Journal of Clinical Lipidology (2015) 9, 396–399

Journal of Clinical Lipidology

Myocardial infarction in a 36-year-old man with combined ABCA1 and APOA-1 deficiency

Julian C. van Capelleveen, MD, Ruud S. Kootte, MD, G. Kees Hovingh, MD, PhD, Andrea E. Bochem, MD, PhD*

Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands

KEYWORDS:
HDL cholesterol;
Reverse cholesterol transport;
Genetics;
ABCA1;
APOA1

Abstract: In this report, we present a patient who suffered from a myocardial infarction at an extremely young age. The only remarkable finding in the risk factor workup was a near undetectable high-density lipoprotein (HDL)-cholesterol plasma level (0.09 mmol/L). Genetic analysis of key genes involved in HDL metabolism resulted in the discovery of 2 very rare mutations in the *ABCA1* and *APOA1* genes. We discuss the effects of these mutations on HDL metabolism and reverse cholesterol transport and interpret these findings in relation to the extensive atherosclerosis at a very young age in this patient.

Case study

A 36-year-old man was admitted to the emergency room with acute chest pain that radiated to his right arm and was accompanied by vegetative symptoms. Symptoms did not subside with rest. The electrocardiogram showed ST-segment elevations in II, III, and aVF and elevated cardiac enzymes (maximum creatine kinase - MB, 622 U/L; maximum troponin-T, 9.88 μg/L). Percutaneous coronary angiography confirmed an acute ST-elevated myocardial infarction as the ramus circumflex of the left coronary artery was occluded (100% stenosis). Although no additional lesions were found in the left anterior descending branch, the right coronary artery showed a significant stenosis (90%) in the middle segment. Initially, the ramus circumflex stenosis was stented with a bare metal stent. A week after initial presentation, the patient underwent an elective percutaneous coronary intervention of the right coronary artery with bare metal stent placement. He started on simvastatin 40 mg, metoprolol 200 mg, perindopril 4 mg, and dual platelet inhibition (acetylsalicylic acid and clopidogrel) and was discharged from the hospital. The patient recovered relatively well, but he was not able to perform intense physical labor.

He had no relevant medical history but reported to smoke 10 cigarettes per day for 20 years (total 10 pack-years). The patient has 2 younger brothers who are in good health. The father of the patient suffered from a myocardial infarction at the age of 48 years. His father's brother had a myocardial infarction at the age of 50 years, and his father's sister died from an unknown cause at the age of 50 years. The mother of the patient has type 2 diabetes and extremely low high-density lipoprotein (HDL) cholesterol (HDL-C; 0.21 mmol/L). Pedigree is summarized in Figure 1. Blood pressure was 133/79 mm Hg, heart rate of 65 beats/min, and body mass index of 26.6 kg/m^2. No abnormalities were found during carotid, chest, and abdominal auscultation. There were no signs of corneal arcus lipoides, tendon xanthomas, or xanthelasma. Laboratory results were unremarkable except for a near absence of HDL-C and very

* Corresponding author. Department of Vascular Medicine, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
E-mail address: a.e.bochem@amc.uva.nl
Submitted November 6, 2014. Accepted for publication January 18, 2015.

1933-2874/
http://dx.doi.org/10.1016/j.jacl.2015.01.006

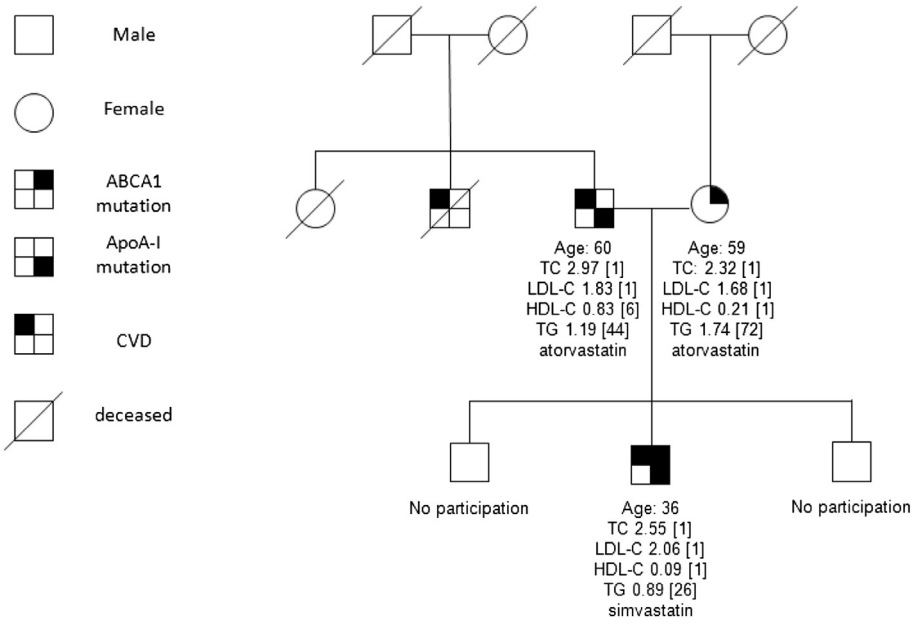

Figure 1 Pedigree of patient. Lipid profiles are in mmol/L, and percentiles for age and gender are shown between brackets. CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

low apolipoproteinA-1 (apoA-1) levels: total cholesterol (TC), 2.55 mmol/L; low-density lipoprotein cholesterol, 2.06 mmol/L; HDL-C, 0.09 mmol/L; triglycerides, 0.89 mmol/L; apoA-1, 0.18 g/L; apolipoprotein B (apoB), 0.71 g/L; lipoprotein (a), 5.8 mg/dL; and glucose, 5.4 mmol/L (during simvastatin 40 mg once daily therapy). The low HDL levels were first measured on a Roche Modular P analyzer (HDL-C, 0.10 mmol/L) the morning after presentation, and this was confirmed several months later using commercially available kits on a Cobas Mira autoanalyzer (HDL-C, 0.09 mmol/L).

Molecular analysis of the genes implicated in HDL-C metabolism resulted in the identification of 2 mutations in 2 key genes involved in HDL-C metabolism. One mutation in the ATP-binding cassette transporter 1 (*ABCA1*) gene, c.A5398C, p.Asn1800His, and a mutation in the apolipoprotein A1 (*APOA1*) gene, c.T6051C; p.Leu202Pro. Overall, our patient's risk factors contributing to the development of the extensive atherosclerosis at this extremely young age were smoking, a positive family history for cardiovascular disease (CVD), and notably an extremely low HDL-C of 0.09 mmol/L.

Discussion

Herewith, we present a patient with extremely low HDL-C due to mutations in *ABCA1* and *APOA1*, resulting in premature atherosclerosis. The inverse association between HDL-C levels and CVD risk is unequivocally found in large prospective epidemiologic population studies.[1] The hypothesis that HDL is atheroprotective was supported by a number of studies in genetically engineered animal models, where several biological activities of HDL were shown to result in the reduction or regression of atherosclerosis.[2] Nonetheless, the hypothesis was severely challenged by the results in clinical trials that addressed the effect of pharmacologic interventions aiming to increase HDL-C. Many of these interventions have not resulted in CVD risk reduction.[3] Moreover, Mendelian randomization studies have shown that genetically defined alterations in HDL-C levels are not associated with CVD risk.[4]

The main mechanism of HDL to protect against the development of CVD is the induction of reverse cholesterol transport (RCT). In addition, HDL has important antioxidative and anti-inflammatory effects.[2,5] For the remainder of the discussion, we focus on RCT as this is the most discussed parameter for ABCA1 and apoA-1. In RCT, cholesterol is taken up from the vessel wall by HDL and transported back to the liver for subsequent excretion in bile. In fact, the hallmark study by Khera et al[6] has shown that cholesterol efflux capacity, a marker of RCT, is inversely related to carotid intima thickness and the likelihood of angiographic CVD, independent of HDL-C levels. It is now increasingly acknowledged that not HDL-C levels per se but more specific markers of RCT and HDL functionality are required to assess the protective functions of HDL.[2]

Two key proteins in the initiation of RCT are the ABCA1 and apoA-1.[5] ABCA1 is a membrane protein that transfers cholesterol from peripheral cells and macrophages onto circulating apoA-1 , which acts as the main acceptor for ABCA1-mediated cholesterol efflux. The enzyme lecithin-cholesterol acyltransferase esterifies the cholesterol at the surface of the newly formed HDL particle creating additional capacity for cholesterol uptake.[7] The patient we present in this report has an almost unique