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□ Case report □

A case of Niemann-Pick disease type A

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Niemann-Pick disease is a group of autosomal recessive disorders associated with hepatosplenomegaly, variable neurologic deficits, and the storage of sphingomyelin and other lipids. Seven cases have been reported in Korea. We report an additional case presenting with hypotonia, early neurodevelopmental delay, hepatosplenomegaly and death by persistent pneumonia and asphyxia at the age of 23 months. MRI of brain and fundoscopic findings of our case at 4 months of age were normal. However, abnormal intensity of the thalamus and atrophy of the right temporal lobe on the MRI and macular cherry red spots were noticed at the age of 17 months. A bone marrow biopsy showed large foamy cells, while hexosaminidase A and B levels were normal. Although biochemical or molecular workup was not done, these findings led to the diagnosis of infantile onset Niemann-Pick disease, probably type A. A brief review of the related literatures was made. **(Korean J Pediatr 2006;49:1358-1362)**

Key Words : Niemann-Pick disease, Hepatosplenomegaly, Cherry red spot, Foam cell

Introduction

Niemann-Pick disease (NPD) is a group of autosomal recessive disorders associated with splenomegaly, variable neurologic deficits, and the storage of sphingomyelin[1]. Type A and B NPD, resulting from deficiency of acid sphingomyelinase (ASM) activity are characterized by the progressive accumulation of sphingomyelin and other lipids in the lysosomes of various tissues, with the reticuloendothelial system being a prominent site of pathology. Patients with type A NPD have a uniform phenotype, presenting in infancy with hepatoslenomegaly, xfailure to thrive, cherry red spot, as well as neurological involvement. Foamy cell infiltration and viceromegaly are common features in all cases of NPD, whereas severe neurologic involvement occurs only in type A and C and not in type B. Although we now have an understanding of the molecular basis of NPD, there is no specific treatment for NPD. In Korea, 7 cases were reported overall after Chung[2] et al. first reported NPD type A in 1962[3-8]. We report a case of an 18 month-old boy presenting with hepatosplenomegaly, neurodevelopmental delay, cherry red spot, and lipid laden foamy cells on the bone marrow biopsy with a brief review of the related literatures.

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Case Report

A 4-month-old baby, the second of two children of a normally looking young couple, was first presented to us with developmental delay and wandering ocular movement. He was born at 41 weeks of gestation with a birth weight of 4,850 g and had no proceeding infection, fever, jaundice nor head injury. His 5-year-old sister was completely normal in physical and mental development.

The patient's body weight, head circumference and height at the age of 4 months were 7.5 kg, 41 cm, and 74 cm, respectively, all of these measures were above the 95th percentile. His blood pressure, pulse rate, respiratory rate, and body temperature were 100/60 mmHg, 149 bpm, 58 bpm, 36.8℃, respectively. On examination, the fontanel was normal on palpation, however his eyes showed wandering ocular movement and he was unable to make eye contact. Rales and wheezings were audible in both lungs. His liver and spleen were enlarged below the costal margin up to 5.5 cm and 3.5 cm, respectively. He could not hold his

head upright during arm traction. A knee jerk reflex was difficult to obtain but present.

A complete blood count showed a hemoglobin concentration of 11.4 g/dL, a white blood cell count of 7,860/mm^3 with a normal differential count and a platelet count of 258,000/mm^3. His blood chemistry results revealed BUN 1 mg/dL, Cr 0.3 mg/dL, total protein 6.4 g/dL, albumin 4.1 g/dL, AST 60 IU/L, ALT 30 IU/L, total bilirubin 0.5 mg/dl, direct bilirubin 0.3 mg/dL, LDH 859 IU/L, lactic acid 10.3 mg/dL, uric acid 2.9 mg/dL, Ca 8.2 mg/dL, P 4.0 mg/dL, Mg 2.2 mg/dL, creatinine kinase 31 U/L, Cu 66 μg/dL, ceruloplasmin 18.6 mg/dL, PT 13.0 sec, aPTT 37.3 sec, and negative CRP. The alkaline phospatase level was above 3,000 U/L which is higher than normal. The thyroid function tests, serum amino acid and organic acid test revealed no abnormality. The urine homocystine level was 8,152 μmol/g creatinine (reference level; 6-67 μmol/g creatinine) which is significantly higher than normal, while the serum methionine level was normal. The brain MR image at age of 4 months showed no abnormality and the CSF analysis showed only a mildly elevated protein level of 50 mg/dL with a normal WBC count 2/mm^3, and a normal level of glucose 74 mg/dL. The fundoscopic finding showed no abnormality and the BAEP revealed left sensorineuronal hearing loss. The liver biopsy showed most of the liver cells containing excessive glycogen and a microvesicular fatty change in some hepatocytes, which is commonly seen in patients with glycogen storage disease.

Subsequent examinations thereafter showed progressive deterioration in motor function. The baby ceased to gain after 13 months of age and began to show opisthotonic posture and could not roll over which had been noticed starting at the age of 5 months. He had not experienced developmental milestones such as sitting up, head control or eye contact. At the age of 17 months, he developed tonic clonic seizure with 20 or more attacks a day. Despite an increasingly prominent and stronger knee jerk reflex, muscle tone decreased continuously to a degree of a floppy infant. Feeding became more difficult and the patient weighed only 9 kg, lower than the 3rd percentiles for his age.

At 15 and 17 months of age, macular cherry red spots were detected on his fundoscopy (Fig. 1). Radiologic findings at 17 months revealed diffuse atrophy of the brain in both MR and CT images with symmetric thalamic hypointensity on axial T2WI MR and hyperdense thalamus on the CT which could be seen in Tay-Sachs disease[9] (Fig. 2), but the hexosaminidase A and B levels were not increased as in Tay-Sachs disease. A bone marrow biopsy showed abundant foamy histiocytes thought as the Niemann-Pick cell (Fig. 3). Measurement of sphingomyelinase activity of a cultured fibroblast could not be done due to technical difficulties.

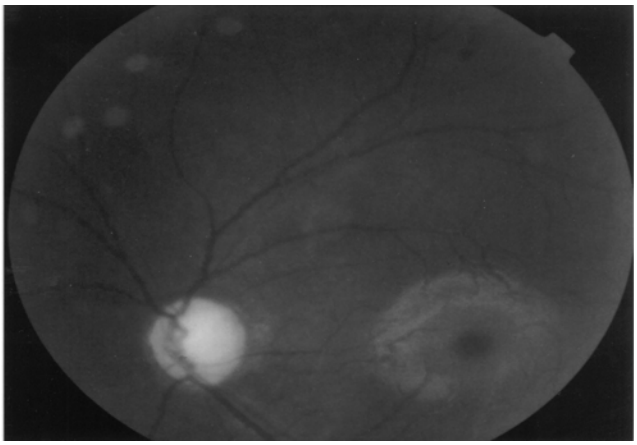

Fig. 1. Fundoscopic finding revealed macular cherry red spot.

The patient, occasionally, showed Moro reflex to very loud sounds, but never showed any blinking responses on light or mild sound stimuli, and never followed moving objects, or smiled socially. He died of asphyxia at the age of 23 months, and during his life, he had been admitted for the care of pneumonia more than 10 times and was kept on tubal feeding for the last 2 months of his life.

Discussion

NPD (sphingomyelin-cholesterol lipidosis) is a group of autosomal recessive disorders associated with splenomegaly, variable neurologic deficits, and the storage of sphingomyelin and other lipids, due to the decreased activity of acid sphingomyelinase[1]. In 1914, Niemann[10] first reported a 17-month-old girl who had been thought as having a type of Gaucher disease, and in 1927, Pick[11] contended that this disease is both histologically and clinically different from Gaucher. Afterward, Brady[12] demonstrated a deficiency of sphingomyelinase in 1966, and Huterer et al.[13] reported the decresed activity of phospholipase C activity accompanying with the sphingomyelinase deficiency.

NPD originally is categorized from A to E by clinical features, progression of disease, and neurologic manifestation[1, 14, 15]. In 1994, Weisz et al[16]. subdivided on the basis of biochemical and molecular criteria into two separate classes: I and II. This categorization is based in part upon the discovery

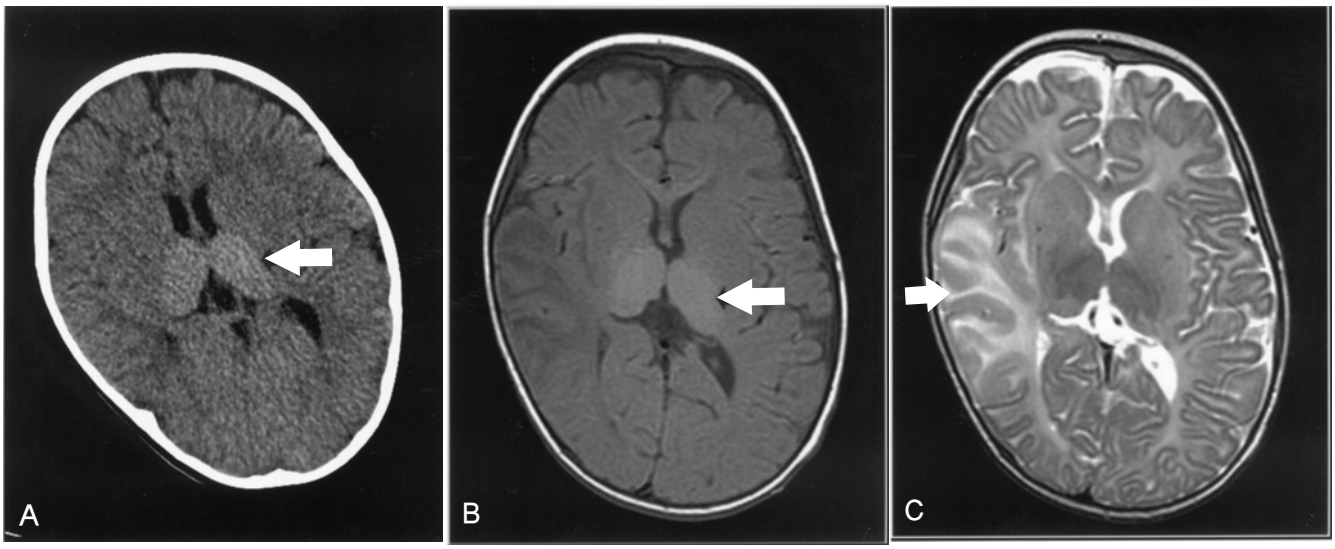

Fig. 2. Brain CT and MR images obtained at 17 months of age showed hyperdense thalamus in CT image (A, arrow) and symmetric, diffuse hyperintensity within the thalamus in axial T1WI MR (B, arrow). Axial T2WI MR shows symmetric thalamic hypointensity, and the white matter in the right temporal lobe with abnormal high signal intensity indicating brain atrophy (C, arrow).

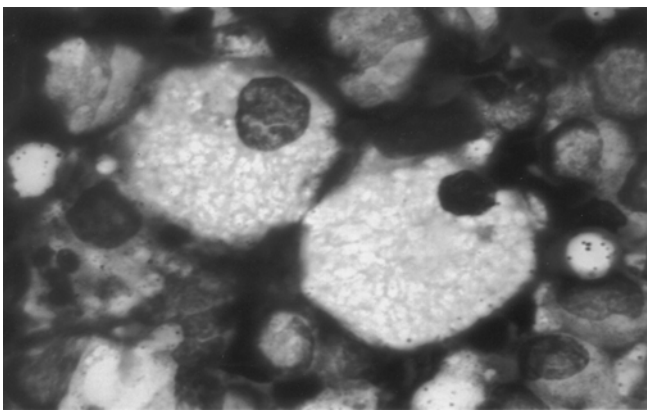

Fig. 3. Microscopic finding of bone marrow biopsy showed foamy histiocytes (Wright-Giemsa stain, ×1,000).

of genes for acid sphingomyelinase, 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[17]. The types are subdivided further according to age at onset and severity into acute (A), subacute (S), and chronic (C). Type A (IA) is the acute neuronopathic form and is the most common type of NPD; the incidence is highest among Ashkenazi Jews, in whom the gene frequency is estimated to be 1 per 100. Affected patients present with hepatosplenomegaly, feeding difficulties and loss of early motor skills in the first few months of life. Rapid, progressive, and profound loss of neurologic function leading to death occurs by two to three years of age. Macular cherry red spots can be seen on fundoscopic examination in approximately 50 percent of patients. Large lipid laden foamy cells are seen in the reticuloendothelial system of the spleen, bone marrow, lymph nodes, blood vessels, Schwann cells in peripheral nerves, CNS, and retinal cells[1, 14, 18]. Type A (IA) disease is caused by mutations in the acid sphingomyelinase gene on chromosome 11p15, which results in no residual acid sphingomyelinase activity and subsequent lysosomal accumulation of sphingomyelin[19].

Type B (IS) is a chronic non-neuronopathic form. It is characterized by the onset of hepatosplenomegaly during infancy or childhood and has a good prognosis for survival into adulthood. Type B (IS) is associated with milder mutations of the acid sphingomyelinase gene, which cause residual activity of the enzyme[20, 21]. Type E (IC) is the adult non-neuronopathic form and also has a good prognosis for survival. Type C and D (IIS) are caused by mutations in NPC1 and appear to represent abnormalities of intracellular transport of exogenous cholesterol with sequestration of unesterified cholesterol in lysosomes. Most patients with type C disease have a neurologic disease with juvenile or late infantile onset after normal early development[1, 14, 22]. These patients typically have cerebellar involvement, dystonia, vertical supranuclear ophthalmoplegia, cataplexy, and eventually seizures. It may be misdiagnosed as ADHD, learning difficulty, or developmental delay.

This case is thought to be type A (IA) as the patient

revealed hepatosplenomegaly and neurodevelopmental delay at the age of 4 months. As the disease progressed, he showed macular cherry red spot on fundoscopy 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 this disease, it is important to have a suspicion when encountered with a similar group of symptoms such as hepatosplenomegaly, neurodevelopmental delay, foamy cells on bone marrow or peripheral blood, or macular cherry red spots. The macular cherry red spot can be found in about 30 to 50% of type A or type B NPD[23]. Other diseases which also can show the cherry red spot are Tay-Sachs disease, Sandhoff disease, GM 1 gangliosidosis, and Mucolipidosis[1]. The foamy histiocyte, so called Niemann-Pick cell can be found in the reticuloendothelial systems of bone marrow, spleen, liver, lymph node and nervous system. This cell is round and rather large at 10-90 μm 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 Gaucher cells which have a wrinkled paper appearance[24]. The vacuoles of Niemann-Pick cells react strongly positive with Sudan black B, Oil red O, Luxol fast blue and Acid fast stain, but negative or weakly positive with PAS stain.

The diagnose can be achieved by quantitative analysis of sphingomyelin in the liver, spleen, leukocytes and kidney, or measuring the acid sphingomyelinase activity level in peripheral leukocytes or cultured fibroblasts. Prenatal diagnosis can be made by measuring the acid sphingomyelinase activity level in cultured amniocytes or chorionic villi[25].

Currently, there is no specific treatment for Niemann-Pick disease. Splenectomy, bone marrow transplantation, liver transplantation and amniotic cell transplantation have been attempted but had little or no success[1, 14, 26]. The enzyme replacement and gene therapy are in investigation and had shown some effectiveness in mice models[27].

한 글 요 약

A형 Niemann-Pick 병 1례

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Niemann-Pick병은 lysosome내에 sphingomyelinase의 결핍으로 sphingomyelin이란 지질이 축적된 세포들이 간, 비장, 골수, 폐, 및 뇌 등에 침착되어 간, 비장 종대 및 신경증상을 나타내며, 상염색체 열성으로 유전되는 대사성 질환이다. 1914년 Niemann에 의해 처음 보고되어 Gaucher병의 한 변형으로 분류되어 있다가, 1927년 Pick에 의해 새로 분류되어 Niemann-Pick병으로 명명되었다. 세계적으로도 희귀한 질환으로 국내에서는 1962년 정 등이 처음 보고한 이래 현재까지 저자가 조사한 바로 총 7례 정도가 보고되었다.저자들은 18개월 된 남아에서 임상증상 및 검사 소견으로 A 형 Niemann-Pick병으로 생각되는 1례를 경험하였기에 문헌 고찰과 함께 보고하는 바이다.

References

1) Schuchmann EH, Desnick RJ. Niemann -Pick disease types A and B. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds; Childs B, Kinzler KW, Vogelstein B, assoc. eds. The Metabolic and Molecular Bases of Inherited Disease, 8th ed. New York: McGraw-Hill 2001;3421-52.
2) Chung UC, Lee KS, Ji JH, Lee YB. Niemann-Pick's disease. J Korean Med Assoc 1962;55:1590-2.
3) Yoo YD, Kwak KR, Lee MJ, Kim YI, Lee KS. A case of Niemann-Pick's disease. J Korean Med Assoc 1968;11:143-7.
4) Kim SH, Choi YJ, Kim IH, Kim SW. A case of Niemann-Pick disease. J Korean Med Assoc 1983;26:1039-43.
5) Kim YS, Lim SH, Seo JK, Ahn HS, Moon HR. A case of Niemann-Pick disease with sea-blue histiocytes in the bone marrow. J Korean Med Assoc 1985;28:1238-44.
6) Cho HN, Lee HJ, Song JW, Choi JH, Moon HR, Ji JK. A case of type A Niemann Pick disease. J Korean Med Assoc 1987;30:1461-7.
7) Moon YB, Lim YB, Lee DH, Lee SJ, Kim IS, Kwon TJ, et al. A case of type A Niemann Pick disease. J Korean Med Assoc 1989;32:402-11.
8) Jeon EY, Choi KA, Koo CH, Lee WM, Jeon YS. A case of type A Niemann-Pick disease. J Korean Pediatr Soc 1998; 41:275-80.
9) Fukumizu M, Yoshikawa H, Takashima S, Sakuragawa N, Kurokawa T. Tay-Sachs disease : progression of changes on neuroimaging in four cases. Neuroradiology 1992;34:483-6
10) Niemann A. Em unbekanntes Krakheitbild. In : Weisz B, Spirer Z, Rief S. Niemann-Pick Disease : Newer Classification Based on Genetic Mutations of the Disease. Adv Pediatr 1994;41:415-26.
11) Pick L. Uberdie lipoizelling splenohepatomegalie typus Niemann-Pick als stoffwechselekrankung. In : Weisz B, Spirer Z, Rief S. Niemann-Pick Disease : Newer Classification Based on Genetic Mutations of the Disease. Adv Pediatr 1994;41: 415-26.
12) Brady RO. The sphingolipidoses. N Engl J Med 1966;275: 312-8.
13) Huterer H, Wherrett JB, Poulos A, Callahan JW. Deficiency of phospholipase C acting on phosphatidylglycerol in Niemann-Pick disease. Neurology 1983;33:67-73
14) Kolodny EH. Niemann-Pick disease. Curr Opin Hematol

2000;7:48-52.
15) Fredrickson DS, Sloan HR, Sphingomyelin lipoidosis; Niemann-Pick disease. 3rd ed. New York : McGraw-Hill Book Co 1982:34-6.
16) Weisz B, Spirer Z, Rief S. Niemann-Pick disease : Newer classification based on genetic mutations on the disease. Adv Pediatr 1994;41:415-26.
17) Greer WL, Riddell DC, Gillan TL, Girouard GS, Sparrow SM, Byers DM, et al. The Nova Scotia (type D) form of Niemann-Pick disease is caused by a G3097→T transversion in NPC1. Am J Hum Genet 1998;63:52-4.
18) McGovern MM, Aron A, Brodie SE, Desnick RJ, Wasserstein MP. Natural history of type A Niemann-Pick disease. Neurology 2006;66:228-32.
19) da Veiga, Pereira L, Desnick RJ, Adler DA, Disteche CA, Schuchman EH. Regional assignment of the human acid sphingomyelinase gene (SMPD1) by PCR analysis of somatic cell hybrids and in situ hybridization to 11p15.1-p15.4. Genomics 1991;9:229-34.
20) Wenger DA, Kudoh T, Sattler M, Palmieri M, Yudkoff M. Niemann-Pick disease type B: prenatal diagnosis and enzymatic and chemical studies on fetal brain and liver. Am J Hum Genet 1981;33:337-44.
21) Graber D, Salvayre R, Levade T. Accurate differentiation of neuronopathic and nonneuronopathic forms of Niemann-Pick disease by evaluation of the effective residual lysosomal sphingomyelinase activity in intact cells. J Neurochem 1994; 63:1060-8.
22) Vanier MT. Phenotypic and genetic heterogeneity in Niemann-Pick disease type C: current knowledge and practical implications. Wien Klin Wochenschr 1997;109:68-73.
23) McGovern MM, Wasserstein MP, Aron A, Desnick RJ, Schuchman EH, Brodie SE. Ocular manifestations of Niemann-Pick disease type B. Ophthalmology 2004; 111:1424-7.
24) Gardner LI. Endocrine and genetic disease of childhood and adolescence. 2nd ed. Philadelphia : WB Saunders Co 1975: 1127-30.
25) Vanier MT. Prenatal diagnosis of Niemann-Pick diseases type A, B and C. Prenat Diagn 2002;7:630-2.
26) Victor S, Coulter JBS, Besley GTN, Ellis I, Desnick RJ, Schuchman EH, Vellodi A. Niemann-Pick disease : Sixteen-year follow-up of allogenic bone marrow transplantation in a type B variant. J Inhert Metab 2003;26:775-85.
27) Desnick RJ. Enzyme replacement and enhancement therapies for lysosomal diseases. J Inhert Metab 2004;27:385-410.