Development of hypertriglyceridemia due to GPIHBP1 autoantibodies prior to clinical diagnosis of systemic lupus erythematosus in a 14-year-old girl.

Allergology International 71 (2022) 555–557

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Letter to the Editor

Development of hypertriglyceridemia due to GPIHBP1 autoantibodies prior to clinical diagnosis of systemic lupus erythematosus in a 14-year-old girl

Dear Editor,

Glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1) is a glycolipid-anchored protein expressed on capillary endothelial cells. It binds and transports lipoprotein lipase (LPL) to its site of action in the capillary lumen.[1] Recently, homozygous pathogenic mutations in GPIHBP1 have been reported to cause severe lifelong hypertriglyceridmia.[2] GPIHBP1 autoantibodies have been shown to cause hypertriglyceridemia by preventing the binding of GPIHBP1 to LPL and are sometimes associated with the development of autoimmune diseases such as systemic lupus erythematosus (SLE).[3] Here, we report the case of a female with hypertriglyceridemia due to GPIHBP1 autoantibodies before the diagnosis of SLE.

A 14-year-old girl presented with recurrent upper abdominal pain after eating on day X-14 months (Fig. 1, Table 1). She had been suffering from this symptom for 1 year. Physical examination revealed that she was lean (weight, 49 kg) and had a normal height (165.0 cm) with a body mass index of 18 kg/m^2. She had no other medical history, and her vital signs were normal. A physical examination revealed no eruptive xanthomas or lipemia retinalis. An abdominal CT scan showed hepatosplenomegaly and pancreatic enlargement. She had no family history of autoimmune diseases or dyslipidemia and no history of obesity, alcohol abuse, or pregnancy. The level of serum triglycerides (TGs) was 638 mg/dL after fasting and 2591 mg/dL after eating. The levels of total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were 207, 16, and 14 mg/dL, respectively. The diagnosis was that her abdominal pain was caused by acute pancreatitis. The level of double-stranded DNA (dsDNA) autoantibody was 12.9 IU/mL. Although she did not fulfill the Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) criteria (2012) for SLE,[4] she was suspected of having SLE. After administration of a low-fat diet (15–20 g/day) for several weeks, her serum TG levels (after eating) decreased to a range of 200–400 mg/dL. The patient's abdominal pain also diminished owing to her serum TG levels.

The patient was examined in detail on day X-11 months (Fig. 1, Table 1). Her plasma LPL levels before and after injection of heparin were 6.9 ng/mL and 17.3 ng/mL, respectively. However, autoantibodies against LPL were not detected. The plasma GPIHBP1 level was determined using a sandwich enzyme-linked immunosorbent assay (ELISA; #27179; IBL, Fujioka, Japan), which showed levels below the detection range. The level of autoantibody against GPIHBP1 was determined using ELISA (#27267; IBL, Fujioka, Japan), resulting in a value of 650.1 U/mL (normal range <58 U/mL). Sanger sequencing did not reveal any mutations in *LPL* or *GPIHBP1* gene. Ultimately, the patient was diagnosed with hypertriglyceridemia due to GPIHBP1 autoantibodies. We continued to monitor her carefully for approximately 1 year, and she finally fulfilled the SLICC criteria (2012).[4] On day X, she had oral ulcers, leukopenia (3000/μL), ANA positivity (1:40, speckled), dsDNA autoantibody positivity (60.1 IU/mL), low levels of complement 4 (11 mg/dL), and a positive result of direct antiglobulin (Coombs) test. Renal biopsy was performed, which showed lupus nephritis classII. Immunosuppressive therapy comprising prednisone and mycophenolate mofetil was administered on day X+2 weeks. Prednisone was started at a dose of 1.0 mg/kg/day and tapered slowly, and mycophenolate mofetil was started at a dose of 500 mg/day and increased to 1500 mg/day. The dsDNA autoantibody level decreased to within the normal range on day X+6 weeks. The GPIHBP1 autoantibody level decreased to within the normal range, accompanied by an increase in the serum GPIHBP1 level to within the normal range on day X+8 weeks. The low-fat diet was terminated on day X+10 weeks, and her TG levels after eating have been within the normal range since then. Although she continued to take immunosuppressive agents, she did not require a low-fat diet for the next few years.

Hypertriglyceridemia with GPIHBP1 autoantibodies was firstly reported in 2017, and some case reports and case series have since been published.[2,5,6] However, we first emphasize that hypertriglyceridemia with GPIHBP1 autoantibodies could occur several years before the clinical onset of autoimmune disease. To the best of our knowledge, there are two case reports of pediatric patients with hypertriglyceridemia due to GPIHBP1 autoantibodies associated with autoimmune disease.[2,5] Those two cases and our presented case reported the same clinical order of onset. In other words, especially in pediatric patients with GPIHBP1 autoantibodies, hypertriglyceridemia might be an early complication of autoimmune disease. The prevalence of dyslipidemia at the time of SLE diagnosis was reported as 36% and 63%, in adult and pediatric patients, respectively.[7] Some patients might be undiagnosed because GPIHBP1 autoantibodies are not examined routinely. If hypertriglyceridemia due to GPIHBP1 autoantibodies is found, the

Peer review under responsibility of Japanese Society of Allergology.

https://doi.org/10.1016/j.alit.2022.05.001

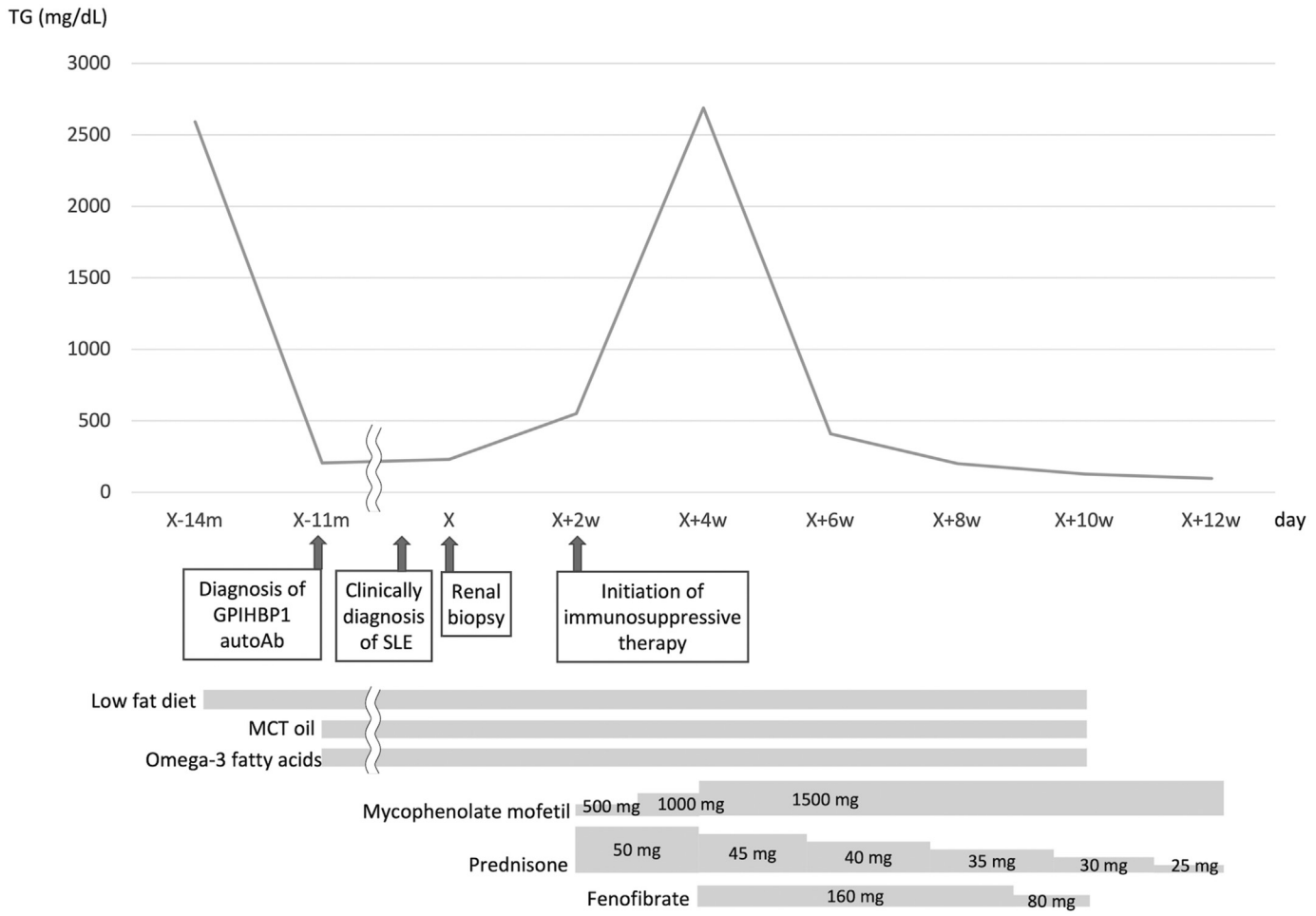

Fig 1. Triglyceride levels are plotted in time series. Clinical events and therapeutic agents are listed below. Renal biopsy was performed on day X. 180 × 135mm (300 × 300 DPI).

Table 1
Results of TG, LPL, GPIHBP1, GPIHBP1 autoantibody, dsDNA autoantibody, and C4.

	normal range	X − 14m	X − 11m	X	X + 6w	X + 8w	X + 12w
TG	90-150 (mg/dL)	2591	205	230	410	201	97
LPL	70-140 (ng/mL)	no data	6.9	6.2	10.5	32.8	29
GPIHBP1	550-1528 (pg/mL)	no data	0	0	13.7	626.8	1045.1
GPIHBP1 autoAb	<58 (U/mL)	no data	650.1	6012.7	621	38.4	24.7
dsDNA autoAb	<15 (IU/mL)	12.9	no data	60.1	11.8	8.4	6.4
C4	14-40 (mg/dL)	15.2	no data	11	12	14	18

TG, triglyceride; LPL, lipoprotein lipase; GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; autoAb, autoantibody; m, month; w, week.

patient should be monitored carefully in anticipation of the onset of autoimmune diseases.

In conclusion, we described the case of a 14-year-old girl who developed severe hypertriglyceridemia due to GPIHBP1 autoantibodies. We would like to emphasize that the patient was diagnosed with SLE 1–2 years after the onset of hypertriglyceridemia. As the patient was carefully monitored for the onset of SLE, she was diagnosed early, and immunosuppressive therapy resulted in her remission from SLE and hypertriglyceridemia.

Conflict of interest

KM is an employee of Immuno-Biological Laboratories. KNa holds stock in Immuno-Biological Laboratories. The rest of the authors have no conflict of interset.

Tomoaki Kunitsu [a,*], Mariko Harada-Shiba [b], Tomomi Sato [c], Kazuo Nonomura [a], Takao Kimura [d], Kazuya Miyashita [d,e], Katsuyuki Nakajima [d], Masami Murakami [d]

[a] *Department of Pediatrics, Saiseikai Moriyama Municipal Hospital, Japan*
[b] *Department of Molecular Innovation in Lipidology, National Cardiovascular Center Research Institute, Japan*
[c] *Department of Pediatrics, Shiga University of Medical Science, Japan*
[d] *Department of Clinical Laboratory Medicine, Gunma University Graduate School of Medicine, Japan*
[e] *Immuno-Biological Laboratories Co., Ltd., Japan*

* Corresponding author. Department of Pediatrics, Saiseikai Moriyama Municipal Hospital, 4-14-1 Moriyama, Moriyama, Shiga 524-0022, Japan.
E-mail address: kunitsutmhdk@gmail.com (T. Kunitsu).

References

1. Beigneux AP, Davies BSJ, Gin P, Weinstein MM, Farber E, Qiao X, et al. Glycosyl-phosphatidylinositol-anchored high-density lipoprotein-binding protein 1 plays a critical role in the lipolytic processing of chylomicrons. *Cell Metab* 2007;**5**:279–91.
2. Beigneux AP, Fong LG, Bensadoun A, Davies BSJ, Oberer M, Gårdsvoll H, et al. GPIHBP1 missense mutations often cause multimerization of GPIHBP1 and thereby prevent lipoprotein lipase binding. *Circ Res* 2015;**116**:624–32.
3. Beigneux AP, Miyashita K, Ploug M, Blom DJ, Ai M, Linton MF, et al. Autoantibodies against GPIHBP1 as a cause of hypertriglyceridemia. *N Engl J Med* 2017;**376**:1647–58.
4. Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012;**64**:2677–86.
5. Imai M, Yamamoto H, Hashimoto T, Koyama H, Kihara S. Acquired marked hypertriglyceridemia with anti-GPIHBP1 antibodies. *Pediatr Int* 2020;**62**:651–3.
6. Miyashita K, Lutz J, Hudgins LC, Toib D, Ashraf AP, Song W, et al. Chylomicronemia from GPIHBP1 autoantibodies. *J Lipid Res* 2020;**61**:1365–76.
7. Tyrrell PN, Beyene J, Benseler SM, Sarkissian T, Silverman ED. Predictors of lipid abnormalities in children with new-onset systemic lupus erythematosus. *J Rheumatol* 2007;**34**:2112–9.

Received 4 February 2022
Received in revised form 30 March 2022
Accepted 8 April 2022
Available online 2 June 2022