examination, the liver was palpable with liver span 14 cm and the spleen was enlarged about 5 cm from the left costal margin along with its long axis. Developmentally she had speech delay, motor delay and cognitive impairment which correspond to 10 months of age. Other systemic examinations showed normal findings.

After admission, we had initially done the complete blood count, random blood sugar, blood grouping, alanine aminotransferase, fasting serum triglyceride, prothrombin time, activated partial thromboplastin time, alpha fetoprotein, ultrasonography of the whole abdomen, chest x-ray, etc (Table I).

X-Ray chest was normal. The ultrasonography of the abdomen showed hepatosplenomegaly. There was no ascites.

After evaluating the clinical data, the physical findings and investigation results, the case was diagnosed provisionally.

Provisional Diagnosis

Storage disease

After doing the baseline investigations to confirm the storage disease, we have done the following investigations: eye evaluation for the storage disease, bone marrow study and liver biopsy. Fundoscopic examination of eye showed cherry-red macule on both eyes. Bone marrow findings were normal. Liver biopsy showed Niemann-Pick cell

Differential Diagnosis

Dr. Afsana Yasmin: Patient of glycogen storage disease also present with similar type of clinical features. So, I thought it could be a case of glycogen storage disease.

Glycogen storage disease

Glycogen storage disease is an autosomal recessive disorder except subtype IX that is X-linked. There are different glycogen storage disorders which are due to different enzyme lack or malfunction which are responsible for the synthesis and degradation of glycogen. Type I glycogen storage disorder is the most common. The disease mainly involves the liver, skeletal muscle and the kidney. Hypoglycemia is the primary feature of the hepatic glycogenose, whereas weakness and muscle cramps are the main features of the muscle glycogenoses. The dietary carbohydrate converts to lactate which results in the postprandial hyperglycemia and hyperlacticacidemia alternating with fasting hypoglycemia and hyperketonemia. Early morning hypoglycemia may occur in infants when they stop feeding during the night, but also may be asymptomatic unless they are ill. The postprandial hyperglycemia and glucosuria may be mistaken as diabetes or renal glucosuria.[1]

Glycogen storage disease is diagnosed by the clinical findings along with blood glucose, lactate, and ketones in both fed and fasting states. The definitive diagnosis depends on the liver biopsy. Hepatocytes contain small amounts of glycogen and show moderate steatosis

Table I

Investigation reports of patient

Parameters	Findings	References
Hemoglobin (g/dL)	10.4	13.5 ± 1.3
White blood cell count (×10⁹/L)	11	7.0 ± 3
Differentials		
Neutrophil (%)	48	40-80
Lymphocyte (%)	48	20-40
Eosinophil (%)	3	1-06
Monocyte (%)	1	2-10
Platelet count (×10⁹/L)	400	150-400
ESR (mm in 1st hour)	25	0-10
Serum triglyceride (mg/dL)	280	<150
Random blood sugar (mmol/L)	4.3	3.5-6.0
Serum alanine aminotransferase (U/L)	39	30-65
Prothrombin time (sec)	14	11.8
INR	1.20	
Activated partial thromboplastin time (sec)	34	28
α- Fetoprotein (ng/mL)	1.90	<8.10

which are periodic acid schiff positive but diastase labile. The diagnosis can be confirmed by mutation analysis. Prenatal diagnosis and carrier detection is also possible by the DNA test.[1, 2]

The complications may be present as seizures, hepatic adenomas, hepatocellular carcinoma, and renal failure. Renal failure is more common in type 1 variety.[3]

TORCH infection

Patient of TORCH infection can be present with abdominal distension, organomegaly and developmental delay which is similar with our patient's clinical features. So, the TORCH infection will be one of the differential diagnoses.

The TORCH infection includes toxoplasmosis, rubella, cytomegalovirus and herpes infections. They spread through poor hygiene, contaminated blood, water, soil and airborne droplet. Infection during the pregnancy results in the production of immunoglobulin M (IgM) antibodies followed by IgG. This IgM antibody against TORCH usually persists for about 3 months, while the IgG may be detectable for lifetime. Intrauterine infection by the TORCH can cause congenital malformations of the central nervous system, intracranial calcification, microcephaly, hydrocephalus, visual defect and deafness in addition to other malformations like congenital heart disease. Only 5% of them may develop complications like anemia, thrombocytepenia, jaundice, hepatomegaly, maculopapular rash, CNS sequelae, etc.[4]

The severity of infection depends on the gestational age of the fetus. The TORCH infection in the first trimester may cause miscarriage. The infection of the fetus in third trimester is often asymptomatic at birth. Toxoplasma and herpes simplex virus are responsible for the miscarriage but rubella and cytomegalovirus usually don't cause any miscarriage.[4, 5]

The TORCH infection may remain latent and there is no obvious clinical symptoms in women during the childbearing age and also in pregnant women. The diagnosis of infection is done based on the clinical features, antibody detection and virus isolation by the PCR method.[4, 6]

Dr. Nahar: After evaluating the patient's presenting features and physical findings, this issue of consanguineous parents presented with the history of sib death, hepatosplenomegaly since birth which are favorable of storage disease. Develop-mental delay, presence of cherry red spot in the fundus and Niemann-Pick cell in the liver tissue indicate the case as Niemann-Pick disease probably type C variety. Her investigation reports showed almost normal findings.

Niemann-Pick disease

Niemann-Pick disease is an autosomal recessive lysosomal storage disorder. It usually presents in childhood and rarely presents in adulthood. In 1914, Albert Niemann first described an infant with hepatosplenomegaly with progressive neurological deterioration who had large foam cells in the liver and spleen. In 1920, Albert Niemann and Ludwig Pick worked together and since then the disease is termed as Niemann-Pick disease.[7-9]

There are various types of Niemann-Pick disease. Among them, type A and B are due to deficiency of sphingomyelinase; type C is the lipid trafficking defect and type D is a genetic isolated form.

Type C has another subdivision: C1 (95%) and C2. All types of Niemann-Pick disease occur due to mutation in the chromosome 11, 14 or 18 which result in lipid accumulation.[8, 9] Type A and C both have neurological involvement. But type C is slower than A and the patient of type A usually die earlier within 4 years of age. The presentation of type C is variable from the perinatal period to adult age and the majority of death occur between 10 to 25 years of age.[9-11]

In perinatal life, it usually presents with cholestatis, fetal ascites, respiratory problem, but neurological symptoms don't appear during the neonatal period. Later they develop developmental delay, gait problem, spasticity with the pyramidal tract involvement. The gait problem is mainly due to hypotonia, imbalance and ataxia which lead to frequent fall.[10, 12]

It is also reported that a girl of Niemann-Pick disease presented with eczematous dermatitis,

delayed puberty and an infant reported with skin lesion, involving both cheeks. Histological report of skin showed deposition of huge foamy histiocytes in the dermis resembling Niemann-Pick cell.[13, 14]

The clinical feature includes neurovisceral manifestations. The visceral involvement occurs in the liver, spleen, lung, eyes, etc. Hepatosplenomegaly develops due to the accumulation of sphingomyeline in the reticulo-endothelial systems. The neurological disorders present as speech delay, developmental delay, cerebellar ataxia, dysarthria, dysphagia, dementia, seizure, dystonia, hearing loss, learning disabilities, etc. The characteristic ophthalmological symptom is the vertical supranuclear gaze palsy.[7, 12, 14]

Adult patient may present with the involvement of bone marrow, liver, spleen, lungs and coagulopathy. Patient also reports with abnormal platelet function, pingueculas and late onset of menarche.[15] Patient may also present with neuropsychiatric disorders as schizophrenia, epilepsy, central nervous system neoplasms, Huntington's disease, mania, hypersexuality, bipolar mood disorder, etc. All of these occur due to the accumulation of cholesterol in neurons and result in axonal and neuronal loss in the callosal, cerebellar and hippocampal regions.[16, 17]

Psychiatric illnesses like attention deficit disorder, Asperger-like symptoms, Alzheimer's disease, depressive disorder are the common presentations in adolescence or early adulthood but not so common in the school going children with Niemann -Pick type C disease. But patient may present with those features along with poor school performance, attention deficit, difficulties in the classroom which may misinterpreted as developmental coordination disorder and bullying. So, these patient should consider as Niemann-Pick type C disease in the differential diagnosis.[12, 18] Convulsion and interstitial lung disease are also the rare manifestation of Niemann-Pick disease.[19, 20] Hearing loss may also present and the cherry red spot may found in the maculae of the Niemann-Pick patient.[16, 21]

The diagnosis of Niemann-Pick disease should be done based on the history, clinical findings like hepatosplenomegaly, mental retardation, foam cells in the bone marrow, liver, spleen and cherry red spot on the macula.

This disease is characterized by the presence of lipid laden pick cells in different organs like liver, spleen, bone marrow and lymph node. Specific investigation is the identification of sphingomyelinase deficiency in leukocytes or cultured fibroblast and genetic analysis. Demonstration of free cholesterol accumulation in the lysosomes is done by the filipin staining of fibroblast and it is the characteristic of Niemann-Pick type C disease.[20-24]

So, the neurological and ophthalmological evaluation along with other investigations are the important diagnostic tool for the Niemann-Pick disease.

Imaging study like magnetic resonance imaging and magnetic resonance spectroscopy may show the signs of leukodystrophy and cerebral atrophy.[16]

Dr. Nahar's Diagnosis

Niemann-Pick disease type C variety

Discussion

Dr. A. S. M. Bazlul Karim: Lysosome is the cellular component which contains multiple enzymes needed for the digestion of mucopolysaccharides, oligosaccharides, glycosphingolipids, etc. Lysosomal storage disease is a group of over 40 diseases and the majority of them are autosomal recessive. Sphingolipidoses is one of them. So, the history of consanguinity is an important clue for the diagnosis.

There are various types of sphingolipidoses like Niemann-Pick disease, Gaucher disease, Farber disease, GM1 gangliosidosis, etc.[25]

Lipid storage disease as Niemann-Pick is rare in our country and it is more common in Ashkenazi Jewish descent, Spanish-American population of Southern New Mexico and Colorado and French Canadian population of Nova Scotia and Maghreb region.[21, 25] Some authors recommended about six variants of Niemann-Pick disease from A to F.[20] Niemann-Pick disease type C is due to the mutation in NPC1 and NPC2 which causes error in cellular trafficking of exogenous lipid as phospholipid, cholesterol, sphingomyelin in lysosome of affected cell. Neonatal life accounts for 20-30% of NPC. Niemann-Pick disease type C should be considered in unexplained neonatal hepatitis especially when splenomegaly is a persistent feature.[25-27]

Dr. Md. Rukunuzzaman: All types of Niemann-Pick disease don't have neurological presentation. Among them, type A and C have neurocognitive dysfunction. Type A progressive neurovisceral disease presents within the first few months of life and type C presents slower than A. The mutation of Niemann-Pick disease gene causes accumulation of cholesterol systemically and glycosphingolipids in the nervous system. As a result, there is reduced gray matter in the cerebrum, thalamus, hippocampus, cerebellum, etc. Also there is reduction of myelination and myelin water in the white matter tract. All of these are responsible for the neurological manifestations of Niemann-Pick type C disease. Dystonia with preserved intellectual functionis is an atypical presentation due to basal ganglia involvement which may be mistaken as Wilson disease.[23, 25, 28]

Dr. Wahiduzzaman Mazumder: Pulmonary involvement is an another presentation of Niemann-Pick disease. The pulmonary symptoms are common in adults but not in children. Mild pulmonary involvement may be found in type B. Usually they remain asymptomatic but may convert to bronchopneumonia or corpulmonale around 15 to 20 years of age. It is due to the alveolar infiltration of Niemann-Pick cell which causes decrease in pulmonary blood flow. This infiltration involves initially in the base and then gradually the entire lungs. Chest X-ray shows diffuse reticular or finely nodular infiltration predominantly in the basal field and there may be honeycomb of the lung field. High resolution computer tomography may show ground glass appearance in the upper lung zone with thickening of septa in the lower zone but cavitation is rare.[20, 21, 26]

Dr. Kamrun Nahar: What is the management plan?

Dr. Karim: There is no specific treatment for the Niemann-Pick disease. Symptomatic management is the mainstay of treatment. Liver transplantation may be done in the liver failure, amniotic cell transplantation; or bone marrow transplantation is done in some patients who had no neurological symptoms but the results are unsatisfactory. Newer trials are going on the enzyme replacement therapy and gene therapy.[19, 25]

Type C is a progressive neurological disorder. Lipid lowering drugs and bone marrow or liver transplantation are ineffective in this type. The only currently available specific drug treatment is miglustat, this drug has shown positive outcomes in the clinical trials.[23, 25, 29] Studies suggest that the treatment with miglustat for 24 months may stabilize the saccadic eye movement, ambulation and other neurological manifestations in type C variety.[23]

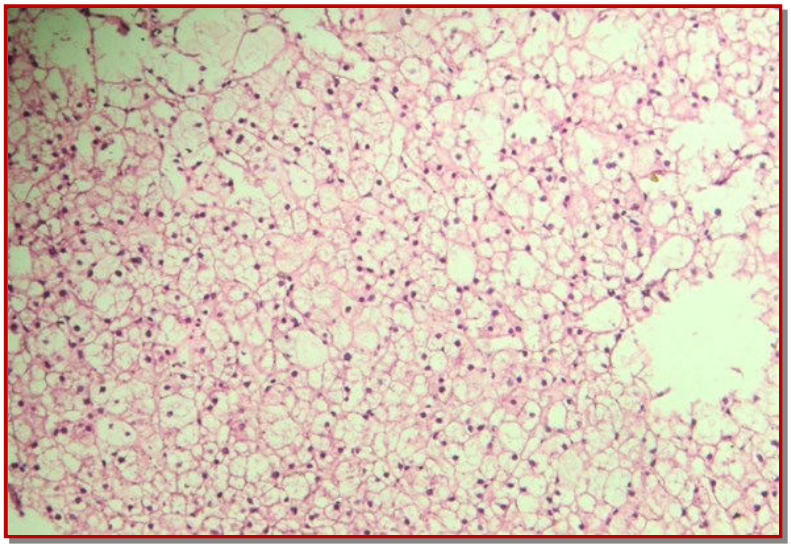

Figure 1: Hepatocytes shows the accumulation of fat (Niemann-Pick cell), Hematoxylin and eosin stain, x400 magnification

Miglustat is also helpful to improve dysphagia and swallowing function.[30]

Dr. Archana Sreshtha: What is the mechanism of action of miglustat?

Dr. Nahar: Now-a-days miglustat is the recommended drug of choice which can slow the neurological manifestations. It is an inhibitor of glycosphingolipid synthesis which reduces the lipid storage and cellular pathology in the brain.[18]

Dr. Parisa Marzan: What are the ophthalmological manifestations of Niemann-Pick disease?

Dr. Rukunuzzaman: Affected child of Niemann-Pick disease may be found with cherry red spot, macular halo and vertical supraneuclear gaze deformity. The entire retina may be opaque, due to intracellular lipid accumulation of retinal neuron, pigment cell and receptor. The cornea may be hazy and lens may be brownish in color. The vision is usually intact in early life which may be defective in the late stage.[16, 25, 31, 32]

Dr. Mohua Mondol: What is cherry red spot?

Dr. Nahar: Cherry red spot indicates the ocular involvement. It occurs due to the pathological accumulation of lipid sphingomyelin in retinal ganglion cells. It may also be found in Gaucher's disease, GM1 and GM2 gangliosidoses, Metachromatic leukodystrophy, Farber disease and Krabbe disease. This patient had developmental delay and she was less cooperative, so the color fundoscopic photography of cherry red spot couldn't be possible.[21, 33]

Dr. Shuborna Rani Das: What is Niemann-Pick cell?

Dr. Mazumder: It is also called foam cell. It is rounded or polygonal mononuclear cell about 25-75 µm in diameter which has foam like cytoplasm that contains numerous droplets of sphingomyelin (Figure 1). These cells are negative for periodic acid schiff stain but positive for sudan black. It is pathognomic for Niemann-Pick disease.[25]

Dr. Hazera Akter: What is the mode of death in Niemann-Pick disease?

Dr. Nahar: The main cause of death in Niemann-Pick disease is bronchopneumonia or aspiration pneumonia. Pulmonary infiltration of Pick cell may progress to respiratory failure. Dysphagia is also responsible for fluid or food aspiration which subsequently develop aspiration pneumonia. Other causes of death are liver failure and severe neurological impairment.[20, 26, 30, 34, 35]

Dr. Sayma Rahman Munmun: What should be the genetic counselling?

Dr. Nahar: It is an autosomal recessive disorder. So in every pregnancy there is 25% chance of sufferer, 25% normal and 50% chance of carrier.

Prenatal diagnosis is possible if cholesterol processing abnormalities could be clearly identiced in the index case.[23] But this facility is not available in our country.

Dr. Maimuna Sayeed: What is the prognosis of this patient?

Dr. Nahar: This patient presented with neurological features and she had also history of sib death. There is no available specific treatment for Niemann Pick disease in our country. So, the prognosis of this patient is guarded.

Dr. Nazneen Sarker: What are the available diagnostic facilities in our country?

Dr. Nahar: Clinical suspicion is the main diagnostic clue. History, physical examinations and some investigations are essential for diagnosis of Niemann-Pick disease. Bone marrow study, liver biopsy, hearing and ophthalmological evaluation are available in our setting. But enzyme assay, genetic analysis and antenatal diagnosis are still not possible in our country.

Follow-up

Our patient have neurological features like developmental delay. So, we consulted with the pediatric neurology department. They advised for developmental therapy and neurological follow-up after 1 month. Though she had no hepatic abnormality, so she was advised for routine follow-up after 3 months by doing liver function tests.

Final Diagnosis

Niemann Pick disease type C

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