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A rare cause of non-immune hydrops fetalis: congenital sialidosis

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Summary

Sialidosis is a rare congenital lysosomal storage disease with autosomal recessive transmission caused by a deficiency of alpha-N-acetyl-neuraminidase (sialidase). The findings begin in the intrauterine period in congenital type of sialidosis and the cases die in the postnatal period due to hydrops fetalis with multiorgan failure. Here, a case of premature baby born to a consanguineous parents and diagnosed as sialidosis with hydrops fetalis is presented. It was learned that the first pregnancy of the mother ended in spontaneous abortion and the second pregnancy was ended up with intrauterine exitus due to hydrops fetalis in the 28th gestational age. On the first physical examination, generalized edema, abdominal distantion due to hepatomegaly and generalized ascites was observed. Direct hyperbilirubinemia and cytoplasmic vacuoli in the lymphomonocyte series in both the bone marrow and peripheral blood smear were detected. The same vacuoli were also observed in hepatocytes in the hystopathological sections of the liver biopsy. Sialidosis was diagnosed by showing that there was no activity of sialidase enzyme in the fibroblast culture. The case died due to cardiorespiratory insufficiency on the 53rd day of admission. In cases with hydrops fetalis which can have various etiologies, careful examination of the peripheral smear is very important in the differential diagnosis in addition to detailed familial history and physical examination. *(Turk Arch Ped 2012; 47: 286-289)*

Key words: Hydrops fetalis, sialidosis

Introduction

Sialidosis is an autosomal recessive lysosomal storage disease characterized by accumulation of sialyloligosaccharides in the blood, tissues and urine occuring as a result of mutaton of the gene coding lysosomal sialydase (neuraminidase) enzyme localized on the short arm of th 6th chromosome (1,2). The disease was firstly described by Spranger et al. (3) in 1968 as lipomucopolysaccharidosis. The disease is divided into two groups as type I and type II according to age of onset and the severity of the findings. Type I is the milder form and is also named as "normosomatic" type or "cherry red spot-myoclonus" syndrome. The symptoms begin in the second decade of life and has a beter prognosis compared to type II. The characteristic findings include progressive vision loss accompanying nistagmus, ataxia and convulsion. No somatic or bone defects are present. The intelligence is normal (4,5). Sialidosis type II has an earlier onset and is the more severe form. It is also known as "dysmorphic" type, mucolipidosis I or lipomucopolysaccharidosis. Type II sialidosis is divided into three groups as congenital, infantile and juvenile according to age of onset. The main characteristics include coarse face, dysostosis multiplex (deficient ossification), hepatomegaly and splenomegaly, growth failure and mental retardation. The congenital form causes intrauterine death or hydrops fetalis (6,7).

Here, a premature infant with congenital sialidosis who was born with non-immune hydrops fetalis and lost in the early period was presented.

Case

A female infant was delivered by cesarean section prematurely at the 30th gestational week because of non-immune hydrops fetalis. She was the only living infant born from the third pregnancy of the parents who had third degree consanguinty. It was learned that the first pregnancy resulted in abortus and the

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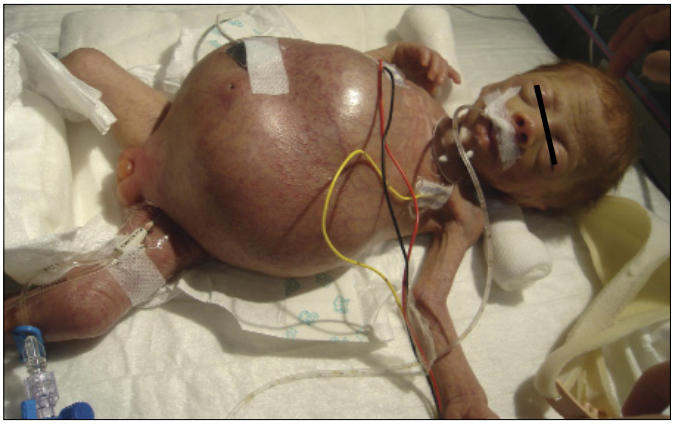
second pregnancy resulted in intrauterine death because of non-immune hydrops fetalis at the 27th gestational week, but no autopsy was performed and the gender of this infant was male.

It was learned that the baby had normal female karyotype in the prenatal follow-up, inversion (9) (p11;q13) which did not affect the phenotype was found, direct, indirect Coombs tests and TORCH and parvovirus serologic tests were negative and erythrocyte transfusion was performed by chordocentesis one week before the birth.

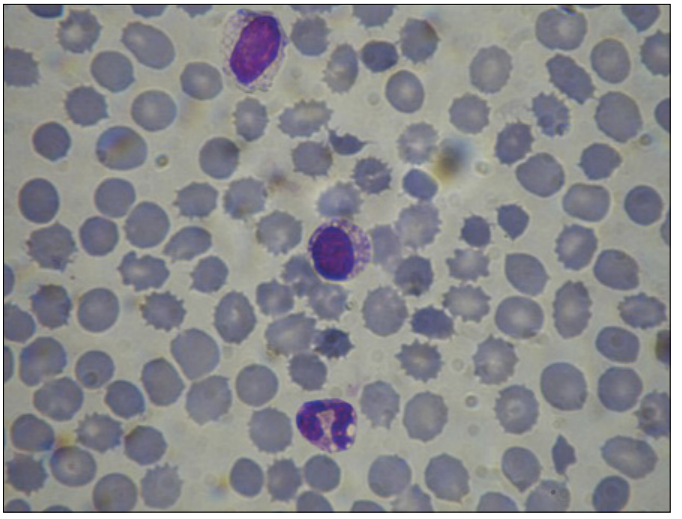
Physical examination revealed the following findings: weight: 1340 g, height: 37 cm, head circumference: 27.5 cm. These values were found to be compatible with age-appropriate percentiles. The general status was poor, marked ascites was found in the abdomen and diffuse body edema was found predominantly in the extremities and labia. The abdominal circumference was found to be 34 cm. The anterior fontanel had a size of 3x2 cm and was not bulging. A hard liver was palpable at 4 cm below the rib edge in the middle clavicular line. Telengiectasies were observed on the abdominal skin and the superficial veins were prominent. A coarse face was observed with anteverted nostrils, large and low-set auricles and increased forehead lines (Picture 1).

The patient was intubated just after delivery because of respiratory distress and ventilation support was started. Since ascites compressed the diaphragm, 200 ml fluid was removed in the delivery room. The ascitic fluid had a clear straw color and did not contain cells. Creatinine, amilase and bilirubin levels in the ascitic fluid were found to be normal. The protein concentration was found be 2.05 g/dL in the ascitic fluid, serum total protein was found to be 2.8 g/dl and serum albumin level was found to be 1.6 g/dL. At the baseline, hemoglobin was found to be 20.3 g/dL, hematoctrite was found to be 59%, white blood cell count was found to be 9500/mm^3, platelet count was found to be 130 000/mm^3, the blood type of the mother and the baby was found to be 0 Rh (+) and the direct coombs test was found to be negative. The other laboratory values were as follows: serum creatinine: 0.8 mg/dL, SGOT: 480 U/L, SGPT: 104 U/L, GGT. 1168 U/L, PT: 17 s, PTT: 40.4 s, INR: 1.4, fibrinogen: 299 mg/dL, amonia was found to be within normal limits, total bilirubin: 7.7 mg/dL, direct bilirubin 0.6 mg/dL. There was no protein in the urine. Total IgM was found to be 40 mg/dL (N<145 mg/dL), Toxoplasmosis, CMV, Rubella, HSV type 1 and 2 were found to be negative. Abdominal ultrasonography revealed that hepatic and portal veins were open, the liver had a heterogeneous coarse granulated structure and hypoechoic areas which suggested necrosis or abscess. The spleen and kidneys had normal structure.

When the history, physical examination and laboratory findings were evaluated together, an autosomal recessive storage disease was considered and bone marrow aspiration was performed. Storage cells containing multiple vacuoli in the cytoplasm were observed in the lymphoid series cells. Similar vacuoli were also observed in the leucocytes in the peripheral smear (Picture 2). Fundoscopic examination was found to be normal. Disostosis was not observed on skeletal graphies. It was learned that the level of 16 lysosomal enzyme which was tested by lysosomal enzyme screening in the leucocytes was normal. The patient was extubated on the 9th day and tolerated enteral feeding. The transaminase levels improved to normal values, while direct bilirubin was observed to be increased. Echocardiographic examination performed to evaluate cardiac involvement because of a murmur and suspicion of storage disease was found to be normal. On the 14th day, her general status detorieted while she was being fed completely enterally and she had residues with bile. She was re-intubated, abdominal exploration and colostomy and liver biospy were performed considering closed intestinal perforation. Liver biopsy revealed diffuse swelling and vacuoli in the hepatocytes and larger storage cells with foamy cytoplasms (Picture 3). Electron microscopic examination of the liver revealed inclusion bodies in the



Picture 1. Coarse face of the patient with anteverted nostrils, large and low-set auricles, increased forehead lines. Diffuse abdominal ascites, hepatomegaly, telengiectasies on the abdominal skin and prominent superficial veins



Picture 2. Leucocytes containing multiple lysosomal vaculi on peripheral smear. Wright Giemsa, x100

cytoplasm (Picture 4). Total sialic acid level in urine was found to be increased (normal value: 17-243 µmol/nmol; the result: 6504 µmol/nmol Cr).

Fibroblast culture was performed with a prediagnosis of sialidosis or galactosialidosis. β-galactosidase activity was found to be normal in the sample which was sent for enzyme analysis, while no neuroaminidase activity was found (Johannes-Gutenberg Universitat Mainz Kinderklinik Biochemical Laboratory). The patient was diagnosed as infantile type II sialidosis. On the 53rd day, the patient was lost because of circulatory and respiratory insufficieny. Autopsy was performed. Mutation analysis of the DNA sample of the patient performed in St. Jude Children's Research Hospital Memphis revealed point mutation in exone 1 in the neuroaminidase gene.

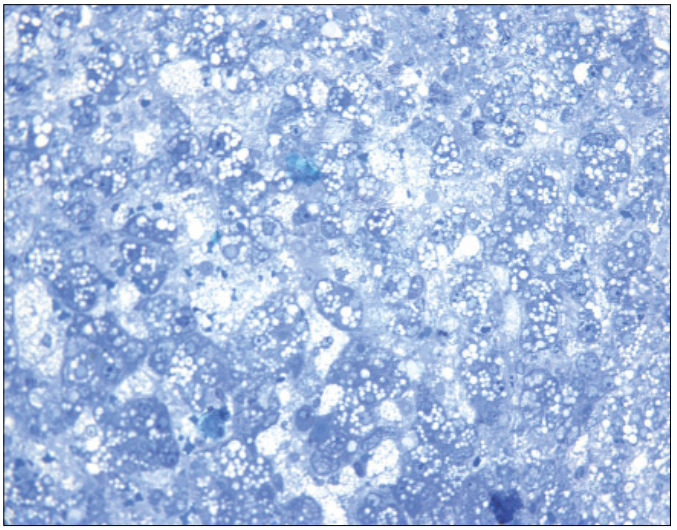
Discussion

Non-immune hydrops fetalis is a clinical picture characterized by diffuse edema. Hematologic, metabolic and cardiac problems, intrauterine infections, tumors and skeletal dysplasies are involved in the etiology. Lysosomal storage diseases which are characterized by non-immune hydrops fetalis include GM1-gangliosidosis, mucopolysaccharidosis type VII, gaucher disease, sialidosis and Salla disease (8).

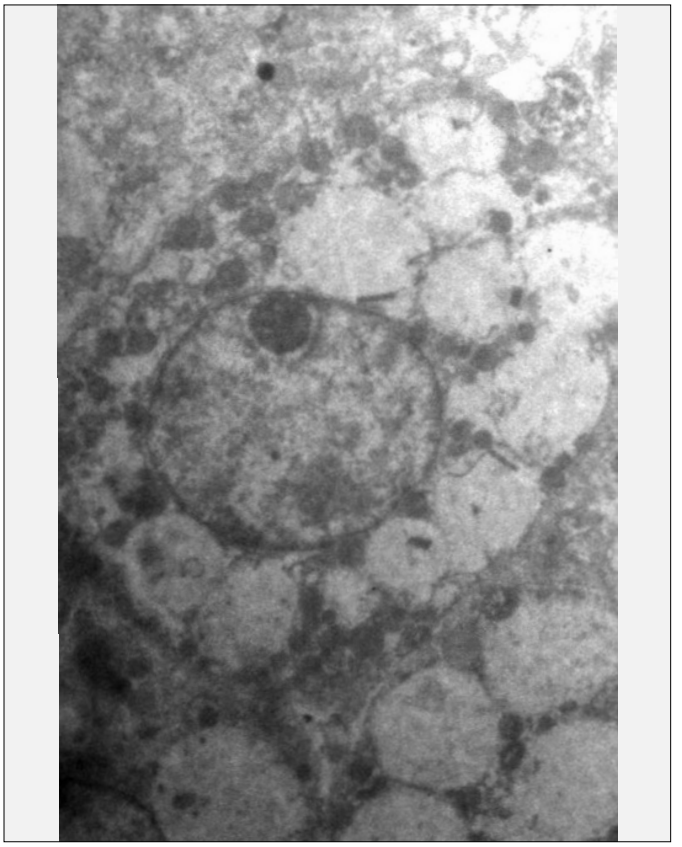
Lysosomal sialidase (neuroaminidase) cleans sialic acid residues located in the last part of gangliosides, oligosaccharides and glycoproteins. There are three known neuroaminidase enzymes. These three enzymes can be differentiated by their different intracellular localizations, enzyme specificities and the most appropriate pH values. In sialidosis, lysosomal neuraminidase is deficient (N-acetyl-α-neuraminidase). Congenital deficiency of the enzyme leads to sialidosis which is characterized by progressive accumulation of sialyl-oligosaccharides and sialyl-glycopeptides in lysosomes. Vacuoli observed in the bone marrow, liver, cutaneous fibroblasts, nerve cells and peripheral lymphocytes reflect this accumulation. The clinical picture of the disease occurs as a result of this accumulation (9). Sialidosis is a rare lysosomal storage disease with an incidence of 1/250 000-2 000 000 live births. Approximately 40 different mutations have been defined (10).

Lysosomal sialidase functions only when it is bound to another enzyme named cathepsin (Protective Protein Cathepsin A: PPCA). β-galactosidase and sulphatase are also components of this enzyme group. In galactosialidosis, there is a defect in the structure of cathepsin. Thus, both neuraminidase and β-galactosidase enzymes are inactive. Although it is very similar to sialidosis clinically, they are completely different genetic diseases (11,12).

The reasons that investigations were focused on storage diseases from the beginning in this patient included presence of a similar history of death of a sibling which supported autosomal recessive transmission and exclusion of chromosomal, infectious and cardiac causes which could lead to non-immune hydrops fetalis in the prenatal follow-up. Hepatomegaly and storage cells observed in both the bone marrow and liver biopsy with diffuse ascites strenghtened the



Picture 3. Light microscopic appearance of the hepatocyte containing multiple lysosomal vacuoli in the cytoplasma on semi-thin resin sections. Nucleus (N). Toluidin bluex100



Picture 4. Electron microscopic appearance of the hepatocyte containing multiple lysosomal vacuoli in the cytoplasma. Nucleus (N), Nucleolus (NL). Uranyl-lead stainx1250

suspicion of lysosomal storage disease. However, normal lysosomal enzyme levels in the leucocytes screened because of this suspicion can not exclude lysosomal storage disease, because these enzymes screened are located in the cytoplasms of the lysosomes. Thus, investigation of deficiency of enzymes located in the lysosomal membrane was started. Free and total sialic acid were tested in urine considering deficiency of sialidase enzyme located in the lyososmal membrane which presents with clinical findings due to sialic acid accumulation in the tissues and urine. When total sialic acid level was found to be very high, a diagnosis of sialidosis was made observing that β-galactosidase enzyme activity was normal, but there was no activation of neuraminidase enzyme in fibroblast culture.

Sialic acid accumulated in the cell is stored as free sialic acid as observed in Salla disease and infantile sialic acid storage disease or accumulates as bound to other glycopeptides or oligosaccharides as observed in sialidosis. There is deficiency of sialin which is a lysosomal membrane protein in Salla disease and infantile sialic acid storage disease. The genetic characteristics are completely different from sialidosis and should be differentiated (11,13).

Mutation analysis of the DNA sample obtained from this patient revealed point mutation in exon 1 of the neuraminidase gene. Presence of a sibling who had been diagnosed with non-immune hydrops fetalis and whose molecular analysis had been performed previously facilitates prenatal diagnosis, however, these patients who are defined as index cases are generally lost before a definite diagnosis is made. In this case, enzyme analysis can be performed in chorion villus samples or amniotic cell cultures. In addition, prenatal diagnosis of lysosomal storage disease can be made by analysis of glycolipids and oligosaccharides in the amniotic fluid using a method called “electrospray ion tandem mass spectrometry” (14).

In cases of hydrops fetalis which has many etiologic causes, examination of peripheal smear in addition to careful history taking and physical examination is significant in terms of early diagnosis of rare causes including congenital sialidosis.

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