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Familial Dysbetalipoproteinemia, Diagnosis and Management: A Short Review

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Abstract

Papers on the familial lipid disorder, dysbetalipoproteinemia (FD), appeared in early seventies of the last century describing the combined elevation in total cholesterol (TC) and triglycerides (TG) in the blood of affected individuals, which is associated with mutations in the apo-lipoprotein E (Apo E) gene. Different methods and measurements for diagnosis and consequent treatment of these cases had been suggested. Stress was put on the E2/E2 homozygotes, Apo B and non-high density lipoprotein cholesterol as the main obvious manifestations of the disease, with a big variation in the results among different workers. This short review will present most of these variations in nature, diagnosis and management of FD, with a reference to a recent Iraqi work on this subject.

Keywords Dysbetalipoproteinemia, mixed hyperlipidemia, Apo E, Apo B, non-HDL cholesterol, lipid lowering drugs

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List of abbreviations: CVD = Cardiovascular disease, FD = Familial dysbetalipoproteinemia, HDL-c = High density lipoprotein cholesterol, LDL-c = Low density lipoprotein cholesterol, T2DM = Type 2 diabetes mellitus, TC = Total cholesterol, TG = Triglycerides

Introduction

Different names were given to type III hyperlipidemia. Familial dysbetalipoproteinemia (FD) is among them [1-3]. It is the most common type of primary hyperlipidemia, with the presence of a controversy about its definition or methods of diagnosis [2].

The important feature of this lipid disorder is the rise in serum apoprotein B (Apo B), which results in different patterns of lipid profile in the sera of affected subjects [2]; most common is the high rise in total cholesterol (TC), with or without triglycerides (TG). The concentrations of both may be as high as 600 mg/dL. Very low-density lipoprotein ratio to triglyceride (VLDL-c/TG) was reported to be high, while low density lipoprotein cholesterol (LDL-c) was low. Xanthomas were found to associate most FD cases [4,5].

Chylomicron remnants clearance is done through binding to hepatic lipoprotein receptors, which is mediated by apolipoprotein E (apo E). At the apo E gene locus, there are three common alleles: E2, E3, and E4 [6]. Genetic studies showed that FD was associated with a mutation in Apoprotein- E (Apo-E) gene. The apo-E2 decreases the ability of the encoded protein to convert VLDL and its remnants, intermediate density lipoprotein (IDL), to LDL particles in the blood. This results in a reduction in the chylomicron remnants clearance [2], and leads to the appearance of remnants, which are rich in cholesterol. Accumulation of these remnants in the blood

has been considered to be one of the causes of premature coronary heart disease [5]. It was reported that only 5% or less of the homozygous carriers of apolipoprotein E2 develop the FD [7].

The main three variants of Apo E gene, E2, E3, and E4, have resulted into 3 homozygotes (E2/E2, E3/E3, and E4/E4) and three heterozygotes (E2/E3, E3/E4, E4/E2). The rise in both TG and TC were found in either the homozygous E2/E2 or the heterozygous E3/E2 genotypes [8-10]. Bennet et al. in 2007 found a linear relationship of apo E genotypes with both LDL-c levels and risk of coronary disease, E3/E3 being the most potent [11]. However, others considered the E2/E2 to be the most common [12].

A study on DNA of 367 hyperlipidemic people showed that FD causes significantly higher levels of TC, TG, LDL-c and non-HDL-c with low HDL-c as compared to the control group [7].

The controversy in the FD might be attributed to other genetic or environmental factors, which has stimulated the research for the disease in different fields of medical diagnosis and management, including epidemiology, genetics, pathophysiology, therapeutics, and cardiovascular risk management [2].

The incidence of premature coronary artery disease risk among FD was found to show a 10-fold increase from the normal control subjects [13]. The reported complications included peripheral vascular disease, obesity, coronary artery disease and insulin resistance [14]. A group of workers reported coronary heart disease (CHD) incidence to be 27.8% among their hyperlipemic patients [7].

Hypercholesterolemia is also, a genetic disorder in which, there is a defect in LDL receptors, which leads to increased LDL in blood. Most reports showed an increase in LDL-c in patients with FD (7.11) The discrepancy in the results of LDL-c could was claimed to come from different methods used in the estimation of this lipoprotein [12].

A recent cross sectional genetic study on two groups of Iraqi patients included 50 patients with type 2 diabetes mellitus (T2DM), 26 patients with cardiovascular disease (CVD) and 73 apparently healthy controls showed that the most common genotype of Apo E was E3E3 representing 76% and 69.23% of patients with diabetes and CVD, respectively, and that the genotype E3E4 was more common among T2DM patients (10%) than controls (1.34%), while the frequency of E2E3 and E3E4 genotypes (15.38% for each) was higher in CVD patients than controls (6.85% and 1.34%, respectively) and concluded that Apo-E polymorphism (rs429358 and rs7412) act as risk factors for T2DM and CVD may be through interfering with lipid profile [15], while another genetic study on normal Iraqi Kurdish people revealed other patterns of frequencies [16].

Diagnostic methods

Early work on dysbetalipoproteinemia revealed that the ratio of TC/Apo B, and of apo B/Apo E, or Apo B/TC had good diagnostic sensitivity and specificity [12,17,18]. A recent article added non-HDL-c/Apo B and TG/Apo B ratios with APO E genotype to improve the rate of FD detection among the population [19].

Nakajima and his colleague in 1994, found that remnant like particle (RLP) cholesterol assay was a good screening test for FD when combined with the assays of serum TG level and genetic Apo E isoform analysis [20]. However, a new assay appeared to detect RLP by using a specific cholesterol esterase with a polyoxyethelene styrenated phenyl ether derivative as a surfactant [21].

Thereafter, other criteria were used as: the ratio of VLDL cholesterol to plasma TG of more than 0.3 on gel electrophoresis [10], TG/Apo B ratio [22], Or TC/TG molar ratio of about 2:1 [12]. Recently the ratio of non-HDL-c/Apo B has been suggested as a better detector of FD [23]. Comparison between different formulae was made to find the best for the diagnosis of FD [23]. However, in general, Apo B measurement (Apo B 100 is the atherogenic type), or its ratio to non-HDL-c have been considered of importance in the evaluation of FD cases [5,24].

Apo A1 and Apo AII ratio to HDL-c has also been found of value in this respect [25].

The Sniderman algorithm, is based on a combination of apo B quantitation and apo E genetic study. The results were originally obtained from a cohort study on 1,771 fasting subjects. By using a combination of many variables, the formula emerged which described the following criteria for detection of FD: Apo B <120 mg/ dl, TG >133 mg/dl, TG/Apo B <8.8, and TC/Apo B >2.4. Apo B was expressed in mg/dL [26].

However, different methods and techniques used for estimating serum lipid parameters gave different results for evaluation of the best way for diagnosis of FD [12].

Management

Despite its high atherogenicity, FD was found to respond well to lifestyle changes and lipid-lowering drugs [3,5,12]. Life style changes involve reduction in the intake of and/or carbohydrates [27], or even replacing low glycemic index carbohydrates for high glycemic carbohydrates will reduce TG substantially [28].

Low carbohydrate intake is essential to counteract insulin resistance which associates FD [29,30]. Statins have been recommended by many reports for management of FD although some precautions were noted on their use [7, 29,31,32]. Moreover, niacin, fibrates, and omega-3 fatty acids were thought to be effective therapies for additional triglyceride reduction [32].

At last, it could be concluded that the lipid disorder, FD, needs phenotyping and genetic testing for better management of the disease and normalizing Apo B, and non-HDL-c level by changing life style and lipid lowering drugs.

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