성인에서 진단된 3a형 당원축적병 1예

영남대학교 의과대학 내과학교실, 병리학교실¹

김경옥 · 이현주 · 최재원 · 은종렬 · 최준혁¹

Abstract

An adult case of glycogen storage disease type IIIa

Kyeong Ok Kim, M.D., Heon Ju Lee, M.D., Jae Won Choi, M.D.,
Jong Ryul Eun, M.D., Joon Hyuk Choi, M.D.¹

Department of Internal Medicine, ¹Department of Pathologic Medicine,
Yeungnam University College of Medicine, Daegu, Korea

Glycogen storage disease type III (GSD III) is a very rare disorder caused by a deficiency in the activities of glycogen debranching enzymes (amylo-1-6-glucosidase and 4- α -glucanotransferase). GSD III is characterized by the accumulation of abnormal glycogen in the liver and skeletal muscle. The primary clinical manifestations are hepatomegaly, fasting hypoglycemia, and hyperlipidemia in infants. We report a rare case of GSD III in an adult. A 52-year-old woman presented to our clinic due to dyspnea on exertion, severe general weakness, and hepatomegaly. Hypertrophic cardiomyopathy was diagnosed based on echocardiogram findings. The microscopic findings of liver and skeletal muscle biopsies were consistent with the diagnosis of GSD. DNA analysis prompted by clinical and pathologic findings led to a definitive diagnosis of GSD IIIa. Diet therapy with cornstarch was started, and the patient was followed closely. This represents the first reported case of GSD IIIa diagnosed in an adult in Korea. (*Korean J Hepatol* 2008;14:219-225)

Introduction

Glycogen storage disease (GSD) is an autosomal recessive disorder caused by abnormalities of the enzymes that regulate glycogen metabolism.^{1,2} There are several subtypes of GSD classified according to the associated enzymes, with the most common being GSD type I (GSD I), III,

and IV.³ GSD III is also called limited dextrinosis, and results from deficiency in the activities of glycogen debranching enzymes (amylo-1-6-glucosidase and 4- α -glucanotransferase; gene AGL).⁴ The primary manifestations of GSD III are fasting hypoglycemia, hepatomegaly, and hyperlipidemia. In cases with muscle involvement, weakness and cramp are observed.⁵ A definitive

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◇ Abbreviations: GSD, glycogen storage disease; RBC, red blood cells

◇ Corresponding author: Heon-Ju Lee, E-mail: hjlee@med.yu.ac.kr; Phone: (053) 620-3834; Fax: (053) 654-8386

주소: 대구시 남구 대명동 317-1 영남대학교의료원 소화기내과 (우)705-717

Figure 1. Abdominal computed tomography scan showing diffuse hepatomegaly without splenomegaly and low-density liver parenchyma.

diagnosis is based on liver and muscle biopsies, analysis of the activities of glycogen debranching enzymes, and DNA studies.⁶

The worldwide incidence of GSD III is 1:125,000,³ with no previous confirmed case in adult having been reported in Korea. We report a case of this rare disorder, with GSD IIIa confirmed based on liver and muscle biopsies and DNA analysis.

Case

A 52 year-old woman presented to our clinic with dyspnea on exertion and general weakness that had been present for several decades. The patient knew that she had a hepatic disease, but this had not been evaluated clinically. She suffered from dyspnea on exertion, general weakness, and progressive muscle weakness of the lower extremities. The patient did not work outside of the home and had no family history of a metabolic abnormality and no history of alcohol consumption.

On presentation, the patient had stable vital signs. The physical examination revealed that

she was 154 cm tall and weighed 59 kg, and had hepatomegaly but not splenomegaly. The laboratory tests showed a fasting serum glucose of 62 mg/dL (normal range: 70–110 mg/dL), lactate dehydrogenase at 2,680 U/L (150–550 U/L), aspartate aminotransferase at 127 U/L (10–35 U/L), alanine aminotransferase at 114 U/L (0–40 U/L), alkaline phosphatase at 276 U/L (180–270 U/L), albumin at 4.5 g/dL (3.5–5.0 g/dL), creatinine phosphokinase at 1,539 U/L (35–230 U/L), total cholesterol at 244 mg/dL (120–200 mg/dL), and uric acid at 7.01 mg/dL (2.2–7.8 mg/dL). Her viral markers for hepatitis B and hepatitis C and several autoantibody studies such as antinuclear antibody, anti-LKM-1 antibody, and anti-smooth-muscle antibody were negative.

A chest x-ray showed cardiomegaly without pneumonic consolidation. The results of contrast-enhanced computed tomography showed no specific findings except for a fatty liver and hepatomegaly (Fig. 1). A liver scan revealed an enlarged left lobe and moderate reticuloendothelial system dysfunction, which was compatible with chronic liver disease. A wrist X-ray showed that her bone structure was typical of a

Figure 2. Echocardiography showing the septal-wall hypertrophy: (A) parasternal long-axis view and (B) four-chamber view.

Figure 3. Microscopic findings of the liver, showing swollen hepatocytes with cytoplasmic rarefaction and glycogenated nuclei (A) (H-E, $\times 100$), glycogen-stained hepatocytes with PAS staining (B) (PAS, $\times 100$), no staining of cytoplasm by diastase-PAS (C) (DPAS, $\times 100$), and portal and periportal fibrosis (D) (trichrome, $\times 100$).

20 year old. The electrocardiogram revealed concentric left ventricular hypertrophy, and the echocardiogram findings were consistent with

hypertrophic cardiomyopathy (Fig. 2).

Liver and muscle biopsies were performed after obtaining informed consent. The liver bio-

Figure 4. Microscopic findings of muscle showing normal muscle fiber and small-to-large vacuolar changes (A) (H-E, $\times 100$), glycogen accumulation in muscle fiber (B) (PAS, $\times 100$), and negative diastase-PAS staining (C) (DPAS, $\times 100$). (D) Electromicroscopy showed accumulation of glycogen in muscle fiber ($\times 20,000$).

psy revealed positive glycogen staining, negative diastase-PAS staining, and glycogenated nuclei. Cytoplasmic rarefaction and periportal and septal fibrosis were present (Fig. 3). Skeletal muscle showed small-to-large vacuolar changes in type I and II fibers, glycogen accumulation on PAS staining, negative diastase-PAS staining, and the accumulation of glycogen in muscle fiber in electromicroscopy (Fig. 4). These microscopic findings were most consistent with a diagnosis of GSD III, IV, or IX, and the clinical findings were most consistent with GSD IIIa. Additional studies performed after obtaining informed consent included the glycogen content in red blood cells (RBC) and DNA studies to confirm the diagnosis. Analysis of the glycogen content in

RBC revealed an elevated glycogen concentration (22.3%). We extracted genomic DNA from peripheral blood leukocytes using the wizard genomic DNA purification kit following the manufacturer's instructions (Promega, Madison, WI, USA). PCR fragments containing all the coding exons (33 exons) and their flanking intron-exon junctions were amplified. The samples were directly sequenced using the same PCR primers and the Big Dye Terminator Cycle Sequencing Kit in an automated sequencing system (model 3100, Applied Biosystems, Foster City, CA, USA) and the results were analyzed with the Sequencer program (Gene Codes Corporation, Ann Arbor, MI, USA).

The direct sequencing of 33 exons after analy-

Figure 5. DNA analysis of AGL gene (GeneBank accession number: NM_000028). (A) Compound heterozygous to p.Arg285X, produced by the nucleotide substitution c.853C>T on exon 6 was noted. (B) Heterozygous c.1391-1392insG mutation on exon 10 was detected.

zing the AGL gene (GeneBank accession number: NM_000028) on chromosome 1p21 revealed 2 mutations: c.853C>T (R285X) on exon 6, and c.1391-1392insG on exon 10 (Fig. 5). This result was consistent with the clinical diagnosis of GSD IIIa.

Therapy with cornstarch was started, and the patient was followed up.

Discussion

Glycogen is primarily stored in the liver and muscle, with the stored glycogen being the body's principal endogenous reservoir of immediately available energy.⁷ GSD is an autosomal recessive disorder due to abnormality of the enzymes that regulate glycogen metabolism.¹² GSD I, III, and IV account for approximately 80% of cases.³ GSD I is widely believed to be the most common among the subtypes, and GSD III is considered to be relatively rare. Moreover,

the mild clinical presentation of GSD III compared to GSD I might result in underestimation of its incidence.⁷ In Korea, there has been no previous reported confirmed case of GSD III in adult. A wide spectrum of clinical severity from only hepatomegaly to severe hypoglycemia, myopathy, and failure to thrive has been reported.⁷ If patients are not treated in infants, growth and puberty can be delayed.⁵ However, our patient had a normal stature and puberty. Fortunately, the symptoms and signs usually improve with age except for the myopathy. In addition, the liver size decreases to normal during puberty. However, some patients show hepatic fibrosis on biopsy, and some adults develop cirrhosis and associated complications.⁵

The typical histologic finding is abnormal accumulated glycogen, which is also known as limit dextrin. Deficient enzyme activity in white blood cells can be an important diagnostic clue, but measurement of the enzyme activity is not

available in Korea. Furthermore, the DNA analysis allows for diagnosis and the classification of the subtype.⁶

Several previous studies have used biochemical analysis of RBC in patients with GSD III to show that the glycogen content is high when the enzyme is inactive. The elevated glycogen in the RBC is consistent with the diagnosis of GSD III.⁸ In our case, there was 22.3% glycogen in the RBC, which is above the normal range of below 10%.

In approximately 80% of GSD III patients, deficiency of debranching enzymes affects the liver, muscle, and myocardium (in subtype IIIa), and in the other cases only the liver (subtype IIIb) is affected by abnormalities in one of two debranching enzymes (subtypes IIIc and III d).^{9,10} The skeletal muscle biopsy showed glycogen accumulation in our case, confirming the IIIa subtype. DNA studies of blood samples can provide information on the subtype, with a finding of axon 3 mutations in the IIIb subtype. Analysis of our patient's DNA showed two mutations (R285X and c.1391-1392insG). R285X has previously been detected in one patient with GSD IIIa.¹¹

Maintaining normoglycemia and normal liver function, and increasing the growth velocity requires treatment with a continuous and adequate supply of glucose, such as by administering uncooked cornstarch at 1.75 grams/kilogram body weight at 6-hour intervals.¹² Cornstarch therapy increases linear growth, decreases liver size, and decreases serum aminotransferase levels in children.¹³ A high-protein diet is important because it can be used as a substrate for gluconeogenesis, which is intact in GSD III. Therefore, supplementation with milk products and fruits is necessary to prevent

deficiencies.¹⁴

Because hepatocellular carcinoma can develop in patients affected by GSD III, usually as a late complication of advanced liver disease, annual serum α -fetoprotein determination and hepatic ultrasound examinations are needed to screen for hepatic adenomas.¹⁵ Cardiomyopathy is not a feature of GSD I, whereas cardiac involvement of GSD IIIa is not rare. Therefore, patients with muscle disease should have intermittent cardiac evaluations, including electrocardiograms and echocardiograms.⁵ Currently, there is no satisfactory treatment for the progressive myopathy.

In conclusion, GSD should be considered in patients with muscle weakness and an abnormal liver function test with hepatomegaly. When it is diagnosed, regular follow-up with monitoring for serious complications such as hepatocellular carcinoma and cardiomyopathy is essential. Future studies should investigate less-invasive diagnostic tools and effective therapies to improve the progressive myopathy.

요 약

3형 당원축적병은 당원 분해 효소의 활성도 결핍이 원인이 되는 드문 질환이다. 비정상적 당원이 간과 골격근에 축적되는 것이 특징으로 임상적으로 간 종대, 공복 시 저혈당, 고지혈증 등이 영아기에 발생하게 된다. 저자들은 드물게 성인에서 조직 검사 및 유전자 분석을 통해 진단된 3형 당원축적병 1예를 보고하고자 한다. 52세 여자 환자가 운동 시 호흡곤란과 심한 전신 쇠약감 및 간비대를 주소로 내원하였다. 심초음파 시행 후 비후성 심근병증을 진단하였으며 간 및 골격근 생검을 통해 당원축적병을 진단하였다. 임상양상과 병리 소견을 근거로 DNA 분석을 시행하였으며 결과 3a형 당원 축적병을 진단하였다. 옥수수 전분 및 고단백 식이 요법 치료 중이며 현재 경과 관찰 중인 환자이다.

결론으로 간종대 및 근 무력감과 비정상 간기능 소견을 보일 경우 반드시 당원축적병의 가능성을 염두에 두어야 하겠으며 아직 국내에서 3형 당원축적병이 보고된 경우는 없고 드물게 성인에서 진단되어 보고하고자 한다.

색인단어: 3형 당원축적병, 당원분해효소

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