Committee Report 6

Primary Hyperlipidemia

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1. Primary Hyperlipidemia and Coronary Artery Disease

Gene mutations have been identified in some types of hyperlipidemia primarily due to genetic causes but not in others. Coronary artery disease (CAD) is likely to develop in familial hypercholesterolemia (FH)^{1, 2}, familial combined hyperlipidemia^{3, 4}, and familial type III hyperlipidemia among the variations of genetically-induced hyperlipidemia⁵. **Table 1** shows diagnostic criteria for these disorders⁶⁻⁸. These variations of hyperlipidemia, particularly FH, require more stringent management.

2. Familial Hypercholesterolemia (FH)

FH is an autosomal dominant disease characterized by 3 major manifestations: marked hypercholesterolemia, tendinous xanthoma, and early-onset coronary arteriosclerosis. Although homozygous FH (homo FH) is a rare disease observed in 1 in about 1 million people, heterozygous FH (hetero FH) is much more common, affecting 1 in every 500 people. Elevation of LDL-cholesterol in FH is caused by mutations of the LDL receptor gene, and more than 40 types of mutations have been reported so far in Japan. Homozygous FH patients show a very high TC level of 500 mg/dL or above, and without treatment, are likely to develop fatal juvenile CAD. Males with heterozygous FH often develop myocardial infarction in about 30 years of age, but females with heterozygous FH rarely develop myocardial infarction before the age of 50 years². While the treatment of patients with homozygous FH should be started in the childhood (on detection), males with heterozygous FH should be going to be treated after the age of about 20 years, and females with heterozygous FH after the age of 30 years, in principle. Treatment for homozygous FH includes LDL apheresis, liver transplantation, and LDL receptor gene therapy.

However, the gene therapy and liver transplantation have not been well established, and therefore LDL apheresis is the only available treatment in the clinical practice in general. Heterozygous FH requires aggressive drug therapy, and HMG-CoA reductase inhibitors (statins) are effective. A combination of statins and anion-exchange resin (resin) is effective for the management of severe hypercholesterolemia of FH. This disease needs particularly intensive treatment among variations of primary hyperlipidemia. Also, as the disease appears by clear dominant inheritance and affects half the family members, familial management is important.

3. Familial Combined Hyperlipidemia (FCHL)

FCHL is an inherited hyperlipidemia of phenotype IIa, during the clinical course and IIb is the most frequent showing various phenotype such as IIa, IIb, or IV. The relatives of first-degree consanguinity shows also various phenotypes IIa, IIb, or IV. Diet therapy is effective in FCHL. Although Goldstein *et al.*¹ reported the disease to be inherit based on a single gene abnormality, FCHL may be induced by excessive VLDL synthesis and secretion secondary to the increased portal influx of free fatty acids due to multiple gene abnormalities or visceral fat accumulation recently. The lipoprotein abnormalities in FCHL are characterized by an excess of apoprotein B content to the LDL-C level caused by excessive VLDL synthesis and secretion due to an increased influx of free fatty acids and thus an elevation in small dense LDL, which is rich in TG with a smaller particle size and is more likely to be oxidized than ordinary LDL. Also, a multigenetic basis that facilitates the induction of hyperlipidemia by acquired factors such as hypernutrition is considered to underlie the development of such a condition.

Conventionally, the diagnostic criteria proposed by the Study Group of Primary Hyperlipidemia, a

Table 1. Diagnostic criteria of primary hyperlipidemia

1) Familial hypercholesterolemia	
Major items	(1) Shows the IIa or IIb phenotype at a serum cholesterol level of 260 mg/dL or above, in principle. (2) Tendinous xanthoma* or xanthoma tuberosum is present. *Evaluation of thickening of the Achilles tendon (maximum diameter ≥ 9 mm in the lateral view) by soft X-ray imaging or xeroradiography is useful. (3) Reduced or abnormal receptor activity is noted by LDL receptor analysis.
Minor items	(1) Xanthoma palpebratum (2) Arcus juvenalis (<50 years) (3) Juvenile (<50 years) ischemic heart disease
Diagnosis	Definitively diagnosed if 2 or more major items are noted. Tentatively diagnosed if 1 major item and 1 or more minor items are noted. Definitively diagnosed with only 1 major item if a relative of 1st-degree consanguinity has been definitively diagnosed.
2) Familial combined hyperlipidemia	
Item	(1) The phenotype is basically type IIb but may also be IIa or IV. (2) Apoprotein B/LDL cholesterol ratio >1.0 or demonstration of small dense LDL (LDL particle size <25.5 nm). (3) Familial hypercholesterolemia and secondary hyperlipidemia such as that in diabetic patients are excluded. (4) There is a relative of 1st-degree consanguinity with type IIb, IIa, or IV hyperlipidemia and at least 1 family member including the patient with type IIb or IIa hyperlipidemia.
Diagnosis	Definitively diagnosed if all of criteria (1)-(4) are fulfilled, but (1)-(3) may be used as simple diagnostic criteria in daily clinical practice.
3) Familial type III hyperlipidemia	
Major items	(1) Serum cholesterol and triglyceride levels are both high. (2) A continuous broad β pattern is observed from VLDL to LDL on electrophoresis of plasma lipoproteins. (3) An abnormality of apolipoprotein E (e.g., E2/2, E defect) is demonstrated by electrophoresis of apolipoproteins.
Minor items	(1) Xanthoma (particularly, xanthoma striatum palmare) (2) Increased serum apolipoprotein E concentration (apolipoprotein E/T-cholesterol ratio ≥ 0.05) (3) VLDL cholesterol/serum triglyceride ratio ≥ 0.25 (4) Reduced LDL cholesterol (5) Concurrence of atherosclerotic diseases such as arteriosclerosis obliterans and coronary artery disease
Diagnosis	Definitively diagnosed if all 3 major items are noted. Tentatively diagnosed if 2 major items and 1 or more minor items are noted.

1), 3): From 1986 and 1987 reports of the Study Group of Primary Hyperlipidemia, a Refractory Disease Specified by the Ministry of Health and Welfare

2): From the 2000 report of the Study Group of Primary Hyperlipidemia, a Refractory Disease Specified by the Ministry of Health, Labor and Welfare

[Partly changed according to the wording of this guideline.]

Refractory Disease Specified by the Ministry of Health and Welfare^{6, 7)} were used for the diagnosis of FCHL, and it requires detailed investigation of the family history. However, it is not so easy in primary care to investigate as the family history. Therefore, new diagnostic criteria were established by the Study Group of

Primary Hyperlipidemia, a Refractory Disease Specified by the Ministry of Health, Labor and Welfare in 2000 on the basis of a lipoprotein, i.e., apoprotein B (mg/dL)/LDL-C (mg/dL) ratio >1.0 or the appearance of small dense LDL⁸⁾.

Lifestyle modification is important for the treat-

ment of this disease, and statins and fibrates are effective among drugs.

4. Familial Type III Hyperlipidemia

This disease occurs on the basis of the apoprotein E2/2 genotype (infrequently apoprotein E deficiency) and is characterized by high-remnant lipoprotein and an early onset of CAD. Type III hyperlipidemia has been reported to be frequently complicated by CAD in Japanese⁹⁾. Since this hyperlipidemia responds well to therapy, early diagnosis and treatment are extremely important. Lifestyle modification with dietary therapy as a core and drug therapy using fibrates or nicotinic acid derivatives are effective.

References

- 1) Goldstein JL, Hobbs HH, and Brown MS: Familial hypercholesterolemia. In: *The metabolic and molecular basis of inherited disease*, ed. 7, vol. 2. ed by Scriver CR et al., pp1981-2030, McGraw-Hill, New York, 1995
- 2) Mabuchi H, Koizumi J, Shimizu M, and Takeda R: Development of coronary heart disease in familial hypercholesterolemia. *Circulation*, 1989; 79:225-232
- 3) Goldstein JL, Schrott HG, Hazzard WR, Bierman EL, and Motulsky AG: Hyperlipidemia in coronary heart disease. II. Genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder, combined hyperlipidemia. *J Clin Invest*, 1973; 52:1544-1568
- 4) de Graaf J and Stalenhoef AF: Defects of lipoprotein metabolism in familial combined hyperlipidaemia. *Curr Opin Lipidol*, 1998; 9:189-196
- 5) Mahley RW and Rall SC Jr.: Type III hyperlipoproteinemia (Dysbetalipoproteinemia): The role of apolipoprotein E in normal and abnormal lipoprotein metabolism. In: *The metabolic and molecular bases of inherited disease*, ed. 7, vol. 2. ed by Scriver CR et al., pp1953-1980, McGraw-Hill, New York, 1995
- 6) Tarui S: The research committee for primary hyperlipidemia, research on measures for intractable diseases by Ministry for Health, Labor, and Welfare in Japan, Annual report 1987
- 7) Tarui S: The research committee for primary hyperlipidemia, research on measures for intractable diseases by Ministry for Health, Labor, and Welfare in Japan, Annual report 1988
- 8) Kita T: The research committee for primary hyperlipidemia, research on measures for intractable diseases by Ministry for Health, Labor, and Welfare in Japan, Annual report 2000
- 9) Eto M, Saito M, Nakata H, Iwashima Y, Watanabe K, Ikoda A, and Kaku K: Type III hyperlipoproteinemia with apolipoprotein E2/2 genotype in Japan. *Clin Genet*, 2002; 61:416-422