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Review Article

Autosomal dominant familial dysbetalipoproteinemia: A pathophysiological framework and practical approach to diagnosis and therapy

Charlotte Koopal, MD, A. David Marais, MD, Jan Westerink, MD PhD, Frank L. J. Visseren, MD PhD*

Department of Vascular Medicine, University Medical Center Utrecht, Utrecht, The Netherlands (Drs Koopal and Westerink); and Department of Chemical Pathology, University of Cape Town Health Science Faculty, Cape Town, South Africa (Drs Marais and Visseren)

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Abstract: Familial dysbetalipoproteinemia (FD) is a genetic disorder of lipoprotein metabolism associated with an increased risk for premature cardiovascular disease. In about 10% of the cases, FD is caused by autosomal dominant mutations in the apolipoprotein E gene (*APOE*). This review article provides a pathophysiological framework for autosomal dominant FD (ADFD) and discusses diagnostic challenges and therapeutic options. The clinical presentation and diagnostic work-up of ADFD are illustrated by two cases: a male with premature coronary artery disease and a p.K164Q mutation in *APOE* and a female with mixed hyperlipidemia and a p.R154H mutation in *APOE*. ADFD is characterized by a fasting and postprandial mixed hyperlipidemia due to increased remnants. Remnants are hepatically cleared by the low-density lipoprotein receptor and the heparan sulfate proteoglycan receptor (HSPG-R). Development of FD is associated with secondary factors like insulin resistance that lead to HSPG-R degradation through sulfatase 2 activation. Diagnostic challenges in ADFD are related to the clinical presentation; lipid phenotype; dominant inheritance pattern; genotyping; and possible misdiagnosis as familial hypercholesterolemia. FD patients respond well to lifestyle changes and to combination therapy with statins and fibrates. To conclude, diagnosing ADFD is important to adequately treat patients and their family members. In patients presenting with mixed hyperlipidemia, (autosomal dominant) FD should be considered as part of the diagnostic work up.

Introduction

Familial dysbetalipoproteinemia (FD) is a genetic lipid disorder characterized by a combination of a lipoprotein phenotype and a genotype that consists of mutations in the apolipoprotein E gene (*APOE*). The lipid phenotype is characterized by increased triglyceride-rich lipoprotein

* Corresponding author. Department of Vascular Medicine, University Medical Center Utrecht, PO Box 85500 3508 GA, Utrecht, The Netherlands.
E-mail address: F.L.J.Visseren@umcutrecht.nl
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(TRL) remnants,[1] that lead to increased plasma levels of total cholesterol and triglycerides (mixed hyperlipidemia). Owing to the use of different definitions for FD, prevalences vary from 1:10.000 to 1:150 in the general population.[2] FD is associated with premature cardiovascular disease (CVD).[3–6] A case control study showed that patients with FD had a 10-fold increased risk for premature coronary artery disease compared to population-based controls.[5] The most common types of CVD in patients with FD are peripheral artery disease (PAD) and coronary artery disease (CAD). A cross-sectional study in 305 European known FD patients showed a CAD prevalence of 19%; a PAD prevalence of 11%; and a cerebrovascular disease prevalence of 4%.[7] A study in 105 FD patients from South Africa showed a prevalence of ischemic heart disease of 45% and a PAD prevalence of 19%.[8] A third study with 113 Dutch FD patients showed a vascular disease prevalence of 41%.[4]

TRL comprise very low-density lipoproteins (VLDL), chylomicrons (CM), and their remnants. The *APOE* gene codes for the apolipoprotein E protein (apoE) that is present on TRL where it acts as ligand for hepatic receptors. The *APOE* gene locus has three main variants, namely ε2, ε3, and ε4, which results in three homozygous (ε2ε2, ε3ε3, and ε4ε4) and three heterozygous (ε2ε3, ε3ε4, and ε4ε2) genotypes. The ε3ε3 form is considered wildtype, as it is the most frequent *APOE* genotype in humans.[9] The ε2 allele is associated with high triglycerides and reduced low-density lipoprotein cholesterol (LDL-C). This is most pronounced in ε2ε2.[9] The low levels of LDL-C are mainly caused by decreased conversion of VLDL to LDL.[10] Approximately 15% of subjects with an ε2ε2 genotype develop FD.[10] The development of FD is associated with secondary risk factors such as obesity and insulin resistance.[11] Carriers of only one ε2 allele generally do not develop a lipid disorder, making FD a recessive disease. However, about 10% of the patients with FD have a mutation in *APOE* with a dominant or codominant inheritance pattern.[12] Diagnosing autosomal dominant FD (ADFD) is important for several reasons. First, in general, ADFD patients have the same atherogenic lipid profile as recessive FD (high levels of TRL remnants), and therefore, they are probably exposed to the same increased risk of atherosclerosis and CVD. Second, there are specific lipid treatment targets and lipid-lowering treatments for FD that will be discussed in greater detail later in this article. Third, diagnosing ADFD will have consequences for family members due to the dominant inheritance of the disease.

These and other issues concerning diagnosis and treatment of ADFD will be addressed in this article, which is illustrated by two cases with ADFD. Furthermore, we provide a pathophysiological framework by briefly summarizing remnant metabolism and by giving a description of the possible role of heparan sulfate proteoglycan receptors (HSPG-R) in the pathophysiology of FD.

Cases

The first index patient was a 58-year-old male Flemish immigrant to South Africa who was found to have hypercholesterolemia on a screening test, shortly before being diagnosed with CAD and undergoing coronary artery bypass graft (CABG) surgery. At 35 years, he presented with severe angina pectoris and ischemic changes on an electrocardiogram. He had a diet with moderate fat intake, was a nonsmoker, and consumed little alcohol. His mother also had premature CAD and hypercholesterolemia. On physical examination, there were no stigmata of dyslipidemia such as eruptive or palmar xanthoma, although he did mention that his mother had striking yellow palmar creases. His body mass index (BMI) was 28 kg/m^2. The lipid investigations revealed a fasting triglyceride (TG) concentration of 3.6 mmol/L and a total cholesterol (TC) concentration of 9.3 mmol/L. The lipoprotein (a) concentration was 17 mg/L. Agarose gel electrophoresis revealed a broad beta band characteristic of FD. Analysis of the extracted DNA by PCR revealed an *APO* ε3/ε4 genotype by restriction enzymatic digests. Sequencing of *APOE* identified substitution of glutamine for lysine at amino acid 146 of the mature protein (p.K146Q or p.K164Q when including the 18 amino acid peptide). The patient responded to gemfibrozil 300 mg twice a day with a fasting TG of 3.5 mmol/L, TC of 5.2 mmol/L, and high-density lipoprotein cholesterol (HDL-C) of 1.0 mmol/L. He had a repeat CABG at age 68 years and was well at 80 years. At the time of presentation, both children (daughters) carried the mutation and were healthy, premenopausal, and normolipidemic. However, the polyacrylamide gradient gel electrophoresis (PGGE) of a recent sample from the elder daughter, now postmenopausal, had staining in the VLDL and IDL regions typical for FD.

The second index patient was a 63-year-old woman from Thailand, who lived in the Netherlands and presented with hyperlipidemia. She had a history of autoimmune hyperthyroidism and Behçet's disease with retinal vasculitis. She had the metabolic syndrome but no hypertension, type 2 diabetes mellitus (T2DM), or vascular disease. She had no history of eruptive xanthomas and did not use lipid-lowering medication. Her father died at age 62 years from a heart attack. She had two brothers who suffered a myocardial infarction around the age of 60 years. Her BMI was 24 kg/m^2 and her waist circumference 88 cm. Her TC was 8.9 mmol/L, LDL-C 5.6 mmol/L (calculated with the Friedewald formula, which is not valid in FD), HDL-C 2.32 mmol/L, and TG 2.3 mmol/L. Her apolipoprotein B (apoB)/TC ratio was 0.13 g/mmol.[13] Routine *APOE* genotyping revealed an abnormal band pattern. A full *APOE* gene sequence revealed a substitution of arginine by histamine at amino acid 136 (p.R154H). In two of her three children, a son and a daughter, the same mutation was found. Both children carrying the mutation had an apoB/TC ratio $<$0.15 g/mmol, metabolic syndrome and their lipid profiles suggested FD based on the diagnostic algorithm of apoB