Committee Report 10

Other Types of Primary Hyperlipoproteinemia (Hyperlipidemia)

Executive Summary of the Japan Atherosclerosis Society (JAS) Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases in Japan – 2012 Version

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1. Primary Hyperlipoproteinemias (Hyperlipidemias) Other Than Familial Hypercholesterolemia

There are various types of primary hyperlipoproteinemias (hyperlipidemias) other than familial hypercholesterolemia (FH). These types are clinically important and classified according to their associated pathophysiology and genetic abnormalities (**Table 1**)¹. Familial lipoprotein lipase (LPL) deficiency manifests as severe hyperchylomicronemia and may present with eruptive cutaneous xanthomas or acute pancreatitis, although it does not necessarily accompany atherosclerotic cardiovascular disease (CVD). On the other hand, familial type III hyperlipoproteinemia and familial combined hyperlipidemia (FCHL) are often associated with CVD; therefore, providing early diagnosis and treatment is mandatory. Patients suspected of having these abnormalities must be investigated for the underlying causes of disease and evaluated for lifestyle and diet improvement, drug therapy and the presence of atherosclerosis. The major clinical types of this condition are described below.

2. Familial Combined Hyperlipidemia (FCHL)

1) Genetic and Environmental Background

The basic phenotype of FCHL is type IIb hyperlipoproteinemia, although it varies from type IIa to IV depending on secondary factors, such as dietary effects. This is a genetic hyperlipoproteinemia, and the first degree relatives of affected patients may develop hyperlipoproteinemias of type IIa, IIb or IV. This condition used to be considered an autosomal dominant disease caused by a single gene mutation; however, more recently, it has been found to be associated with

enhanced hepatic apolipoprotein (apo) B-100 synthesis, decreased LPL activity, increased very-low-density lipoprotein (VLDL) secretion from the liver and the accumulation of visceral fat as factors for the development of symptoms and has been reported to be related to abnormalities of the *LPL* and *APOC-II* genes or *APOA-I/C-III/A-IV* gene cluster. However, none of these findings have been proven to be definitive. It has also been suggested that FCHL is caused by a polygenic background that tends to induce hyperlipoproteinemia due to environmental factors, such as overnutrition and a low level of physical activity. The prevalence of this disease is as high as 1/100 in the general population.

2) Clinical Manifestations

In patients with FCHL, hyperlipoproteinemia appears after puberty, and the increase in the serum LDL-cholesterol (LDL-C) levels is relatively mild compared with that observed in patients with FH. In contrast to FH, Achilles tendon thickening is not observed in patients with FCHL. The frequency of coronary artery disease (CAD) is high, although not as high as that observed in FH patients^{2, 3}. In Japan, among patients with FCHL, myocardial infarctions are observed in men ≥ 35 years of age and women ≥ 55 years of age⁴. FCHL is detected in 32% of patients ≤ 65 years of age with myocardial infarctions in Japan⁵, indicating that FCHL is the most common primary hyperlipoproteinemia in CAD patients.

3) Laboratory Findings and Diagnosis

Insulin resistance frequently develops in patients with FCHL, and the synthesis and excessive secretion of VLDL occur due to the increased input of free fatty acids to the liver. As a result, the serum apo B levels

Table 1. Classification of Primary Hyperlipoproteinemia (Hyperlipidemia) According to the Research Committee for Primary Hyperlipidemia, Research on Measures Against Intractable Diseases Established by the Japanese Ministry of Health, Labour and Welfare

Primary hyperchylomicronemia	Familial lipoprotein lipase deficiency Apolipoprotein CII deficiency Primary type V hyperlipoproteinemia Unexplained hyperchylomicronemia
Primary hypercholesterolemia	Familial hypercholesterolemia Familial combined hyperlipidemia Idiopathic hypercholesterolemia
Endogenous hypertriglyceridemia	Familial type IV hyperlipoproteinemia Idiopathic hypertriglyceridemia
Familial type III hyperlipoproteinemia	
Primary hyper-HDL cholesterolmia	

(The 1987 report of the Research Committee for Primary Hyperlipidemia, Research on Measures Against Intractable Diseases established by the Japanese Ministry of Health, Labour and Welfare (issued in March 1988). Classification and diagnostic criteria of primary hyperlipidemia (pp. 26-34, 1988).

are relatively high in affected patients, and the amount of apo B is relatively more excessive than that of LDL-C. LDL becomes small, dense LDL, which is rich in triglycerides (TGs), has a smaller particle size and is easily oxidized and likely to transform macrophages into foam cells, thereby promoting atherosclerosis.

Small, dense LDL is diagnosed using polyacrylamide gel (PAG) electrophoresis of lipoproteins. The diagnosis should be made according to the diagnostic criteria of the Research Committee for Primary Hyperlipidemia, Research on Measures against Intractable Diseases established by the Japanese Ministry of Health, Labour and Welfare (**Table 2**)^{6, 7)}. It is desirable to determine the presence of hyperlipoproteinemia of mixed phenotypes IIa, IIb and IV using a family survey. If it is difficult to conduct a family survey or the LDL particle size cannot be measured, an apo B/LDL-C ratio of >1.0 or the presence of small, dense LDL on PAG electrophoresis should be established. It is also important to rule out FH.

4) Treatment

Treatment for FCHL is similar to that for FH. Lifestyle modification and obesity management achieved via dietary and exercise therapy are most important. Patients with FCHL respond well to dietary therapy, and the effects of drugs are greater than those observed in patients with FH. With respect to drug therapy, statins, fibrates and nicotinic acid derivatives are effective. The presence or absence of CVD, such as CAD, is a prognostic factor.

3. Familial Type III Hyperlipoproteinemia

1) Cause

Familial type III hyperlipoproteinemia, a hereditary type of hyperlipoproteinemia also called broad β disease, is a disease in which remnant lipoproteins, such as intermediate-density lipoprotein (IDL), chylomicron remnants and β -VLDL (cholesterol-rich VLDL that migrates in the β position on electrophoresis), accumulate. Familial type III hyperlipoproteinemia is caused by abnormalities in apo E (apo E2/E2 or apo E deficiency). Apo E is an important apolipoprotein in the uptake of IDL and chylomicron remnants by the liver. Variants include wild-type E3 and isoforms E2 and E4. The proportion of the population with the *APOE2/E2* genotype is estimated to be approximately 0.2% in Japan, while very few individuals are diagnosed with familial type III hyperlipoproteinemia (0.01% to 0.02% of the general population).

Abnormalities in apo E result in the impaired uptake of chylomicron remnants and IDL by the liver, leading to the accumulation of these lipoproteins in the blood. However, in many cases, remarkable hyperlipoproteinemia does not occur in the presence of apo E2/E2 only, as this condition usually develops in association with other abnormalities [e.g., diabetes mellitus (DM), obesity or hypothyroidism]. The reported abnormalities of APOE include the *APOE2/E2* genotype in addition to other gene mutations, such as *APOE1*, abnormal *APOE3* and *APOE* deficiency.

2) Clinical Manifestations

Xanthoma striatum palmare and/or xanthoma

Table 2. Diagnostic Criteria for Familial Combined Hyperlipidemia According to the Research Committee for Primary Hyperlipidemia, Research on Measures Against Intractable Diseases Established by the Japanese Ministry of Health, Labour and Welfare

Criteria	(1) Familial combined hyperlipidemia is associated primarily with phenotype IIb and possibly with phenotypes IIa or IV. (2) An apoprotein B/LDL-C ratio of >1.0 or the presence of small, dense LDL (particle size <25.5 nm) should be established. (3) Secondary hyperlipidemia, such as familial hypercholesterolemia or DM, should be excluded. (4) One or more of the first-degree relatives have phenotype IIb, IIa or IV hyperlipoproteinemia and at least one of such relatives, including the patient himself/herself, has phenotype IIb or IIa.
Diagnosis	The diagnosis is confirmed if all of the above criteria ((1) to (4)) are met. However, in daily practice, a diagnosis may simply be made if criteria (1) to (3) are met.

(Cited from the 2000 report of the Research Committee for Primary Hyperlipidemia, Research on Measures Against Intractable Diseases established by the Japanese Ministry of Health, Labour and Welfare)

Table 3. Diagnostic Criteria for Familial Type III Hyperlipoproteinemia According to the Research Committee for Primary Hyperlipidemia, Research on Measures Against Intractable Diseases Established by the Japanese Ministry of Health, Labour and Welfare

Major criteria	(1) Both the serum cholesterol and serum TG levels are high. (2) Electrophoresis of plasma lipoproteins shows a continuous broad β pattern from VLDL to LDL. (3) Abnormalities in apolipoprotein E (E2/E2, E deficiency, etc.) are established by electrophoresis of apolipoproteins.
Minor criteria	(1) Xanthoma (particularly xanthoma striatum palmare) (2) An increased serum apolipoprotein E concentration (apolipoprotein E/TC ratio ≥ 0.05) (3) A VLDL-C/serum TG ratio of ≥ 0.25 (4) A decreased level of LDL-C (5) The presence of cardiovascular disease, such as arteriosclerosis obliterans or ischemic heart disease
Diagnosis	The diagnosis is confirmed if all three major criteria are met. Familial type III hyperlipoproteinemia is suspected if two of the three major criteria and at least one of the minor criteria are met.

(Cited from the 1987 report of the Research Committee for Primary Hyperlipidemia, Research on Measures Against Intractable Diseases established by the Japanese Ministry of Health, Labour and Welfare)

tuberosum may appear in patients with this disease. Patients with familial type III hyperlipoproteinemia are likely to develop premature CVD [e.g., CAD, carotid atherosclerosis, renal arteriosclerosis or peripheral arterial disease (PAD)] and may have renovascular hypertension or intermittent claudication due to PAD. The incidence of CAD in patients with familial type III hyperlipoproteinemia is high in both Japan and Western countries⁸⁾.

3) Laboratory Findings and Diagnosis

Both the serum TC and TG levels are raised in this patient population. However, the ranges of these parameters vary from slightly increased in patients with normal TC or TG levels to up to 500 mg/dL or 2,000 mg/dL, respectively. The diagnosis is made based on the diagnostic criteria of the Specific Disease Primary Hyperlipidemia Research Group of the Ministry of Health and Welfare (Table 3)^{6,7)}. For patients with both increased TC and TG levels, a lipoprotein

analysis is performed to establish the presence of phenotype III. Patient screening can be performed in daily practice using lipoprotein electrophoresis to establish the presence of a broad β pattern and an apo E/TC ratio of ≥ 0.05 . In lipoprotein analyses using ultracentrifugation or high-performance liquid chromatography (HPLC), the level of LDL-C does not increase, but instead decreases. Since the amount of cholesterol in the IDL fraction ($1.006 < d < 1.019$) dramatically increases, the presence of a high cholesterol/TG ratio (≥ 0.42) in the VLDL fraction ($d < 1.006$) should also be assessed. Next, the existence of any abnormalities in the apo E isoforms should be established according to the apo E phenotype or genotype.

4) Treatment

Dietary fat restriction is essential. Patients with familial type III hyperlipoproteinemia respond relatively well to lifestyle modification resulting from dietary and exercise therapy; thus, early diagnosis and

treatment are extremely important. Treatment of complications, such as DM, obesity or hypothyroidism, that occur in such patients is also effective for treating dyslipidemia. With respect to drug therapy, fibrates are the first-line drugs; however, nicotinic acid derivatives and statins are also effective. Early detection and treatment can prevent a poor prognosis, while conducting periodic examinations is essential for preventing the development of CAD, carotid atherosclerosis and PAD. Consultations with specialists are also desirable.

4. Other Types of Primary Hyperlipoproteinemia

Other types of primary hyperlipoproteinemia include familial LPL deficiency and familial apolipoprotein C-II deficiency. These deficiencies can take the form of remarkable hyperchylomicronemia or hypertriglyceridemia, although they usually present as type I hyperlipoproteinemia. While the relationship between marked hyperchylomicronemia and CVD is weak, caution should be exercised because hyperchylomicronemia is a frequent cause of acute pancreatitis. It is important to inhibit any increases in the levels of chylomicrons by enforcing strict fat restriction (≤ 20 g per day), and referring affected patients to specialists is recommended.

Footnotes

This is an English version of the guidelines of the Japan Atherosclerosis Society (Chapter 10) published in Japanese in June 2012.

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