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# 제Ia형 당원병 1례 (Glycogen Storage Disease 〈Von Gierke〉, Type Ia)

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## < 한 글 요 약 >

**목 적** : 제Ia형 당원병 (Type Ia Glycogen storage disease)은 Glucose-6-phosphathase 결핍으로 간, 신장, 장 (intestine)에 글리코겐이 축적되는 대사성 질환으로 상염색체 열성으로 유전되는 매우 드문 질환이다. 1929년 von Gierke에 의해 처음으로 보고된 이래, 현재 외국에서는 prenatal molecular diagnosis까지 가능하고 국내에서는 1972년 서등이 최초로 보고하였으며, 그 이후 임상양상 및 조직생검소견으로 진단된 예가 십여례 있었고, 1990년 김 등이 간조직내에 결핍된 효소를 검사하여 4례를 보고하였다. 이에 연자들은 임상소견, 간 및 신장 조직생검, 그리고 간조직내에서의 Glucose-6-phosphatase 효소의 결핍을 확인하여von Gierke disease로 확진된 1례를 경험하였기에 보고하는 바이다.

**증 례** : 환아는 18년 7개월된 남아로 출생시부터 복부 팽만을 보여 2세경 본원에 내원하여 복부초음파 및 동위원소 촬영상 간의 혈관종 진단받고, 추적 관찰없이 지내다가 13세때 신장이 135 cm으로 3 percentile 미만의 저신장을 주소로 내원하여, 혈액검사상, SGOT/PT는 51/44 IU/L로 약간 증가되어 있으며, 복부 초음파상 간종대는 지속적으로 보였으나, 그외 특이소견은 없었다. 가족성 저신장으로 진단후 2년6개월간 성장호르몬 치료받으며 외래 추적관찰중 내원 5개월전 고혈압, 단백뇨, 고지혈증 및 elevated SGOT/PT를 주소로 정밀검사위해 입원하였다. 내원당시 키는 159 cm(<3 percentile),몸무게는 54 kg(10-25 percentile)이었고 혈압은 160/110 mmHg(>95 percentile)로 고혈압 소견보였다. 금번 입원시 말초혈액검사, 전해질 검사 및 혈당은 모두 정상이었고, SGOT/PT 가 51/60 IU/L 약간 증가 되었고, 혈중 콜레스테롤치는307 mg/dL, 요산이 9.2 mg/dL로 증가된 것 외에는 특이소견 없었다. 24시간 소변검사상 단백은 1.3 gm, 크레아티닌 1028 mg, Ccr 114 ml/min/1.73m² 이였다. 복부 초음파와 CT scan상 간에 다발성 선종이 보였고, 상기 임상소견상 당원병 의심되어 신장과 간의 생검을 시행화여 간과 신장에서 모두 글리코겐의 축적을 관찰할 수 있었고, 선종부위의 생검에서도 선종으로 확인되었으며 악성변화는 없었다. 간조직을 이용한 효소검사상 Glucose-6-phosphatase에 대한 정량검사상 0.847 nM/min/mg protein으로 상당히 저하되어 있었다. 위, 소장 내시경 검사도 시행하여 조직검사까지 시행하였으나 글리코겐의 침착을 볼수 없었다. 환아는 현재 고혈압 치료제 및 Allopurionol과 식이조절하며 외래에서 추적 관찰 중이다.

**결 론** : 저자들은 임상증세, 간과 신장의 조직생검, 그리고 간 조직의 Glucose-6-phosphatase효소 검사를 시행하여 제 Ia형 당원병으로 확진된 1례를 보고하는 바이다.

## INTRODUCTION

The glycogen storage diseases primarily affect liver, heart and muscles. There are more than thirteen distinct types in this group of diseases[1,2]. Type I glycogen storage disease (GSD-I) is an autosomal recessive disorder caused by a deficiency of glucose-6-phosphatase in the liver, kidney and intestine[3]. According to that enzyme activity, there are several subtypes in GSD-I. The most common one is a disorder with deficient glucose-6-phosphatase activity (Type Ia) and other subtypes have been shown to involve defects in various cellular translocase system(Type Ib, Ic)[1-5].

Alhtough the clinical manifestations of GSD-I

including short stature, hepatomegaly and hypoglycemia, it is difficult to diagnose without liver or renal biopsy[6,7]. Clinical evidences of renal disease are seldom recognized in patients with GSD-I[8]. We are presenting renal and hepatic histopathologic findings and the results of enzyme assay of a GSD-I patient who had proteinuria.

## CASE REPORT

An 18-year-old male was admitted to our hospital beasause of proteinuria on urimalysis. He was suspected to have GSD at the age of 12 years because of the family history of short stature and hepatomegaly. However, he had not been treated specifically. When he was 2 years old, he was disgnosed as having liver hemangioma, Five months before admission, he was noted of having proteinuria and hypertension. On admission, physical examination revealed short stature (159 cm; less then 3 percentile), hepatomegaly, and high blood pressure of 160/110 mmHg. He had proteinuria (1.3 g/24 h) and hemoglobin level was 12.5 g/dL and hematocrit 39.1%. Blood urea nitrogen was 16 mg/dL, serum creatinine 0.5 mg/dL, serum uric acid 9.2 mg/dL, fasting blood glucose 114 mg/dL, total serum cholesterol 307 mg/dL, serum SGOT/PT 51/44 IU/L, and serum albumin 4.7 g/dL. abdominal ultrasonography and CT scan suggested multiple hepatic adenoma, A percutaneous renal biopsy was performed.

The biopsy specimen consisted of 19 glomeruli including two with global sclerosis(Fig.1). Remaining glomeruli appeared normal or showed minimal mesangial prominence. The glomerular basement membrane was evenly thin(Fig. 2). The Tubules, especially of proximal type, showed nuclear enlargement and emptying, suggesting of nuclear glycogenosis and cytoplasmic clearing. The Distal tubules were relatively intact on light microscopy. There was focal mild tubular atrophy associated with interstitial fibrosis(Fig. 3). The Blood vessels were unremarkable. Immunofluorescence examination revealed C3 and IgM depositions in the glomerular sclerotic areas. On electron- microscopy, there were many glycogen particles in the mesangium. Lipid droplets were seen in the tubular epithelial cells(Fig. 4).

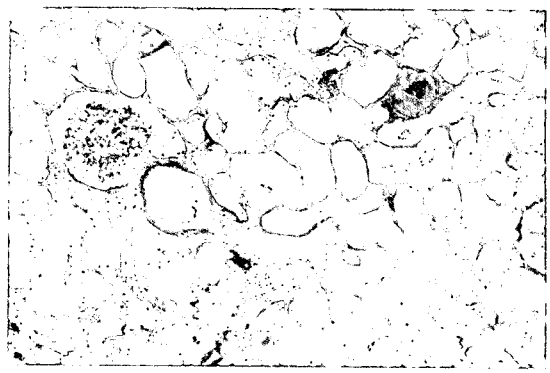

**Fig. 1.** Light microscopic fidings of kidney : The section of the core of renal cortex and medulla shows relatively preserved lobular architecture with focal global sclerosis(H-E stain X 100).

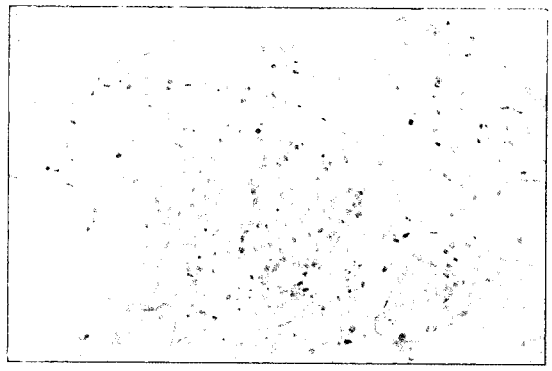

**Fig. 2.** Light microscopic fidings of kidney : Glomerulus show mesangial prominence, but cellular proliferation is not prominent Basement membrane change is not definite(H-E stain X 400).

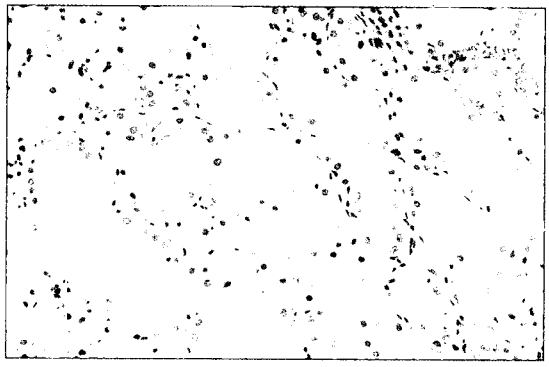

**Fig. 3.** Light microscopic fidings of kidney : Tubules, especially of proximal type, show nuclear enlargement and emptying suggestive of nuclear glycogenosis and cytoplasmic clearing. Distal tubules art relatively intact and there is focal mild tubular atrophy associated with interstitial fibrosis(H-E stain X 400).

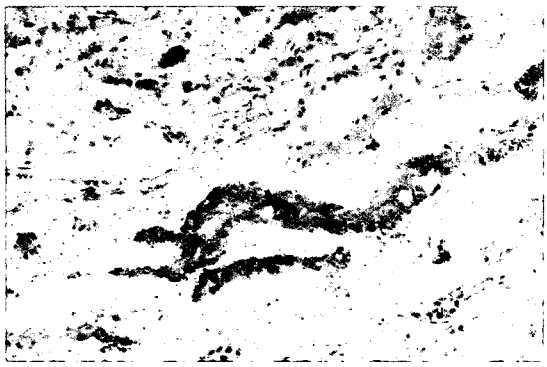

**Fig. 4.** Light microscopic fidings of kidney : Oil-red-O Stain shows infiltrated lipid droplers(Oil-red-O stain X 400).

There were no abnormalities including immune complex in the glomerular basement membrane.

The diagnosis of GSD-I was confirmed by liver biopsy and enzyme assay. The biopsy specimen consisted of 2 elongated fragment of liver tissue, measuring 0.7 cm and 2.2 cm. The hepatocytes with pale-stained cytoplasms and uniformly distended and compressed the sinusoids to form mosaic pattern. A glycogenated nucleus of extreme degree was present. The stored glycogen was demonstrated with PAS stain. In this core of the liver, there was no portal tract containing bile dust while there were many thin-walled dilated vessels. The neohepatocytes has abundant eosinophilic cytoplasms with occasional glycogenated nuclei. Macro and microvesicular fatty change 1+ was noted. Immunohistochemical staining for smooth muscle actine showed prominent thin walled dilated vessels in the adenoma(Fig. 6). On enzyme assay, glucose-6-phosphatase was 0.847 nM/min.mg protein (5.9-9.3).

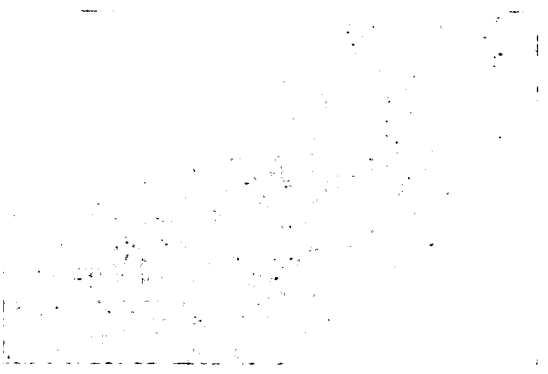

**Fig. 5.** In this core of the liver, there is no portal tract containing bile duct while there are many thin-walled dilated vessels. The neohepatocytes have abundant eosinophilic cytoplasm with occasional glycogenated nucleus. Macro and microvesicular fatty change 1+ is noted(H-E stain X 400).

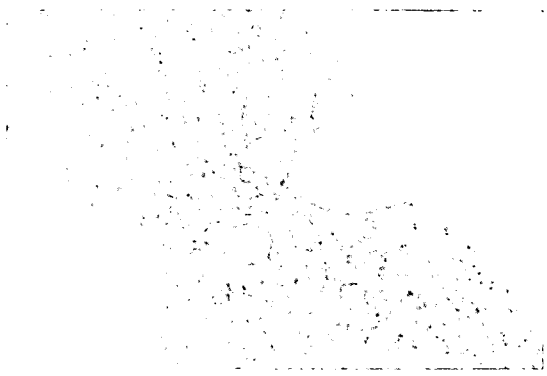

**Fig. 6.** Immunohistochemical staining for smooth muscle actine shows prominent thin-walled dilated vessels in the liver adenoma(Immunohistochemical stain X 40).

Symptomatic treatment was done using antihypertensive drugs and allopurinol. Diet control was done.

## DISCUSSION

The glycogen storage diseases involve mainly liver, heart and muscles caused by a deficiency of glucose-6-phosphatase[1-3]. Type I is the most common type in glycogen storage diseases and clinical manifestations of GSD-I include growth retardation, hepatomegaly, hypoglycemia, lactic acidemia, hyperuricemia and hyperlipidemia[1-5]. The late complications of GSD-I include gouty arthritis, osteoporosis and hepatic adenomas that may undergo malignant transformation, and chronic renal disease[1-2]. Our patients had growth retardation, hepatomegaly, hyperuricemia, hyperlipidemia and hepatic adenoma.

GSD-I can be confirmed by enzyme assay of glucose-6-phosphatase in fresh liver specimen[4,5]. Histopathological findings of liver and kidney are helpful for confirming the diagnosis[9]. In our patient has low level of glucose-6-phosphatase(0.847 nM/min.mg protient : NL 5.9-93) in enzyme assay with fresh liver specimen. Renal histology in our patient showed compatible findings of GSD. On light microscopy, There

were focal glomerulosclerosis, interstitial fibrosis, tubular atrophy and tubules, especially of proximal type, which showed nuclear enlargement and emptying, suggestive of nuclear glycogenosis and cytoplasmic clearing. On electron-microscopy, there were many glycogen particles in mesangium. Lipid droplets were seen in the tubular epithelial cells. In liver biopsy, histologic finding was also compatible for diagnosis of GSD. The hepatocytes had pale-stained cytoplasm and uniformly distended and compress the sinusoids to form msaic pattern and glycognated nucleus of extreme degree was present. The stored glycogen was demonstrated with PAS stain and the neohepatocytes had abundant eosinophilic cytoplasm with occasional glycogenated nucleus. Macro and microvesicular fatty change 1+ was also noted.

Renal involvement in GSD-I results in glycogen accumulation within the kidney due to deficient activity of glucose-6-phosphatase in proximal and distal tubules. The renal glycogen deposition in GSD-I occurs mainly in the proximal convoluted tubules[8,9]. We present nuclear enlargement and emptying, suggestive of nucler glycogenosis and cytoplasmic clearing in proximal tubular epithelium. Renal disease in patients with GSD-I begins with a glomerulosclerosis followed by chronic renal failure[10]. We are not sure whether our patient will have the course of chronic renal failure. However, hyperlipidemia and numerous lipid deposits in the glomerular mesangium and tubular epithelial cells and these may be considered to contribute progressive renal insufficiency.

Methods of effective therapy include total parenteral nutrition, nocturnal nasogastric infusion of glucose, and frequent oral administration of uncooked cornstarch. This methods improve hypoglycemia and secondary metabolic abnormalities, but most of their patients with renal dysfunction have been ineffectively treated by these current standards and is still doubtful for preventive effect on the evolution of renal disease[11-13]. Our patient treated with antihypertensive drugs and allopurinol. Diet control was done with similar method as above.

In conclusion we have presented a patient with growth retardation, hepatomegaly, hypertension and renal invovement(proteinuria) due to GSD-Ia confirmed by renal and hepatic histopathological findings and decreased glucose-6-phosphatase level by enzyme assay with fresh hepatic tissue.

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**= Abstract =**

## A Case of Glycogen Storage Disease Type Ia Confirmed by Biopsy and Enzyme Assay

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The author exprienced a case of glycogen storage disease type Ia(GSD-I) in an 18-year-old male patient who was admitted to our hospital due to proteinuria and hypertension. he was suspected to have GSD when 12 years old because of his family history of short stature and hepatomegaly. On admission, physical examination revealed short stature, heparomegaly, andThe diagnosis of GSD-I was confirmed by compatible liver biopsy finding and enzyme assay which ervealeddeficiency of glcose-6-phosphatase if hepatocyte. Sympromatic treatment was done using antihypertensive drugs and allopurinol with diet control. The authors report a case of glycogen storage disease type Ia completely confirmed by typical clinical manifestation, pathologic findings of the liver and the kidney, and the result of enzyme assay which revealed deficiency of glucose-6-phosphatase in hepatocytes with brief review fo related literatures.
**(J Korean Soc of Pediatr Nephrol 2:77-81, 1998)**

**Key Words :** Glycogen storage disease type Ia, Liver and kidney biopsy, Enzyme assay