TURNITIN_Nieman-Pick_disease

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Submission date: 10-Apr-2023 11:21AM (UTC+0700)
Submission ID: 2060227721
File name: document_1_4.docx (264.46K)
Word count: 2330
Character count: 13085

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2021; vol 8 (1) : 129–132

Case Report

Niemann-Pick disease type A: a case report

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v8i1.577

Accepted: 03rd April 2019
Approved: 16th April 2020

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Abstract

Background : Niemann–Pick disease (NPD) types A result from the deficient activity of sphingomyelinase. NPD type A is characterized by early-onset, progressive neurodegenerative course; systemic disease manifestations, including massive hepatosplenomegaly, interstitial lung disease, and cherry–red macula; and death in early childhood. The objectives of this reports was to enhance the recognition of health care providers about the potential undiagnosed NPD because nonspecific clinical manifestation.

Case presentation : A 18-months-oldboy was admitted to Dr. Kariadi Hospital with enlarged abdomen since seventh month old with failure to thrive. He also showed progressive loss of neurologic function, microcephaly with open major fontanelle, recurrent pulmonary and systemic infection. Physical examination revealed facial dysmorphic, milestone regression, under–nutrition, crackles in both lungs, hepatosplenomegaly with petechial in extremities and floppy infants. Laboratory investigations showed anemia (9.4 g/dL) and thrombocytopenia (73.000/mm^3). The lactate dehydrogenase (482 U/L) and alkaline phosphatase (159, 03 IU/L) were higher than normal. Abdominal ultrasound revealed hepatomegaly with normal parenchyma and splenomegaly without nodule. Skeletal survey revealed Erlenmeyer flask deformity. Foam cell are detected in bone marrow puncture. Retcamexamination showed cherry red spot at the macula. Bera revealed auditory neuropathy. The enzyme activity showed normal βGlucosidase (5.55 uM/hr) and chitotriosidase (105,8nmol/ml) but low sphingomyelinases activity (0.30 uM/hr) which confirmed the diagnosis of NPD.

Discussion : Niemann–Pick disease (NPD) types A result from the deficient activity of sphingomyelinase. NPD type A is characterized by early-onset, progressive neurodegenerative course; systemic disease manifestations, including massive hepatosplenomegaly, interstitial lung disease, and cherry-red macula; and death in early childhood. Type A is very rare and a severe infantile form with neurologic degeneration resulting in death usually by 3 years of age. No treatment available for type A and It's a rare disease in Indonesia.

Conclusion : These investigations were able to diagnose this child as a NPD-Type A. Patient was closely monitored and symptomatic treatment was provided.

Keywords : Niemann–Pick disease type A, hepatosplenomegaly, failure to thrive

INTRODUCTION

Niemann–Pick Disease is an autosomal recessive disorder of infancy, characterized by failure to thrive, hepatosplenomegaly and neurodegenerative changes. It is caused by inherited deficiency of an enzyme, acid sphingomyelinase. It leads to deposition of sphingomyelin and cholesterol within the lysosome of reticuloendothelial cells of various organs. There are increased levels of sphingomyelin and cholesterol in bone marrow, liver, spleen and brain and the enzyme defect is sphingomyelinase deficiency. Failure to cleave phosphocholine from sphingomyelin results in the storage of sphyngomyelin. It is classified into two major entities.[1,2,5]

- Acid spingomyelinase deficient Niemann-Pick Disease which result from mutations in SMPD1 gene and it includes type A and type B, The incidence of type A and B in general population is estimated to be 1 in 250,000
- Niemann–Pick Disease type C and type D result from mutations in NPC1 and NPC2 gene with the estimates that of type C is 1 in 150,000.[3]

This disease begins at 3–4 months of age with feeding difficulties and failure to thrive. Neurologic function is gradually deteriorated and ultimately development is globally retarded. The diagnosis is based on hepatosplenomegaly, mental retardation, and foam cells in the bone marrow, cherry red spot on the macula and sphingomyelinase deficiency in white blood cells, cultured fibroblast and other tissues as well. NPD type A is more common in Ashkenazi Jewish population with estimated incidence of 1 in 40,000 and the carrier frequency among this population is 1 in 90. Both sex is affected equally, A review of English medical literature shows that 1,200 cases of NPA and NPB worldwide have been reported with the majority being Type B or an intermediate form.[4]

CASE REPORT

A-18 months-old-boy was admitted to Kariadi Hospital with Abdomen enlarged and failure to thrive. Abdomen enlarged since seventh month, his body weight difficult to increase, he also showed progressive loss of neurologic function and repetitive pulmonary and systemic infection. Head Circumference: 43 cm, body Weight: 5,8 kg and Height: 69 cm were below 3rd centile NCHS standard. He was conscious with noticeable pallor, physical examination revealed facial dysmorphic, milestone regression and under-nutrition. The large fontanels still open with 6 x 9 cm and microcephaly. Crackles were audible in both lungs, hepatosplenomegaly were added characteristic features. Liver was enlarged 8 cm below costal margin, it was firm, smooth and non–tender. Spleen was enlarged schuffner

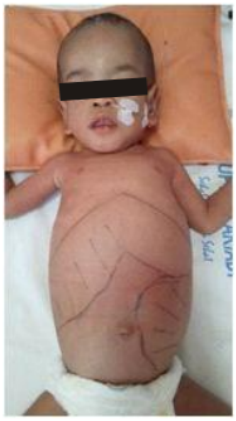

Figure 1. Clinical photograph of patient showing hepatosplenomegaly

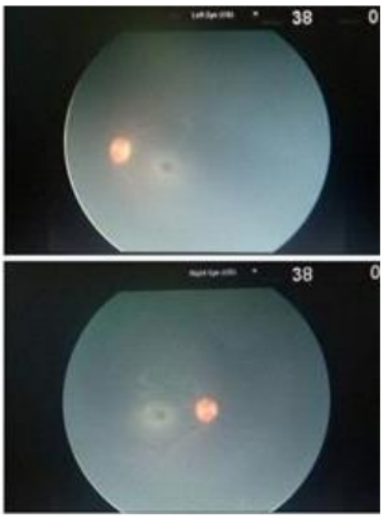

Figure 2. Funduscopic finding revealed macular cherry red spot

grade 5 and petechial in extremities, he could not hold his head upright during arm traction, muscle tone decreased continuously to a degree of a floppy infant. A Complete blood count showed a hemoglobin concentration of 9.4 g/dL, a white blood cell count of 4800/mm^3 with a normal differential count and a platelet count of 73.000/mm^3. The lactate dehydrogenase 482 U/L, and alkaline phosphatase 159, 03 IU/L which is higher than normal. The enzyme activity showed β–Glucosidase 5,55 (> 1,8 uM/hr) chitotriosidase 105,8 (<109.9 nmol/ml) in normal level but Sphingomyelinase : 0,30 (>0,5) low sphingomyelinases activity. Abdominal ultrasound revealed hepatomegaly with normal parenchyma and

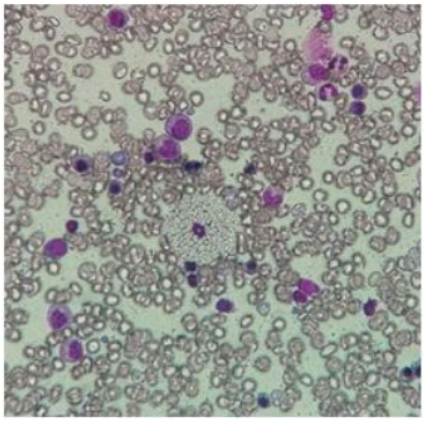

Figure 3. Bone marrow aspiration : showing foamy histiocyte

splenomegaly without nodule. X-ray chest showed retinogranuler spots on perihillerdexrtra ,sinistra and paracardialdextra. Skeletal survey revealed Erlenmeyer flask deformity Foam cell are detected in bone marrow puncture. Retcam examination showed cherry red spot at the macula. Bera revealed auditory neuropathy. The enzyme activity showed normal β–Glucosidase (5.55 uM/hr) and chitotriosidase (105,8nmol/ml) but low sphingomyelinases activity (0.30 uM/hr) which confirmed the diagnosis of NPD.

DISCUSSION

Niemann Pick Disease is autosomal recessive disease associated with hepatosplenomegaly, variable neurologic deficits, and the storage of Sphingomyelin and other lipids, due to decrease activity of acid sphyngomyelin and other l ipids. The name Niemann–Pick is derived from two German pediatricians - Albert Niemann, who first identified the Type A in 1914, and Ludwick Pick, who first identified the Type B in 1927. Both forms of NPD are caused by the deficient activity of the enzyme acid sphingomyelinase (ASM) leading to the accumulation of sphingomyelin in the monocytes, reticulo endothelial system and in type A even in the central nervous system. In 1994, Weisz *et al* sub divided on the basis of biochemical and molecular criteria inti two separate classes I & II. This categorization is based in part upon the discovery of genes for acid sphyngomyelinase, deficient in types A and B and for the NPC1 (niemann–pick C1) protein, which is deficient in types C and D, type D is an allelic variant of type C.[3,4] The types are sub divided further according to age onset and severity to acute (A), sub–acute (S) and chronic. Type A is the acuteneuronopathic form and is the most common type NPD, the clinical spectrum of this disorder ranges from the infantile, neurological form that results in death by 3 years of age (type A NPD). Macullarycherry red spots can be seen on funduscopicexamination in approximately 50% percent of patients. Large lipid lade foamy cells are seen in reticuloendothelial system of the spleen, bone marrow, lymph nodes, blood vessel, schwann cell in peripheral nerves, CNS and retinal cells. Type A is caused by mutation in the acid sphingomyelinase gene on chromosome 11p15, which results in no residual acid sphingomyelinase activity and subsequent lysosomal accumulation of sphyngomyelin.[1,2,6,7]

Type B is a chronic non–neurological form (type B NPD), it is characterized by the onset of sphlenomegaly during infancy or childhood and has a good prognosis because that is compatible with survival into adulthood. A review of English medical literature shows that 1,200 cases of NPA and NPB worldwide have been reported with the majority being Type B or an intermediate form. Cause of this type of deficiency in sphingomyelinase ismutation in SMPD gene. Thus patients present with progressive lung disease, hepatosplenomegaly, short stature and pancytopenia. Niemann Pick Disease type A is usually fatal. It leads to severe neurological symptoms, hepatosplenomegaly and cherry red spot in eye. In later stages, spasticity and rigidity may be seen.[1,2,6,7](Level of Evidence 4)

Classically Niemann–Pick Disease is classified into four subtype:

1. Niemann Pick Disease type A: classic infantile
2. Niemann Pick Disease type B: visceral
3. Niemann Pick Disease type C: subacute / juvenile
4. Niemann Pick Disease type D: Nova Scotial

Some intermediate forms are also there, type E patients are adults with moderate hepatosplenomegaly and some increase in sphingomyelin in the liver, spleen, and bone marrow. Type F for a form characterized in 2 patients by childhood onset of splenomegaly, lack of neurologic involvement, diminished sphingomyelinase activity, and thermolabile enzyme. Niemann–Pick disease types E and F have not been well-characterized.[1,2,6,7](Level of Evidence 4)

Diagnosis of Niemann Pick Disease is by clinical picture, liver biopsy and histopathology finding of Niemann–Pick cells on bone marrow examination. Diagnosis is confirmed by measurement of sphingomyelinase enzyme on cultured fibroblasts. No specific treatment is known for type A, but symptoms are treated. In Type–B the cholesterol level is kept in limit. For Type–c treatment with 2–hydroxypropyl–βcyclodextrinhas showed some good results. Prognosis is very bad in type A (85% die before 18 months). Type B children live comparatively longer but require supplemental oxygen due to lung impairment. Genetic counselling and genetic testing is recommended for families who maybe carriers of Niemann Pick.[1,2,3](Level of Evidence 4)

This case is thought to be type A as the patient revealed hepatosplenomegaly and neurodevelopmental delay at the age 6 moths. As the disease progressed, he showed macular cherry red spot on funduscopy and lipid laden foamy cells on bone marrow biopsy. He also showed progressive loss of neurologic function and repetitive pulmonary and systemic infection. To diagnose the disease, it is important to have a suspicion when encountered with a similar group of symtomps such as hepatosplenpmegaly and neurodevelopmental delay, foamy cells bone marrow, or macular cherry red spot. The macular cherry red spot found in 30 to 505 type A or type B NPD other disease can show the cherry red spot are Tay–Sachs disease, Sandof disease, GM1 gangliosidosis, and mucolipidosis. The foamy histiocyte, so called niemann-pick cell can be found in reticuloendothelial system of bone marrow, spleen, liver, lymphnode and nervous system. This cell is round and rather large at 10–90µm in diameter. It has one or two peripheral nuclei with scattered chromatins. The cytoplasm is filled with large lipid droplets which look like mesh or foam, distinguishable from goucher cells which have a wrinkled paper appearance. The vacuoles of niemann–pick cells react strongly positive with Sudan Black B, Pir Red O, Luxol Fast Blue and Acid Fast stain, but negative or weakly positive PAS stain.[1,2,6,7] (Level of Evidence 4)

Diagnose can be achieved by quantitative analysis of sphyngomyelinase in the liver, spleen and kidney, or measuring the acid sphyngomyelinase activity level in pheripheralleukosite or culture fibroblast. Prenatal diagnosis can be made by measuring the acid sphyngomyelinase activity level in cultured amniocytes or chrionicvili.[3] (Level of Evidence 4)

Currently, there is no specific treatment for niemann-pick disease for type A, but symptoms are treated. Splenectomy and bone marrow transplantation have been attempted but had little or no success, the enzyme replacement and gene therapy are in investigation and had shown some effectiveness in mice models, Prognosis is very bad in type A (85% die before 18months). Type B children live comparatively longer but require supplemental oxygen due to lung impairment. Genetic counselling and genetic testing is recommended for families who maybe carriers of Niemann Pick.[7,8] (Level of Evidence 4)

CONCLUSION

NPD type A is a fatal disease of infancy. No treatment is available for it. Early diagnosis and management of complications plays a significant role to add extra years to their life.These investigations were able to diagnose this child as a NPD–Type A. Patient was closely monitored and symptomatic treatment was provided.

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