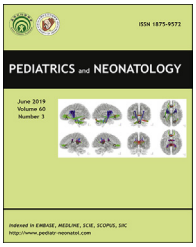
Pediatrics and Neonatology (2019) 60, 348–349

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.pediatr-neonatol.com



Letter to the Editor

Acute pancreatitis in a patient with glycogen storage disease type 1a

To the Editor,

A female child, 13 months of age, presented to our institution and was of short stature (68.2 cm;−2.5 standard deviation [SD]) and low weight (7655 g,−1.5 SD). She had hypertriglyceridemia (triglyceride (TG): 1100 mg/dL, total cholesterol (TC): 237 mg/dL) with mild hepatomegaly and did not present with hypoglycemia. We initially suspected a lipid metabolism disorder. At 19 months, the child was admitted to our institution again because of a viral infection. She had hypoglycemia (64 mg/dL), hyperlactatemia (84.7 mg/dL), hyperuricemia (13.5 mg/dL), hypertriglyceridemia (1124 mg/dL), and exacerbated hepatomegaly. The oral glucose tolerance test revealed blood sugar/lactate levels of 52/45.9, 301/34.6, 432/49.7, 217/58.5, and 116/53.6 mg/dL at 0, 30, 60, 90, and 120 min after oral glucose loading. We suspected glycogen storage disease (GSD) Ia. After discharge, she was frequently given pastries because she liked them, and her mother was pleased to see her eating. At 22 months, she presented to our institution again with abdominal pain and vomiting. Laboratory tests revealed hyperlipidemia (TG: 3791 mg/dL, TC: 505 mg/dL), increased white blood cell counts (max: 26,900/μL), high blood C-reactive protein (max: 33.2 mg/dL), and lipase (455 U/L) levels (Fig. 1A). Her abdominal computed tomography revealed a slightly irregular outline of the pancreas. She was diagnosed with acute pancreatitis and treated with fasting, infusions with 10% glucose, and medical therapy including nafamostat and famotidine. At 23 months, she was definitively diagnosed with GSD Ia by the homozygous c.648G > T mutation in the *G6PC* gene, and we advised a restricted-sugar diet, except glucose, and allopurinol and pitavastatin calcium therapy. Her hypertriglyceridemia gradually improved.

We previously published an update on the status of patients with hepatic GSD in Japan that included 65 patients with GSD Ia.[1] Patients with GSD Ia presented with hepatic disorders (97%), hepatomegaly (92%), hyperlipidemia (94%), hyperlactatemia (92%), hyperuricemia (88%), and/or hypoglycemia (69%). The frequency of patients with hyperlipidemia and without symptomatic hypoglycemia was 31% (20/65). Only one patient with GSD Ia developed acute pancreatitis. Eighty-one percent (29/36) of patients with GSD Ia had c.648G > T homozygous mutations, and 17% (6/36) were compound heterozygotes with c.648G > T mutations in the G6PC. Most Japanese patients with GSD Ia had a c.648G > T mutation. Akanuma et al.[2] reported that the c.648G > T mutation was detected in 88 of 102 mutant alleles in 51 Japanese patients with GSD Ia. Therefore, the GSD Ia with c.648G > T mutation is a mild type of GSD Ia. Frequent consumption of breast milk can contribute to the prevention of hypoglycemia symptoms in GSD Ia patients. In Japan, the onset of GSD Ia in most cases is >6 months,[1] which could be attributed to factors such as the mild type of GSD Ia with c.648G > T mutation and frequent consumption of breast milk during infancy.

The underlying mechanism for the development of pancreatitis in GSD Ia is not known. Factors such as hypoglycemia, lactic acidosis, hyperuricemia, and hyperlipidemia are known contributors to the onset of pancreatitis.[3] We considered that this patient developed acute pancreatitis because of severe hyperlipidemia, which was exacerbated by frequent consumption of pastries containing both lactose and sucrose. Galactose and fructose cannot be converted to glucose in hepatocytes of patients with GSD Ia, thereby accelerating the synthesis of both fatty and uric acids.[4] Diets that do not restrict galactose and fructose lead to deteriorated liver disease, hepatomegaly, and fatty liver. Therefore, restricting sugar, except glucose, in the diets of these patients, is important.

The effect of hyperlipidemia on acute pancreatitis is controversial.[5,6] However, a blood triglyceride level ≥1000 mg/dL is a risk factor for acute pancreatitis. We demonstrated elevated blood TG and TC levels in nine patients with GSD Ia who were followed at Kumamoto University Hospital (Fig. 1B,C). Four patients presented with reversible hypertriglyceridemia (≥1000 mg/dL), two intermittently developed hypertriglyceridemia (≥2000 mg/dL),

https://doi.org/10.1016/j.pedneo.2019.01.009

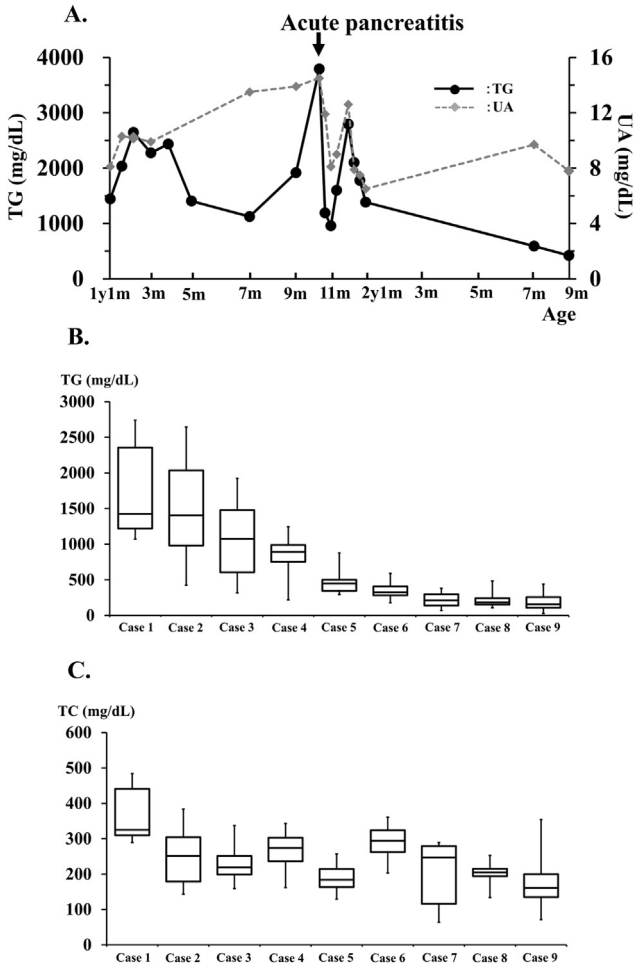


Figure 1 (A) Clinical course of developing acute pancreatitis in GSD Ia. Blood (B) TG and (C) TC levels in nine patients with GSD Ia. Blood TG and TC levels between patients with good and poor medical compliance were significantly different. Even TG levels in cases 2, 3, and 4 were controlled under 1000 mg/dL during the medication and dietary compliance period. GSD: glycogen storage disease, TG: triglyceride, TC: total cholesterol, UA: uric acid.

and none developed acute pancreatitis. Blood TG and TC levels are different in each case, and considerable differences exist in blood lipid levels during the follow-up period even in the same patient. Blood lipid levels reflect the basic pathogenic state of the liver in patients with GSD Ia. Although sustained hypoglycemia enhances lipid synthesis in the liver, and blood TG and TC levels increase, excessive intake of carbohydrates can also increase lipid synthesis in the liver.

Therefore, patients with poorly managed GSD Ia sometimes develop hypertriglyceridemia ($\geq$1000 mg/dL) and severe hypertriglyceridemia ($\geq$3000 mg/dL), which are significant risk factors for acute pancreatitis.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgements

This case report was supported in part by a grant-in-aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. We would like to thank Dr. Sawada. H (Department of Pediatrics, Miyazaki University Hospital) for help and advice in diagnosis and treatment in this case.

References

1. Kido J, Nakamura K, Matsumoto S, Mitsubuchi H, Ohura T, Shigematsu Y, et al. Current status of hepatic glycogen storage disease in Japan: clinical manifestations, treatments and long-term outcomes. *J Hum Genet* 2013;**58**:285—92.
2. Akanuma J, Nishigaki T, Fujii K, Matsubara Y, Inui K, Takahashi K, et al. Glycogen storage disease type Ia: molecular diagnosis of 51 Japanese patients and characterization of splicing mutations by analysis of ectopically transcribed mRNA from lymphoblastoid cells. *Am J Med Genet* 2000;**91**:107—12.
3. Simon P, Weiss FU, Zimmer KP, Koch HG, Lerch MM. Acute and chronic pancreatitis in patients with inborn errors of metabolism. *Pancreatology* 2001;**1**:448—56.
4. Bandsma RH, Smit GP, Kuipers F. Disturbed lipid metabolism in glycogen storage disease type 1. *Eur J Pediatr* 2002;**161**:S65—9.
5. Toskes PP. Hyperlipidemic pancreatitis. *Gastroenterol Clin North Am* 1990;**19**:783—91.
6. Fortson MR, Freedman SN, Webster 3rd PD. Clinical assessment of hyperlipidemic pancreatitis. *Am J Gastroenterol* 1995;**90**:2134—9.

Kaname Hirashima
Department of Pediatrics, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan
Department of Pediatrics, National Hospital Organization Miyakonojo Medical Center, Miyazaki, Japan

Jun Kido*
Shirou Matsumoto
Kimitoshi Nakamura
Department of Pediatrics, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

*Corresponding author. Department of Pediatrics, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Chu-ou-ku, Kumamoto City, Kumamoto, Japan. Fax: +81 096 366 3471.
E-mail address: kidojun@kuh.kumamoto-u.ac.jp (J. Kido)

Aug 8, 2018