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Type III Hyperlipoproteinemia: Still Worth Considering?

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ABSTRACT

Familial type III hyperlipoproteinemia (HLP) was first recognized as a distinct entity over 60 years ago. Since then, it has proven to be instructive in identifying the key role of apolipoprotein E (apoE) in removal of the remnants of very low density lipoproteins and chylomicrons produced by the action of lipoprotein lipase on these triglyceride-transporting lipoproteins. It has additionally shed light on the potent atherogenicity of the remnant lipoproteins. This review describes the history of development of our understanding of type III HLP, discusses the several genetic variants of apoE that play roles in the genesis of type III HLP, and describes the remarkable responsiveness of this fascinating disorder to lifestyle modification, especially carbohydrate restriction and calorie restriction, and, when required, the addition of pharmacotherapy.

Familial type III hyperlipoproteinemia (HLP), also called dysbetalipoproteinemia, is characterized by hyperlipidemia due to accumulation of remnants of the triglyceride (TG)-rich lipoproteins (TGRL), very low density lipoproteins (VLDL) and chylomicrons (CM), in response to dysfunctional genetic variants of apolipoprotein (apo) E or absence of apo E.

History of diagnostic approach to type III hyperlipoproteinemia

The modern era in the study of lipid transport in plasma began in the late 1940s when Gofman and colleagues began studying plasma lipoproteins with the analytical ultracentrifuge which had recently become commercially available.[1] In a 1952 report on 14 patients with xanthomatous disorders, they noted that until then although there had been 'intensive investigations of the blood lipids…little attention [had been directed to] the lipoprotein molecules which contain most of the blood lipids'.[2] That report focused on 14 patients with tuberous or planar xanthomas of the skin or tendon sheath xanthomas. Lipoproteins were characterized according to rates of flotation (S_f values; S honoring Theodore Svedberg, the inventor of the ultracentrifuge) when subjected to high centrifugal force. They recognized 2 conditions with distinct patterns of xanthomas and with distinct patterns of lipoprotein abnormalities. The first, with xanthomas arising from tendon sheaths, was associated with increased concentrations of lipoproteins S_f 6–20, subsequently found to correspond to low density lipoproteins (LDL), and was associated with an increased frequency of atherosclerotic disease. The second condition, with tuberous and planar xanthomas arising from the skin, demonstrated 'extreme increases in the concentration of S_f 10–20 and S_f 20–40 classes of

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Abbreviations and Acronyms

apo = apolipoprotein

CHD = coronary heart disease

CM = chylomicron

FCH = familial combined hyperlipidemia

HDL-C = high-density lipoprotein cholesterol

HLP = hyperlipoproteinemia

HSPG = heparan sulfate proteoglycan

LDL = low-density lipoprotein

LDL-C = low-density lipoprotein cholesterol

LDLR = low-density lipoprotein receptor

LPL = lipoprotein lipase

LRP = low-density lipoprotein receptor like protein

PAD = peripheral arterial disease

T2DM = type 2 diabetes mellitus

TG = triglyceride

TGRL = triglyceride rich lipoprotein

VLDL = very low density lipoprotein

lipoproteins', subsequently found to correspond primarily to remnants of TGRL. These patients evidenced a very high prevalence of atherosclerotic disease.

In 1967, Fredrickson, Levy, and Lees presented a phenotyping system for hyperlipoproteinemias.[3] They gave the appellation type III HLP to patients evidencing mixed hypercholesterolemia and hypertriglyceridemia who had VLDL with beta electrophoretic mobility (as compared to normal VLDL with pre-beta mobility). They recognized this disorder as probably identical to xanthoma tuberosum described by Gofman and colleagues over a decade earlier, and the identity of these 2 conditions was confirmed shortly thereafter.[4]

In 1972, having previously noted that CMs from patients with type III HLP were cholesterol-rich,[5] Hazzard et al. observed an increased ratio of cholesterol/triglyceride in the VLDL of patients with type III HLP.[6] They proposed this as an improved diagnostic criterion for this condition although the metabolic basis for the cholesterol enrichment of VLDL was not defined. Concurrently, it was becoming apparent that an accumulation of remnants formed from VLDL and CMs by lipoprotein lipase (LPL)-mediated hydrolysis of TG was the cause of the relative cholesterol enrichment of TGRL.[7]

Shortly afterwards, Havel and Kane noted a predominance of apoE in the TGRL of patients with type III HLP,[8] and then Utermann reported that patients with type III HLP exhibited a genetic variant of apoE.[9] The nature of this variant (homozygosity for the ε2 variant of the APOE gene, which encodes apoE2) was made clear by Zannis and Breslow.[10] Three common variants of apoE can be discerned according to their isoelectric points; they are termed apoE2, apoE3, and apoE4. The normal variant is apoE3; while homozygosity for apoE2 is found in >90% of patients with type III HLP, apoE4 is associated with Alzheimer's disease. The underlying basis for the classic ε2 variant of APOE was determined by Mahley and coworkers to be a single base substitution resulting in the amino acid substitution of cysteine for arginine at residue 158.[11] However, it soon became apparent that a small minority of patients with type III HLP had other variants of APOE or produced no apoE at all. All variants of apoE associated with type III HLP share one crucial characteristic: they interact poorly with the LDL receptor.[12,13]

Thus, a contemporary definition of type III HLP is hyperlipidemia due to accumulation of remnants of TGRL in response to dysfunctional genetic variants of apolipoprotein E or absence of apolipoprotein E. Unfortunately, identification of an accumulation of remnant lipoproteins has generally involved chemical analysis of VLDL after it has been isolated by preparative ultracentrifugation, a labor-intensive procedure not generally available in clinical laboratories. Therefore, efforts have been made to infer remnant lipoprotein accumulation from measurements on whole plasma or serum. Sniderman and colleagues devised the best such procedure, which requires measurement of the concentrations of apoB, cholesterol and TG in a fasting sample of plasma or serum.[14] A diagnosis of type III HLP is made when plasma TG > 160 mg/dL and the ratios of total cholesterol (mM/L)/apoB (g/L) ≥ 6.2 and TG (mM/L)/apoB (g/L) < 10. These ratios convert to the following when cholesterol, TG, and apoB are expressed as mg/dL: total cholesterol/apoB ≥2.4, and TG/apoB <8.85. These criteria were highly sensitive and specific in the population from which they were derived: 1771 consecutive patients in a tertiary lipid clinic including 38 patients with type III HLP. When applied to a different population of 3695 consecutive individuals and compared with an ultracentrifugation-based diagnostic procedure, the method of Sniderman appeared to lack specificity (16 cases identified by ultracentrifugation [prevalence 0.4%] compared with 53 cases identified by the method of Sniderman [prevalence 1.4%]). Concordance improved considerably if the method of Sniderman was modified to require TG > 200 mg/dL rather than 160 mg/dL, yielding 93% sensitivity and 99.5% specificity compared to ultracentrifugation.[15]

Other readily available measurements may provide hints to consider type III HLP in the differential diagnosis, but are not themselves diagnostic. These include the presence of mixed hyperlipidemia with roughly similar elevations of cholesterol and TG, or mixed hyperlipidemia with TG elevated out of proportion to cholesterol. Additionally, a discrepancy between the LDL-cholesterol (LDL-C) level calculated by the Friedewald equation and a lower LDL-C measured by a homogeneous assay (so-called "direct" LDL-C) should suggest the possibility of type III HLP.[16]

Pathophysiology of type III hyperlipoproteinemia

ApoE is the recognition site for receptors involved in the clearance of remnants of VLDL and chylomicrons. These remnants are formed by hydrolysis of much of the TG and phospholipid of VLDL and chylomicrons and the associated transfer of C apoproteins to HDL. The changes in lipid content of TGRL and the reduction of C apoproteins occurring in the course of remnant formation cause a conformational change in apoE allowing its receptor recognition domain to be recognized by the LDL receptor (LDLR), by the low affinity high capacity heparan sulfate proteoglycans (HSPG) receptors responsible for clearing these remnants and by the LDLR like