Korean Journal of Pediatrics Vol. 51, No. 6, 2008
DOI : 10.3345/kjp.2008.51.6.650
Case report

A case of simultaneously identified glycogen storage disease and mucopolysaccharidosis

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= Abstract =

Glycogen storage disease (GSD) and mucopolysaccharidosis (MPS) are both independently inherited disorders. GSD is a member of a group of genetic disorders involving enzymes responsible for the synthesis and degradation of glycogen. GSD leads to abnormal tissue concentrations of glycogen, primarily in the liver, muscle, or both. MPS is a member of a group of inherited lysosomal storage diseases, which result from a deficiency in specific enzymatic activities and the accumulation of partially degraded acid mucopolysaccharides. A case of a 16-month-old boy who presented with hepatomegaly is reported. The liver was four finger-breadth-palpable. A laboratory study showed slightly increased serum AST and ALT levels. The liver biopsy showed microscopic features compatible with GSD. The liver glycogen content was 9.3% which was increased in comparison with the reference limit, but the glucose-6-phosphatase activity was within the normal limit. These findings suggested GSD other than type I. Bony abnormalities on skeletal radiographs, including an anterior beak and hook-shaped vertebrae, were seen. The mucopolysaccharide concentration in the urine was increased and the plasma iduronate sulfatase activity was low, which fulfilled the diagnosis criteria for Hunter syndrome (MPS type II). To the best of the authors' knowledge, this is the first case of GSD and Hunter syndrome being identified at the same time. (Korean J Pediatr 2008;51:650-654)

Key Words : Glycogen storage disease, Mucopolysaccharidosis, Hunter syndrome, Hepatomegaly

Introduction

Glycogen storage disease (GSD) is a heterogeneous group of inherited disorders of carbohydrate metabolism[1-3]. While forming a broad spectrum of clinical phenomena and biochemical diversities, hepatomegaly is the main finding in all GSDs affecting the liver. Because of an enzyme deficiency, glycogen-breakdown is impaired and glycogen accumulates in hepatocytes[1, 3]. Mucopolysaccharidosis (MPS) is also a heterogenous group of lysosomal storage disorders, each caused by a deficiency of an enzyme involved in the degradation of glycosaminoglycans (GAG, previously called *mucopolysaccharides*)[4, 5]. These enzyme deficiencies lead to the accumulation of glycosaminoglycans in the lysosomes of most cells, resulting in cell, tissue and organ dysfunction[6]. The clinical presentation and severity of symptoms can vary widely between the seven major types, but most of the disorders are characterized by a multi-system involvement, abnormal facial features, organomegaly and dysostosis multiplex[4-6]. GSDs and MPSs are independently inherited disorders and they both result from a deficiency of specific enzyme activities of different metabolic pathways and the accumulation of precursors. We report a case of GSD and MPS identified simultaneously in a child with hepatomegaly.

Received : 2 February 2008, Accepted : 7 March 2008
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Case Report

A 16-month-old boy had suffered from recurrent otitis media for 5 months and hepatomegaly was found by chance

at a local hospital. The weight was 11.8 kg (7,590 percentile), the height was 82.9 cm (7,590 percentile) and the head circumference was 50.5 cm (>97 percentile). The patient was born with a weight of 3.6 kg by Cesarean section to healthy, non-consanguineous parents as a second child. A 4-year-old brother is healthy. The patient had been suffering from chronic diarrhea, rhinitis and recurrent otitis media since he was 11 months old. It was during this time that hepatomegaly was found. The patient manifested a coarse facial feature with a prominent forehead and there were Mongolian spots on the back and both ankles. The parents also noticed that the boy had been waking up two to three times during the night and they said that his activity had recently increased.

In addition, speech development was markedly delayed. The liver was four finger-breath-palpable, soft and sharply margined. A laboratory study showed slightly increased serum AST and ALT levels (85 IU/L and 77 IU/L, respectively). The patient did not present with fasting hypoglycemia and the serum lactate, uric acid and cholesterol levels were all within the normal ranges (serum glucose 83 mg/dL, lactate 1.7 mmol/L, uric acid 2.5 mg/dL and cholesterol 123 mg/dL). On abdominal ultrasonography, an enlarged liver had increased echogenicity and there was no evidence of obstruction. Liver tissue, obtained by a needle aspiration biopsy, revealed portal area fibrosis and round glycogenated pale hepatocytes that contained many large glycogen particles that were strongly stained by Periodic Acid-Schiff with some lipid vacuoles. Decolorization of the Periodic Acid-Schiff stain by a bleaching agent proved that these hepatocytes contained glycogen not glycoprotein. If there were accumulation of mucopolysaccharides, these particles might be stained in red after diastase digestion. At an electron microscopic examination, the nuclei of the hepatocytes were round and occasionally glycogenated. The cytoplasm contained many large glycogen particles and giant mitochondrias. The hepatic glycogen content increased to 9.3% as compared to the suggested reference limit (16%/wet liver weight) and

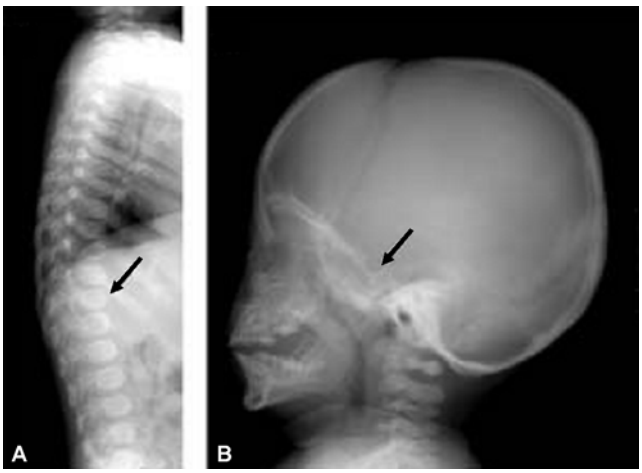

Fig. 1. The X-rays show an anterior beak (arrow) hook-shaped vertebrae (A), J-shaped sella turcica (arrow), odontoid hypoplasia and suspicious narrowing of the spinal canal in the C-spine (B).

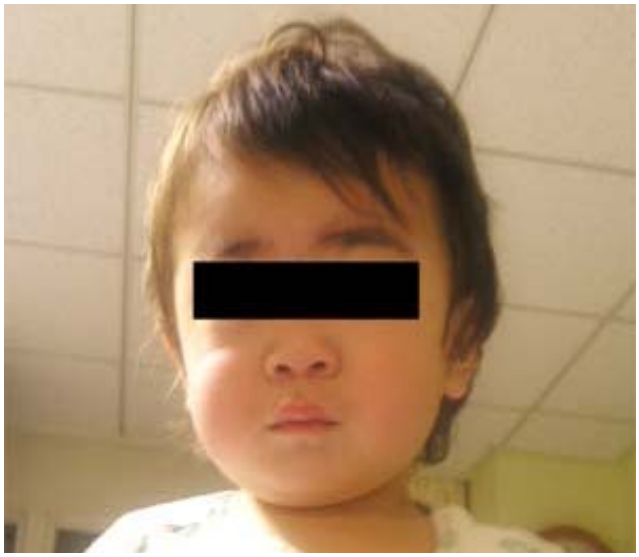

Fig. 2. The patient presents coarse facial features with a prominent forehead.

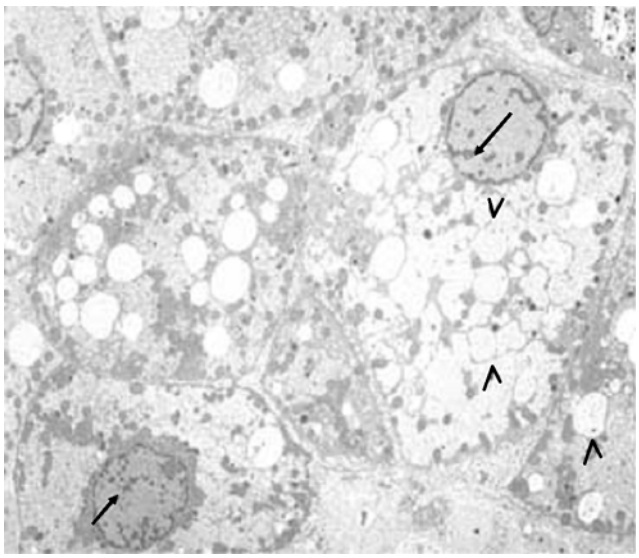

Fig. 3. The electron microscopic exam of liver tissue shows swollen polygonal hepatocytes (×2,500). The nuclei of the hepatocytes are round and occasionally glycogenated (arrows). In addition, the cytoplasm contains many large glycogen particles (arrowheads) and giant mitochondrias. Some fat vacuoles are also noted.

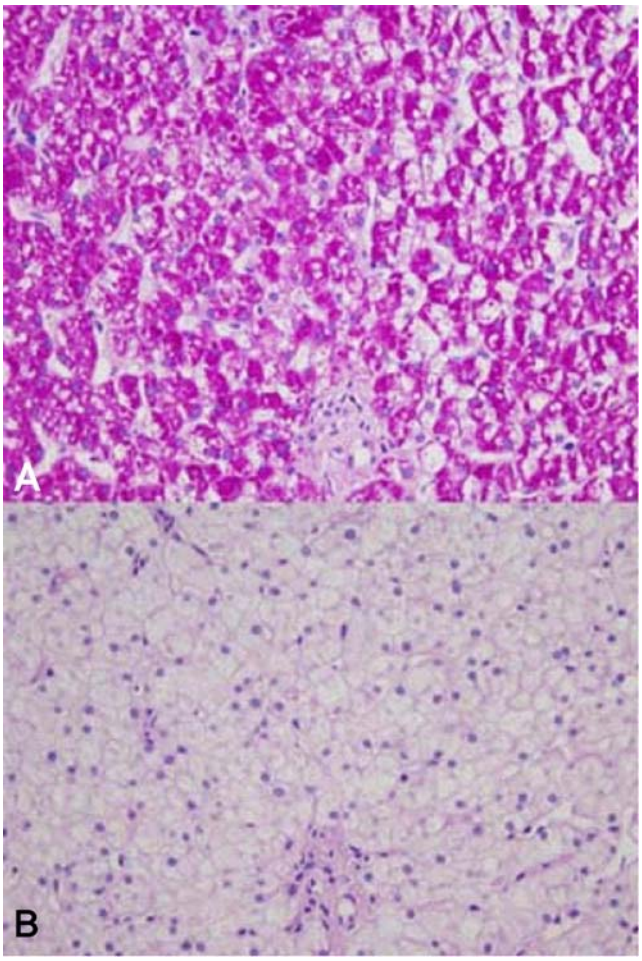

Fig. 4. The light microscopic exam of liver tissue reveals mild fibrosis at the portal area and glycogenated hepatocytes that contain many large glycogen particles (×400). The liver tissue was strongly stained with Periodic Acid-Schiff (A) and decolorized by using a bleaching agent (B).

glucose-6-phosphatase activity was within the normal limit, which implied GSD other than type Ia[7, 8]. However, bony abnormalities on skeletal radiographs including an anterior beak and hook-shaped vertebrae, oar-shaped ribs, J-shaped sella turcica and coarse trabeculation of the metacarpal bones in the hand were noted. A urine MPS spot test was positive and the plasma iduronate sulfatase activity was remarkably low at 0.1 nmol/hr/mg protein, which was consistent with the diagnosis of Hunter syndrome (MPS type II)[9]. The heart size was within the normal limit and echocardiography did not demonstrate intracardiac anomalies or pericardial effusion.

Discussion

Resnick et al. reported on the histological findings in liver biopsy samples from 27 infantile MPS cases, which showed no architectural changes, inflammatory infiltrates or extensive fibrosis[10]. However, in other cases, hepatic fibrosis was reported in the liver histopathologic findings of MPS patients[11, 12]. In those cases, fibrosis was more obvious in the subcapsular parenchyma and was associated with focal intralobular accumulations of foamy, GAG-laden macrophages[11, 12]. In the present case, the liver histology showed mild portal fibrosis as well as pale swollen hyperglycogenated hepatocytes. The liver contained particles that were strongly stained by Periodic Acid-Schiff, decolorized by use of a bleaching agent. If there was accumulation of mucopolysaccharides, these particles might be stained in red after the use of a bleaching agent. These findings met the criteria for the histology of the liver affected not by MPS but with GSD. However, as presented above, the clinical manifestations and the laboratory findings were compatible with the diagnosis of not only GSD but also Hunter syndrome.

Unlike other MPS disorders inherited in an autosomal-recessive manner, Hunter syndrome (MPS type II) is an X-linked recessive disorder and primarily affects male patients. Hunter syndrome results from a defective function of iduronate-2-sulfatase and deposition of GAG, dermatan sulfate and heparan sulfate. Its gene locus has been mapped to chromosome Xq28[9, 13]. The occurrence of two recessive disorders in one individual is extremely rare. It suggests that both causative genes that induce each enzymatic defect are located in the same chromosome.

From this point of view, the patient could have GSD type IXa, a phosphorylase kinase (Phk) deficiency that has been mapped to chromosome X[13-15]. The X-linked hepatic Phk deficiency probably constitutes the largest subgroup of liver glycogenoses and it is usually a benign condition as compared with other types of GSD[1-3, 16, 17]. In contrast to GSD type I, lactic acidosis and clinically apparent hypoglycemia are observed only in a minority of cases[16, 17]. The hepatic architecture typically remains intact, unlike for GSD type III and IV, which usually progress to cirrhosis in childhood. Usually the liver histology of GSD type IXa reveals marked glycogen accumulation in addition to mild portal or septal fibrosis[16, 17]. Several reports have indicated that a uniform mosaic pattern of swollen hepatocytes and prominent nuclear

hyperglycogenation are the main diagnostic features of GSDs[18]. Although the degrees of fibrosis were variable, generally mild portal fibrosis was detected in type VI, IX and X more often than in other types of GSDs[18, 19].

Up to now, there is only one report of a case that GSD and MPS diagnosed at the same time. That was a report of 10-yr-old girl who had GSD type Ia and Sanfilippo syndrome (MPS type III)[20]. To the best of our knowledge, we are reporting the first case of GSD and Hunter syndrome (MPS type II) being identified at the same time.

한 글 요 약

당원병과 뮤코다당체침착증이 동시에 발견된 증례 1예

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당원병(GSD)과 점액다당류증(MPS)은 각각 독립된 유전 질환으로, 각기 다른 대사에 관여하는 효소의 결핍으로 인해 전구물질이 축적되어 임상 증상을 나타낸다. 간비대는 두 질환 모두에서 나타나는 중요한 임상 양상이다. 저자들은 이 드문 두 질환이 한 환자에서 동시에 발견되어 이에 보고하고자 한다. 16개월 남아가 2개월 동안 반복적인 중이염을 앓았고, 인근 병원을 다니던 중 우연히 간비대가 발견되었다. 환아는 이마가 튀어나온 조악한 얼굴 모양을 가지고 있었다. 환아의 간은 4횡지 정도로 촉지되었고, 그 성상은 부드럽고 무른 느낌이었으나 경계가 예리하게 만져졌다. 혈액 검사상, AST와 ALT가 85 IU/L, 77 IU/L로 약간 상승되어 있었다. 공복 저혈당은 보이지 않았고, 혈청 젖산, 요산, 콜레스테롤 모두 정상 소견을 보였다. 복부 초음파에서는 간의 메아리 발생 정도(echogenecity)가 증가되어 있었다. 간 생검을 실시하였고, 현미경 검사상 둥근 간세포들이 관찰되었는데, 그 간세포 내에는 Periodic Acid-Schiff 염색에서 진하게 염색되는 거대한 당원 입자들 다수와 이와 동반된 지방 공포(lipid vacuole)가 포함되어 있었다. 전자현미경에서 간세포의 핵과 세포질 모두에 당원 입자들이 포함되어 있었고 거대한 미토콘드리아도 관찰할 수 있었다. 생검을 통해 채취한 간 조직을 분석한 결과, 간의 당원 함량은 9.3%로 정상수치에 비해 증가되어 있었으나, 간의 glucose-6-phosphatase 활성도는 정상이어서 Ia형이 아닌 당원병으로 진단하게 되었다. 한편, X 선상 척추 앞면의 부리모양(beak-shape)와 J 모양의 안장(sella)과 같은 여러 골격의 이상 소견을 보였으며, 소변의 점액다당류 농도 또한 증가되어 있었다. Iduronate sulfatase 활성도가 0.1 nmol/hr/mg protein로 낮은 소견을 보여 헌터 증후군(제2형 점액다당류증, MPS type II)으로 진단할 수 있었다. 이에 저자들은 상기 환자가 당원병과 헌터증후군이 동시에 발견된 첫 환자로 생각되어 보고하는 바이다.

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