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Lack of evident atherosclerosis despite multiple risk factors in glycogen storage disease type 1a with hyperadiponectinemia

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Abstract

We report a 60-year-old Japanese patient with glycogen storage disease type 1a (GSD1a) who was thoroughly evaluated for risk factors of atherosclerosis. As often observed in patients with GSD1a, this patient has multiple risk factors for atherosclerosis including hyperlipidemia, hypertension, glucose intolerance with insulin resistance, and chronic kidney disease. However, she lacked clinically evident atherosclerosis as generally observed in GSD1a patients. Unexpectedly, this patient had marked hyperadiponectinemia (27.6 μg/mL; reference range, 4.1-18.9 μg/mL) with increase in the ratio of high–molecular weight to total adiponectin. Although the reason for the hyperadiponectinemia was not clear, at least it seemed to protect against enhanced atherosclerogenesis otherwise promoted by a battery of risk factors. Although further studies are needed, hyperadiponectinemia in addition to hypoinsulinemia might explain at least in part the lack of evident atherosclerosis in patients with GSD1a.

1. Introduction

Glycogen storage disease type 1a (GSD1a) is caused by a deficiency in glucose-6-phosphatase, which catalyzes the terminal step in both glycogenolysis and gluconeogenesis in the liver, kidney, and small intestine [1]. Glycogen storage disease type 1a is characterized by impaired glucose production resulting in severe fasting hypoglycemia with hypoinsulinemia, accompanied by hyperuricacidemia and hyperlipidemia. Chronic kidney disease is also one of the most frequently observed complications in patients with GSD1a. In addition, these patients sometimes show glucose intolerance [2]. Based on exposure to long-standing multiple risk factors, these patients are potentially at risk for development of atherosclerosis. However, previous studies reported that such patients usually lack clinically evident atherosclerosis [3,4]. We report an adult patient with GSD1a who was thoroughly evaluated for risk factors of atherosclerosis.

2. Case report and discussion

The patient was a 60-year-old Japanese woman. From late childhood, she had been aware of recurrent episodes of fasting-related general fatigue, which disappeared after food intake. This symptom gradually worsened with advancing age. Based on repeated clinical examinations and laboratory tests, she was diagnosed with GSD1a at the age of 55 years. At that stage, she was treated with simvastatin (10 mg/d) and allopurinol (200 mg/d). She first visited our clinic at the age of 60 years. Clinical signs, such as bleeding tendency, hepatomegaly, and short stature (height, 144 cm), were consistent with GSD1a. Laboratory data showed normal leukocyte count, normocytic anemia, elevated liver enzymes, renal dysfunction, hypoglycemia with hypoinsulinemia, hyperuricacidemia, hyperlactatemia, and hyper–nonesterified fatty acidemia (Table 1). These findings were consistent with GSD1a. The diagnosis of GSD1a was not genetically confirmed because she did not agree to a DNA analysis. However, lactate and glucose level during both glucose and glucagon loading test also supported the diagnosis of GSD1a (data not shown). Arterial blood pressure at the first visit was

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Table 1
Clinical and laboratory data on admission

		Patient	Reference range
Height (m)		1.44	
Weight (kg)		42.2	
BMI (kg/m^2)		20.2	
Blood pressure (mm Hg)		146/82	
Erythrocyte count (10^{12}/L)		2.5	3.5-5.0
Hemoglobin (g/L)		84	120-150
Aspartate aminotransferase (IU/L)		199	<35
Alanine aminotransferase (IU/L)		97	<35
γ-Glutamyltransferase (IU/L)		435	<30
Lactate dehydrogenase (IU/L)		444	50-150
Alkaline phosphatase (IU/L)		780	30-120
Urea nitrogen (mmol/L)		20.7	8-18
Creatine (mmol/L)		160	30-70
Total urine protein (g/d)		1.20	<0.15
Glucose (mmol/L)		2.4	2.8-4.4
Insulin (pmol/L)		4	35-145
Lactate (mmol/L)		2.94	0.5-2.0
Pyruvate (μmol/L)		172	35-100
Uric acid (μmol/L)		570	148-321
Nonesterified fatty acid (mEq/L)		1.22	0.14-0.85
Cholesterol (mmol/L)		6.21	3.62-5.68
HDL (mmol/L)		1.03	1.16-1.78
LDL (mmol/L)		3.36	1.81-3.59
Triglycerides (mmol/L)		3.99	<1.80
2-h glucose (mmol/L)		17.4	<7.7
Lipoprotein fraction (%)			
α	HDL	26	31.5-51.5
Pre-β	VLDL	17	2.6-24.6
	Midband	28	
β	LDL	29	36.5-56.5
Intrahepatic lipid (%)		15.5	3.3 ± 0.8
Intramuscular lipid (S-fat/Cr)		2.83	1.82 ± 0.95
Glucose infusion rate (mg/[kg min])		5.12	11.48 ± 0.45
Splanchnic glucose uptake (%)		5.0	47.2 ± 8.1
Carotid IMT (mm)		Rt 0.62, Lt 0.57	<0.80
Adiponectin (μg/mL)		27.6	4.1-18.9

All blood samples were obtained after an overnight fast under the administration of 10 mg simvastatin and 200 mg allopurinol daily. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; S-fat/Cr, methylene signal intensity/creatine signal; IMT, intima-media thickness; Rt, right; Lt, left.

146/82 mm Hg. The dyslipidemia had been treated by 10 mg of simvastatin for 5 years. Serum total cholesterol level at the first visit was modestly high with high midband fraction (Table 1). Despite the presence of fasting hypoglycemia, 75-g oral glucose tolerance test revealed diabetic pattern (glucose 120 minutes, 17.5 mmol/L). As usually seen in patients with GSD1a, this patient had fatty liver. Hepatic fat content measured by ^{1}H-magnetic resonance spectroscopy [5] was 15.5% (Table 1), which is approximately 7 times higher than that of body mass index (BMI)–matched nondiabetic subjects and similar to that of obese subjects. Furthermore, intramyocellular lipid (2.83 methylene signal intensity/creatine signal [S-fat/Cr]) [5] was also approximately 1.5 times higher than that of normal subjects and similar to that of nondiabetic obese subjects and subjects with type 2 diabetes mellitus.

According to previous reports, hyper–nonesterified fatty acidemia induces excess accumulation of intracellular lipids that reduce peripheral and splanchnic glucose uptake [6]. Thus, we evaluated peripheral and splanchnic glucose uptake in this patient. Euglycemic-hyperinsulinemic clamp combined with oral glucose load is a method that measures glucose uptake by peripheral and splanchnic tissues [5]. The patient showed reduced peripheral glucose uptake (glucose infusion rate, 5.12 mg/[kg min]) that is comparable with that of patients with type 2 diabetes mellitus (glucose infusion rate of type 2 diabetes mellitus [n = 12], 5.96 ± 0.52 mg/[kg min]). The splanchnic glucose uptake of this patient was markedly impaired, even compared with that of patients with type 2 diabetes mellitus (splanchnic glucose uptake of type 2 diabetes mellitus [n = 12], 16.8 ± 6.8 mg/[kg min]) (Table 1). Theoretically, glucose production in patients with GSD1a should be markedly suppressed; however, they often show glucose intolerance. The long-standing hyper–nonesterified fatty acidemia induced by hypoinsulinemia in patients with GSD1a probably induces excess accumulation of intracellular lipids. The reduced peripheral insulin sensitivity, caused by accumulation of intramyocellular lipids [6] and reduced splanchnic glucose uptake due to accumulation of intrahepatic lipids [5], seems to play an important role in the pathophysiology of glucose intolerance in GSD1a.

Accordingly, this patient has multiple risk factors for atherosclerosis including hyperlipidemia, hypertension, glucose intolerance with insulin resistance, and chronic kidney disease. However, she did not show any symptoms related to atherosclerotic disease. In addition, the mean intima-media thickness of the carotid arteries determined by ultrasonography was normal relative to her age; and no atheromatous plaques were observed.

Whereas the BMI was 20.2 kg/m^2, the total body fat measured by dual-energy x-ray absorptiometry was high (45.7%). On the other hand, the visceral-subcutaneous fat ratio determined by computer tomography at the umbilical level was not high (0.29). Accumulation of triglyceride was mainly observed in subcutaneous adipose tissues in this patient. This might be partly because visceral adipose tissue is relatively resistant to insulin suppression of lipolysis compared with subcutaneous fat [7]. Thus, the observed pattern of fat distribution seemed to be induced by the common pathophysiology of GSD1a. Adiponectin is a well-known adipocytokine with antiatherogenic effects. Although low central fat distribution correlates with high adiponectin level [8], this patient had marked hyperadiponectinemia (27.6 μg/mL; reference range, 4.1-18.9 μg/mL). Recently, the high–molecular weight (HMW) form of adiponectin was considered to be an active form of this protein; and the HMW-total adiponectin ratio might be a potentially useful marker for cardiovascular disease [9]. Her HMW-total adiponectin ratio was

0.71. Recent data showed that the mean ± SD value in Japanese nondiabetic women was 0.59 ± 0.10 [9]; thus, her HMW-total adiponectin ratio seems to be also relatively high. Although the reason for the hyperadiponectinemia was not clear, at least it seemed to protect against enhanced atherosclerogenesis otherwise promoted by a battery of risk factors. Although further studies are needed, hyperadiponectinemia in addition to hypoinsulinemia might explain at least in part the lack of evident atherosclerosis in patients with GSD1a.

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