Special Report

Diagnosis and Management of Type I and Type V Hyperlipoproteinemia

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Both type I and type V hyperlipoproteinemia are characterized by severe hypertriglyceridemia due to an increase in chylomicrons. Type I hyperlipoproteinemia is caused by a decisive abnormality of the lipoprotein lipase (LPL)- apolipoprotein C-II system, whereas the cause of type V hyperlipoproteinemia is more complicated and more closely related to acquired environmental factors. Since the relationship of hypertriglyceridemia with atherosclerosis is not as clear as that of hypercholesterolemia, and since type I and V hyperlipoproteinemia are relatively rare, few guidelines for their diagnosis and treatment have been established; however, type I and V hyperlipoproteinemia are clinically important as underlying disorders of acute pancreatitis, and appropriate management is necessary to prevent or treat such complications. Against such a background, here we propose guidelines primarily concerning the diagnosis and management of type I and V hyperlipoproteinemia in Japanese.

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Background

According to Fredrickson's classification of hyperlipoproteinemia (WHO classification), type I and V hyperlipoproteinemia (hyperlipidemia) are characterized by an increase in chylomicrons alone and an

increase in very low-density lipoprotein (VLDL) in addition to chylomicrons, respectively¹⁾. Type I hyperlipoproteinemia is a clinical condition showing the severest hypertriglyceridemia and is classically represented by two rare genetic disorders, i.e., familial lipoprotein lipase (LPL) deficiency (MIM 238600) and familial apolipoprotein C-II deficiency (MIM 207750)²⁾. Even rarer conditions such as familial inhibitor of lipoprotein lipase (MIM 118830) and the presence of autoantibodies also cause type I hyperlipoproteinemia^{3, 4)}. More recently, patients with mutations in two additional genes have also been reported to manifest primary type I hyperlipoproteinemia, i.e., genes for glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1 (GPIHBP1) (MIM 612757) and for lipase maturation factor 1 (LMF1) (MIM 611761)^{5, 6)}. Since LPL is an insulin-dependent enzyme, diabetic lipemia observed in insulin-deficient conditions such as type 1 diabetes is well-known as secondary type I hyperlipoproteinemia. Therefore, type I hyperlipoproteinemia is caused by a decisive abnormality of either LPL, which is a rate-limiting enzyme involved in the hydrolysis of triglyceride (TG)-rich lipoproteins such as chylomicrons and VLDL, or apolipoprotein C-II, a cofactor necessary for the expression of LPL activity.

The cause of type V hyperlipoproteinemia is more complicated, and more miscellaneous clinical conditions are considered to belong to this category. It rarely shows familial occurrence, but its inheritance pattern is variable; therefore, type V hyperlipoproteinemia is usually considered to be triggered by acquired environmental factors in individuals with some congenital susceptibility to altered TG metabolism (genetic factors). While the involved environmental factors vary, involvement of heavy drinking, type 2 diabetes, hormonal therapy using steroids and estrogen, and drugs such as diuretics and β -blockers are frequently observed⁷⁾.

Many guidelines concerning the diagnosis and treatment of hypercholesterolemia have been formulated⁸⁾, and outstanding results of clinical intervention using lipid-lowering drugs, particularly statins, have been reported by large-scale clinical studies. On the other hand, since the relationship of hypertriglyceridemia with atherosclerosis is not as clear as that of hypercholesterolemia, and since type I and type V hyperlipoproteinemia, in particular, are relatively rare, few guidelines for their diagnosis and treatment have been established either in Japan or abroad; however, diagnostic criteria for primary hyperchylomicronemia were issued in the 1988 report by the Study Group on Primary Hyperlipidemia of the Ministry of Health

and Welfare (Group leader: Seiichiro Tarui)⁹⁾. Type I and V hyperlipoproteinemia are important as underlying disorders of acute pancreatitis, which is often lethal, and appropriate management, including restriction of fat intake, is necessary to prevent or treat such complications. Against such a background, the Study Group on Primary Hyperlipidemia of the Ministry of Health, Labour and Welfare (Group leader: Nobuhiro Yamada) proposes guidelines primarily concerning the diagnosis and management of type I and V hyperlipoproteinemia in Japanese.

Characteristics of Hyperchylomicronemia

The half-life of chylomicrons is about 5 minutes, and no chylomicron is observed in the plasma of normotriglyceridemic to moderately hypertriglyceridemic individuals after 12-hour fasting. Chylomicrons are considered to appear in fasting plasma in those with a serum TG level of about 1,000-2,000 mg/dl or above, and physical symptoms usually occur above this level ($\geq 2,000$ mg/dl); therefore, there is a strict viewpoint defining hyperchylomicronemia as a serum TG level of 2,000 mg/dl or above accompanied by characteristic complaints or findings. However, caution is necessary, because there are patients showing no clinical symptom even at a serum TG level of 20,000-30,000 mg/dl, even though they are rare. From a clinical standpoint, it must be explained to the patient that there is risk of pancreatitis when the TG level is 1,000 mg/dl or higher even on casual sampling. This may also apply to neonates whose blood sampling after a long period of fasting is usually difficult. It must also be remembered in clinical laboratory testing that a marked increase in the serum TG level often affects the measurement system, causing apparently low serum amylase, hemoglobin, and electrolyte levels (e.g., sodium appears to be reduced by about 2-4 mEq/l with every 1,000 mg/dl increase in the TG). In particular, acute pancreatitis secondary to hypertriglyceridemia must not be misdiagnosed due to apparently low serum amylase.

Type I Hyperlipoproteinemia

A) Familial Lipoprotein Lipase (LPL) Deficiency

a) Concept and Definition

LPL is an enzyme that hydrolyzes TG of lipoprotein particles in blood, and its abnormal activity underlies type I hyperlipoproteinemia in many cases and type V hyperlipoproteinemia in some. Familial LPL deficiency is a rare monogenic disorder that exhibits the severest hyperchylomicronemia. It was first docu-

mented in 1932 in a boy born to a family with a history of consanguineous marriage¹⁰), and the underlying abnormality was demonstrated to be a congenital defect of LPL activity, the rate-limiting enzyme of chylomicron hydrolysis, by Havel *et al.* in 1960¹¹). Following the classification of familial hypercholesterolemia, it has been proposed to classify this disease as a class I defect causing complete loss of LPL protein, a class II defect characterized by the production of catalytically inactive protein, and a class III defect characterized by the production of inactive protein lacking affinity to heparan sulfate¹²).

b) Etiology

The disease is caused by an abnormality of the human LPL gene, and the patients are homozygotes (including so-called compound heterozygotes) who have inherited LPL gene abnormalities from both parents in an autosomal recessive pattern with penetrance of 100%. The human LPL gene is located on the short arm of chromosome 8 (8p22), is about 35 kb in length, contains 10 exons, and codes for an enzyme protein consisting of 448 amino acids¹³⁻¹⁵).

c) Clinical Symptoms

This disease is a relatively rare autosomal recessive disorder, and more than 30 families with this condition have been reported in Japan. The frequency of the occurrence of homozygous patients is estimated to be 1 in every 500,000 to 1 million people. Many patients have a family history of consanguineous marriage, and since patients exhibit chylous serum due to hyperchylomicronemia from early childhood and abdominal pain due to pancreatitis after the intake of fat, the disease is frequently diagnosed during the suckling period or early childhood. In females, the detection of hyperchylomicronemia during pregnancy may lead to the diagnosis. Attacks of abdominal pain due to acute pancreatitis following hyperchylomicronemia are often mistaken for acute abdomen, and the patient may undergo unnecessary laparotomy. While some patients acquire a dietary habit to avoid the intake of fat and suffer growth impairment, some show no marked attack of abdominal pain until adulthood, with consequent overlooking of the disease. It is the primary disease to be differentially diagnosed in a patient with persistent abdominal pain accompanied by hypertriglyceridemia²).

Hyperchylomicronemia itself is also a major clinical finding, and the serum TG level reaches about 1,500 to even 20,000 mg/dl or more. The presence of chylomicrons can be confirmed by a simple method, i.e., the appearance of a top white cream layer in serum

after standing at 4°C for 24 hours or mild centrifugation. In typical cases, the lower layer is clear and transparent, reflecting an increase in chylomicrons alone. The possibility of LPL deficiency is high if the serum TG level is 1,500 mg/dl or higher, and the serum total cholesterol level is about 1/10 the serum TG level or lower. All other clinical findings are due to the marked increase in chylomicrons. First, eruptive xanthomas, which appear when the serum TG level increases to 2,000 mg/dl or above, are noted in about half of the patients, particularly on the extensor sides of the limbs, buttocks, and shoulders. They appear in association with changes in the serum TG level and disappear gradually over several weeks to a few months. When the serum TG level increases above 4,000 mg/dl, lipemia retinalis, in which the retinal vessels appear whitish pink due to chylous serum on funduscopy, appears, but vision is not impaired. Among other findings, hepatosplenomegaly due to the infiltration of macrophage foam cells that have phagocytosed lipids in the extravascular space, is observed, with hepatomegaly being frequent, but these changes are reversible and are rapidly improved (within 1 week) with correction of the serum lipid levels; however, the most serious complication is acute pancreatitis, and it must be managed carefully as it may be a prognostic determinant. From a clinical viewpoint, the possibility of acute pancreatitis must be explained to the patient if the TG level is 1,000 mg/dl or higher even on casual sampling. Dyspnea and neurological symptoms such as dementia, depression, and memory disorders have been reported as complications of this disorder.

As mentioned above, a major prognostic determinant of homozygous familial LPL deficiency is acute pancreatitis, which is often lethal. LPL deficiency has long been considered not to be closely related to atherosclerosis in humans, because no marked atherosclerotic lesion was noted at the autopsy of several homozygous patients with LPL deficiency who died due to acute pancreatitis. However, detailed research has reported that heterozygotes, which are considered to occur in 1 in every 500 individuals, usually show no marked abnormality in the lipid level but are likely to exhibit hypertriglyceridemia when they develop diabetes or are exposed to burdens such as severe obesity, excessive drinking, and pregnancy^{16, 17}). There have also been reports of the frequent occurrence in heterozygotes of familial combined hyperlipidemia (FCHL)¹²) and monogenic familial hypertriglyceridemia¹⁶), which are common hyperlipidemia related to atherosclerosis; however, it remains controversial whether homozygotes with LPL gene abnormality are likely to develop atherosclerosis. A Canadian group

Fig. 1. Missense and nonsense mutations in the human lipoprotein lipase (LPL) gene

Each number indicates the position of affected amino acids, with + 1 corresponding to the first amino acid of the mature human LPL protein.

† Mutations identified in Japanese patients with familial LPL deficiency.

§ Mutations or polymorphisms not necessarily underlie LPL deficiency.

that followed-up 4 patients with LPL deficiency over 14-30 years reported that coronary angiography established atherosclerotic lesions in all patients before the age of 55 years¹⁸⁾, but studies on homozygotes in Japan^{19, 20)} both reported no advanced atherosclerotic lesion in those Japanese patients.

d) Diagnosis

Since LPL is anchored by binding with heparan sulfate on the surface of capillary endothelial cells, it appears markedly in the circulation by intravenous injection of heparin; therefore, the diagnosis is usually made by measuring plasma LPL activity and/or protein level 10 minutes after intravenous injection of heparin (10-50 U/kg). LPL protein is also present in plasma before heparin injection, but is markedly reduced or undetectable in patients with LPL null mutation (class I defect). LPL accounts for about 1/3 of the total lipase activity in plasma after heparin injection, and most of the remaining lipase activity is due to hepatic triglyceride lipase (HTGL), so diagnosis of this disorder is impossible by simple measurement of the total lipase activity. Anti-LPL and anti-HTGL antibodies are necessary for the differential measurement

of LPL activities, but there is also a method to inactivate LPL using protamine sulfate or 1 M NaCl. Although this technique requires a stable synthetic substrate as well as skill and experience, measurement kits for research use are presently being marketed. Also, if either macrophages derived from peripheral blood monocytes or adipose tissue can be used as samples, differentiation from HTGL becomes unnecessary. If changes in the LPL protein level are involved, the immunological protein assay is effective and there have been a few reports on the use of ELISA in Japan²¹⁻²³⁾, which has been adopted as a general clinical laboratory test²¹⁾. If the LPL activity is markedly reduced, and if the concentration of apolipoprotein C-II, a critical cofactor of LPL, is normal or elevated, the diagnosis of this condition would be considered definite. Naturally, close inquiry into the familial history is often very helpful. While very rare cases with an LPL inhibitor or autoantibody are known, they can be eventually excluded by examining whether the patient's serum inhibits LPL activity in the serum of a normal control.

A diagnosis based on the LPL gene level is also widely practiced. To date, at least 163 gene mutations^{2, 24, 25)}, including 35 in Japan alone²⁶⁾, have been

Table 1. Mutations resulting from deletion/insertion or occurring at splice sites/promoter regions of the human lipoprotein lipase (LPL) gene

Deletion mutation	Insertion mutation	Splice site mutation
<i>small deletions</i>	<i>small deletions</i>	IVS1 ds + 1 G > C
Gln(−12) Ter (del 2bp)	ins CC in 5'UTR (+14~+15)	IVS1 as −4~−2 (del 3bp)
Thr18Ter (del 11bp)	Glu35Ter (ins A)	IVS2 ds + 1 G > A [†]
Val69Ter (del 2bp)	ins 5bp in exon 3	IVS2 as −1 G > A
Ala70Ter (del 4bp)	Lys312Ter (ins C)	IVS3 as −6 C > T ^{†§}
Lys102Ter (del 5bp)	Thr361Ter (ins A)	IVS6 as −3 C > A
Asn120Ter (del 4bp)		IVS8 ds + 2 T > C [†]
Ser172Ter (del 1bp)	<i>gross insertion</i>	
Gly209Ter (del 1bp)	ins 2kb (exon6-IVS6)	
Ala221Ter (del 1bp) [†]		Promoter region mutation
Arg243Ter (del 1bp) [†]	Insertion-deletion (Indel) mutation	T(−93)G [§]
Ser251Ter (del 2bp)	<i>small indels</i>	G(−53)C [§]
Asn291Ter (del 1bp) [†]	Ala70Ter (del 4bp + ins 2bp)	T(−39)C [§]
Leu353Ter (del 2bp)	Thr101Ter (del 1bp + ins 6bp)	
del Ser396-Pro397 (del 6bp)	Ser193Arg + Ile194Thr (del 5bp + ins 5bp)	
<i>gross deletions</i>	<i>gross indels</i>	
del 54kb (5' upstream-IVS1) [†]	del 2.3kb inc. exon2 + ins 150bp <i>Alu</i> element [†]	
del 6kb (IVS2-IVS5)		
del 2.1kb (IVS7-IVS8)		
del (exon8-exon10)		

[†]Mutations identified in Japanese patients with familial LPL deficiency

[§]Mutations or polymorphisms not necessarily underlying LPL deficiency

Abbreviations: Ter, termination of codon; del, deletion; IVS, intervening sequence; UTR, untranslated region; ins, insertion; ds, donor splice site; as, acceptor splice site

identified and reported worldwide (**Fig. 1** and **Table 1**). Mutations are reportedly identified in 97% of patients, nearly 70% of which are missense mutations involving amino acid substitutions²⁵ that are highly concentrated in exons 5 and 6 that code for the catalytic center of LPL (**Fig. 1**); therefore, these exons should be examined first in the gene-based diagnosis of unknown mutations. Many of the amino acid substitutions cause a decrease in lipophilicity of the α -helix or β -sheet region. Other known mutations include nonsense mutations, frame-shift mutations due to insertion or deletion of a few bases, gross rearrangements due to insertion or deletion of a large DNA fragment, and splicing mutations due to mutations at splice donor or acceptor sites (**Table 1**). Since decisive mutations such as those above have been identified in most patients of European ancestry, patients who develop this disorder due to changes in the LPL gene expression levels caused by abnormality of a promoter region etc. are considered to be very rare²; however, since several Japanese patients are reported to be devoid of any such decisive mutations, it seems worth investigating the other region of the LPL gene in such cases.

In Japan, at least 35 mutations have been reported. In particular, as nonsense mutations in exon 3 (Y61X) and exon 8 (W382X)²⁷ and a single-base deletion in exon 5 (A221Ter (del 1bp))²⁸ have been identified in multiple families of Japanese patients, these mutations are considered to be distributed relatively widely in the LPL gene of Japanese. On the other hand, S447X, which is considered to be a gain-of-function polymorphism, has been shown to reduce TG and increase HDL-cholesterol²⁹.

While LPL gene mutations are relatively rare, their diagnosis is considered clinically important because of the severity of the disorders they cause. Examination of a few relatively frequent mutations has already been incorporated into routine clinical laboratory tests. Also, screening for 22 known mutations can be conducted simultaneously using the LPL gene test employing the invader method reported³⁰, and similar attempts are expected to make high throughput screening possible.

e) Treatment

The most problematic complication of this dis-

order is acute pancreatitis, and treatments are carried out to prevent the occurrence or progression of pancreatitis. The basic treatment is restriction of fat intake, i.e., restricting dietary fat intake to 20 g/day or less or to 15% or less of the total energy intake, to maintain the postprandial TG level at a maximum of 1,500 mg/dl or less²⁾. Infants are given milk containing medium chain triglycerides (MCTs), which enter the circulation without being incorporated into chylomicrons, and defatted milk. MCTs can also be used for cooking. In the 2nd or 3rd trimesters of pregnancy, fat intake restriction up to 2 g/day has been reported not to affect neonates²⁾. Acute pancreatitis is treated by fasting and low-calorie infusion, and the intravenous infusion of lipid preparations or high-calorie infusion should be avoided. This disorder barely responds to anti-hyperlipidemic drugs, but the use of fibrates should be considered in adults showing an increase also in VLDL. The effectiveness of gene therapy has been demonstrated experimentally in various animal models³¹⁾.

B) Familial Apolipoprotein C-II Deficiency

a) Concept and Definition

Apolipoprotein C-II is present primarily as a component of chylomicrons, VLDL, and HDL, and it functions on the surface of TG-rich lipoproteins as a cofactor necessary for full activation of LPL; therefore, congenital defect of this molecule causes an autosomal recessive disease that manifests marked type I or type V hyperlipoproteinemia similar to familial LPL deficiency. The first case, reported in 1978, was a 58-year-old man who had repeated episodes of acute pancreatitis accompanied by hyperchylomicronemia. The condition was not alleviated by insulin therapy for complicating diabetes, and the disease was identified incidentally as it markedly responded to transfusion performed as symptomatic therapy for anemia³²⁾. Similarly to LPL deficiency, consanguineous marriage is often observed in the patient's familial history, but the prevalence of this disorder is estimated to be even lower than that of LPL deficiency, and only about 20 families with this disease have been reported worldwide since it was discovered in Canada³²⁾ and Japan³³⁾ in the 1970s.

b) Etiology

The disease is caused by abnormality of the human apolipoprotein C-II gene and occurs in homozygotes who have inherited an abnormal apolipoprotein C-II allele from both parents (including so-called compound heterozygotes). It is inherited in an autosomal recessive pattern with penetrance of 100%. The human apolipoprotein C-II gene is located on the

short arm of chromosome 19 (19q13.2), contains 4 exons, and codes for a protein with a molecular weight of 8,800, consisting of 79 amino acids^{34, 35)}.

c) Clinical Symptoms

Since all clinical symptoms are secondary to hyperchylomicronemia, they are nearly identical to those of LPL deficiency described above; however, as the activation of LPL is partially independent of apolipoprotein C-II, clinical symptoms are often slightly milder, and, consequently, the diagnosis of the disease is often made later than LPL deficiency. As the patients tend not to be subjected to strict fat restriction from early childhood, which is more common in LPL deficiency, the incidence of acute pancreatitis has been reported to be higher in adult patients^{32, 36)}, and hyperchylomicronemia is more often accompanied by a high VLDL level. In heterozygotes, apolipoprotein C-II is present in blood at about 50% of the normal level, and no abnormality is usually observed in the serum lipid levels, including TG.

d) Diagnosis

The diagnosis is based on demonstration of the selective absence of, or a marked decrease in, apolipoprotein C-II on clinically practical laboratory tests of serum apolipoproteins as well as clinical symptoms resembling those of LPL deficiency. The diagnosis is further supported by the presence of familial consanguinity. If LPL activity can be measured, reduced LPL activity in the patient's serum can be promptly recovered by the addition of normal human serum or purified apolipoprotein C-II. This phenomenon was also noted in the first reported Canadian patient, in whom hypertriglyceridemia was markedly improved (reduced from 1,750 to 196 mg/dl) immediately after transfusion for the treatment of anemia³²⁾. Another measurement method using cow's milk, which contains LPL but lacks apolipoprotein C-II, is also known.

Many families known to have this disorder have been analyzed at the gene level, and a wide variety of mutations of the apolipoprotein C-II gene have been identified, including 3 reported in Japanese patients³⁷⁻³⁹⁾. Differently from LPL deficiency, apolipoprotein C-II is completely absent in many patients with this disorder due to splicing or nonsense mutation of the apolipoprotein C-II gene, but there are rare cases in which a low level of apolipoprotein C-II with a structural defect in the activation of LPL is detectable in the blood of patients. Concerning other apolipoproteins, apolipoprotein C-III and E are increased, and A-I, A-II, and B are reduced, reflecting an increase in chylomicrons and decreases in LDL and HDL.

e) Treatment

The objective of treatment for this disorder is to prevent the occurrence or exacerbation of pancreatitis, so it is treated similarly to LPL deficiency. A major difference from LPL deficiency is that serum TG can be reduced rapidly by the transfusion of normal plasma upon emergencies such as acute pancreatitis.

C) Patients Showing Inhibitors of or Autoantibodies to LPL

Families showing inhibitors of LPL in blood have been reported, and this trait is considered to be inherited in an autosomal dominant pattern³⁾; therefore, in such patients, LPL activity is reportedly deficient only in blood and is normal in tissues.

Also, Kihara *et al.* noted symptoms resembling those of LPL deficiency in a young Japanese female with a history of ITP and Graves' disease, and reported the presence of an IgA autoantibody that reacts with both LPL and HTGL in her serum⁴⁾.

D) Patients with a Mutation in the Gene for GPIHBP1 or LMF1

GPIHBP1 is a capillary endothelial protein that provides a platform for LPL-mediated hydrolysis of chylomicrons, and LMF1 plays a critical role in the maturation of lipases including LPL. Recently, a few patients with mutations in these genes have also been reported to manifest type I hyperlipoproteinemia^{5, 6)}.

Type V Hyperlipoproteinemia

According to Fredrickson's classification (WHO classification), type V hyperlipoproteinemia is defined as hyperlipoproteinemia accompanied by an increase in VLDL as well as chylomicrons. In contrast to the fact that type I hyperlipoproteinemia is mostly categorized as a condition caused by congenital abnormality of the LPL-apolipoprotein C-II system or a secondary abnormality due to marked deficiency of insulin action, type V hyperlipoproteinemia is considered to be a category that includes a wide range of pathological conditions having both congenital (genetic) and acquired (environmental) aspects and exhibiting moderate to marked hypertriglyceridemia. Indeed, upon close investigation of the patients' families, some members have been found to be hypertriglyceridemic, while many patients are associated with secondary factors such as diabetes and drinking. Since type V hyperlipoproteinemia is much more prevalent than type I, clinically encountered hyperchylomicronemia is more often type V hyperlipoproteinemia. It is difficult to accurately estimate the prevalence of type V hyper-

lipoproteinemia in the general population, but a survey of about 40,000 people by the Lipid Research Clinic reported the frequency of individuals with a plasma TG level of 2,000 mg/dl or higher to be about 0.018%²⁾. Chylomicrons may also be observed in the blood in type III hyperlipoproteinemia due to the inhibition of chylomicron catabolism.

Although there have been only a limited number of studies in Japan, Murase *et al.* reported the results of the evaluation of 120 Japanese with a serum TG level $\geq 1,000$ mg/dl (22 type I and 98 type V patients)^{7, 40)}. A history of acute pancreatitis was observed in about 17% of these patients, demonstrating that hyperlipidemia is frequently complicated by pancreatitis also in Japanese, in whom the fat intake is lower than in Western people, and stressing the importance of its prevention and management. According to the cause of type I hyperlipoproteinemia, familial LPL deficiency was noted in 11, familial apolipoprotein C-II deficiency in 3, and secondary type I hyperlipoproteinemia such as diabetic lipemia in 8 (Table 2). Of the patients with type V hyperlipoproteinemia, the presence of underlying diseases or contributing factors such as diabetes and drinking was confirmed in about 2/3 but not in the remaining 1/3. Many of the latter patients reportedly usually show type IV hyperlipoproteinemia and have hypertriglyceridemia in the familial history.

Among congenital (genetic) abnormalities that underlie type V hyperlipoproteinemia, (1) familial combined hyperlipidemia (FCHL), which is accompanied by increased apolipoprotein B and VLDL synthesis and usually shows type IIb or IV hyperlipoproteinemia, (2) monogenic familial hypertriglyceridemia accompanied by increased TG synthesis and exhibiting type IV hyperlipoproteinemia, and (3) heterozygosity of LPL gene abnormalities or abnormal expression of the LPL gene are considered important (Fig. 2). Such genetic abnormalities are considered to be present in a few percent of the general population and usually cause type IV hyperlipoproteinemia, some of which is considered to change to type V under the influence of environmental factors. Recently, apolipoprotein A-V was shown to strengthen the interaction between apolipoprotein C-II and LPL, suggesting that familial apolipoprotein A-V deficiency causes hyperchylomicronemia⁴¹⁾. There have also been many reports that abnormalities of apolipoprotein E (E2 or E4) are involved in the pathogenesis of type V hyperlipoproteinemia⁴²⁾.

While homozygous LPL deficiency can be easily diagnosed, heterozygous LPL deficiency is difficult to detect, because its phenotype may be very mild type IV hyperlipoproteinemia alone or completely asymp-

Table 2. Classification of hyperchylomicronemia according to the cause derived from data on 120 Japanese patients with a serum TG level of 1,000 mg/dL or more

A. Hyperchylomicronemia due to abnormalities of the LPL-apolipoprotein C-II system for hydrolysis of chylomicrons		
	Number of patients	(males/females)
Primary hyperchylomicronemia		
Familial LPL deficiency	11	(4/7)
Familial apolipoprotein C-II deficiency	3	(3/0)
Secondary hyperchylomicronemia		
Diabetic lipemia	6	(4/2)
Hyperlipidemia due to acromegaly	2	(0/2)
B. Type V hyperlipoproteinemia of unknown cause or underlying disorders		
Cause unknown (idiopathic)	33	(29/4)
Underlying disorders		
Complicated by diabetes (drinking: none-light)	18	(15/3)
Heavy drinking [†]		
Non-diabetic	29	(22/7)
Diabetic	11	(11/0)
Others [§]	7	

[†]Heavy drinking: habitual drinking of 60 g/day or more of ethanol

[§]2: von Gierke disease, 1: Nelson syndrome, 1: Weber-Christian disease, 1: diabetes due to L-asparaginase, 2: suspect of an LPL inhibitor

Cited from reference no. 40) Murase T: Guidelines for the Diagnosis and Treatment of Hyperlipidemia. (Bunkodo) 2005, pp 100 (in Japanese)

Congenital (genetic) factors

1. Familial combined hyperlipidemia (FCHL)
Prevalence: 2-3%
2. Monogenic familial hypertriglyceridemia
Prevalence: 1-2 %
3. Heterozygous LPL gene abnormality [†]
Prevalence: 0.2%
4. Other genetic abnormalities (abnormalities of apolipoproteins A-IV, A-V, and E)

Acquired (environmental) factors

1. Diabetes (particularly type 2)
2. Drinking
3. Hormonal therapy (estrogen, steroids), pregnancy
4. Drugs such as diuretics, β -blockers, Zolof (SSRI-type antidepressant), isotretinoin (treatment for acne), HIV protease inhibitor, etc.
5. Underlying disorders (diabetes, dysproteinemia), multiple myeloma, SLE, malignant lymphoma, Nelson syndrome, Weber-Christian disease, etc.

Fig. 2. Etiological factors underlying primary type V hyperlipoproteinemia

[†]Reported to be present in 10% of people in Western countries, but no mutation was noted in 100 Japanese subjects with a TG level of 400-1,000 mg/dl examined by Arai *et al.*⁴⁵⁾.

Table 3. Diagnostic criteria for primary hyperchylomicronemia (draft)**Primary hyperchylomicronemia**

The presence of chylomicrons in the serum confirmed after fasting for 12 hours or longer (note) is called hyperchylomicronemia, which is classified into the following 4 types.

Usually, the possibility of this disorder is high when the serum triglyceride level exceeds 1,000 mg/dl.

Note: The presence of chylomicrons can be confirmed by the appearance of a supernatant cream layer after allowing serum to stand for 24 hours or longer at 4°C. The detection of chylomicrons by ultracentrifugation or electrophoresis (agarose or polyacrylamide gel) also contributes to the diagnosis.

1. Familial lipoprotein lipase (LPL) deficiency

- (1) The absence of LPL activity in postheparin plasma, adipose tissue, or macrophages.
- (2) Being a homozygote with a causative LPL gene mutation on both alleles.
- (3) The presence of apolipoprotein C-II.
- (4) The presence of clinical symptoms due to hyperchylomicronemia (acute pancreatitis, eruptive xanthoma, lipemia retinalis, hepatosplenomegaly).
- (5) The presence of consanguinity in the familial history.
- (6) A marked decrease in LPL protein mass measured by ELISA for LPL.

Definitively diagnosed if (1) or (2) is established, and provisionally diagnosed if (3) is concurrent with (4), (5), or (6).

2. Familial apolipoprotein C-II deficiency

- (1) The absence of plasma (serum) apolipoprotein C-II.
- (2) Being a homozygote with a causative apolipoprotein C-II gene mutation on both alleles.
- (3) The appearance of activity after the addition of apolipoprotein C-II or plasma from a normal subject.
- (4) The presence of clinical symptoms due to hyperchylomicronemia (acute pancreatitis, eruptive xanthoma, lipemia retinalis, hepatosplenomegaly).
- (5) The presence of consanguinity in the familial history.

Definitively diagnosed if (1) or (2) is established, and provisionally diagnosed if (3) is concurrent with (4) or (5).

3. Primary type V hyperlipoproteinemia

- (1) Demonstration of an increase in VLDL in addition to hyperchylomicronemia.
- (2) The absence of LPL deficiency, apolipoprotein C-II deficiency, or apolipoprotein E abnormality.

Definitively diagnosed if both (1) and (2) are fulfilled.

4. Idiopathic hyperchylomicronemia

Hyperchylomicronemia not in agreement with 1, 2, or 3 above.

For example, cases suggestive of the presence of an LPL inhibitor or autoantibody have been reported. More recently, a few cases of mutations in the gene for GPIHBP1 or LMF1 have also been reported to manifest primary hyperchylomicronemia.

tomatic. In such heterozygotes, type IV-V hyperlipoproteinemia is often triggered by pregnancy, diabetes, obesity, and excessive alcohol intake. Also, there are patients with low LPL activity in families with common hyperlipidemia such as FCHL and familial hypertriglyceridemia, and the possible involvement of LPL gene abnormalities is attracting attention as a background of these disorders. Such abnormalities include abnormal LPL gene expression. Indeed, the possibility that a single nucleotide polymorphism in the promoter region, which impairs the binding of transcription factor Oct-1 and reduces transcription activity to 15% or less, is related to FCHL and ischemic heart disease has been suggested⁴³⁾. Reports from Western countries include a study in which LPL gene ab-

normalities were observed in 10% of patients with type V hyperlipoproteinemia⁴⁴⁾, but Arai *et al.* found no LPL gene mutations in any of 100 Japanese subjects with a serum TG level of 400-1,000 mg/dl examined⁴⁵⁾.

Generally, poor control of blood glucose in diabetic patients is the most frequent acquired stressor, but drinking, estrogen, steroids, pregnancy, Zoloft (selective serotonin reuptake inhibitor type antidepressant), isotretinoin (treatment for acne), diuretics, β -blockers, HIV protease inhibitors, dysproteinemia, multiple myeloma, SLE, malignant lymphoma, etc., have also been reported. Since all clinical symptoms that accompany hypertriglyceridemia are also reversible in type V hyperlipoproteinemia, fundamental treatment involves reducing the TG level. If there are strong genetic fac-

tors such as in FCHL and homozygous familial hypertriglyceridemia, strict restriction of fat intake, such as in type I hyperlipoproteinemia, may be necessary. Since acquired environmental factors are usually present in type V hyperlipoproteinemia, they must be eliminated first. Among lipid-lowering drugs, fibrates, nicotinic acid, and strong statins are indicated, but caution against possible exacerbation of the glucose tolerance is necessary in the treatment of diabetic patients with nicotinic acid. Also, as marked weight control in obese patients may induce severe hypertriglyceridemia and acute pancreatitis associated with rebound of the body weight, this risk must be considered.

Proposal of Diagnostic Criteria for Primary Hyperchylomicronemia (Draft)

Lastly, against the background described above, provisional diagnostic criteria for primary hyperchylomicronemia are presented (Table 3). Items related to genetic diagnosis, which has become possible, and those related to clinical symptoms and familial history have been added to the diagnostic criteria proposed by the Tarui Group⁹⁾. Since no such diagnostic criteria or management guidelines have been established anywhere in the world, further discussion and rigorous evaluation are needed.

Conflict of Interest

Dr. Oikawa has received unrestricted grants from Daiichi-Sankyo Co. Ltd. Dr. Ishibashi has received unrestricted grants from Takeda Pharmaceutical Co. Ltd. and is an advisor of Kowa Pharmaceutical Co. Ltd. Dr. Arai has received unrestricted grants from Otsuka Pharmaceutical Co., Ltd., received honoraria from MSD, and is an advisor of Kowa Pharmaceutical Co. Ltd. Dr. Yamashita has received unrestricted grants from MSD, Otsuka Pharmaceutical Co., Ltd., Astellas Pharma Inc., and JT, collaborative research grants from Shionogi & Co., Ltd., Otsuka Pharmaceutical Co., Ltd., and National Institute of Biomedical Innovation, honoraria for lectures from MSD, Bayer Yakuhin, Ltd., and Kowa Pharmaceutical Co., Ltd., and is an advisory of Skylight Biotech Co. Dr. Harada-Shiba has received unrestricted grants from MSD. Dr. Eto is an advisor of MSD. The other authors declare that they have no conflict of interest.

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