Single heterozygote splice mutation in the ABCA1 gene is associated with diffuse atherosclerotic disease in a low high-density lipoprotein syndrome

Dimitrios Dimitroulis, Malte Kelm, and Marc Vorpahl*

Division of Cardiology, Pulmonology and Vascular Medicine, Department of Internal Medicine, Medical Faculty, University of Duesseldorf, Moorrenstr. 5, Düsseldorf 40225, Germany

* Corresponding author. Tel: +49 211 81 18801, Fax: +49 211 81 18812, Email: marc.vorpahl@med.uni-duesseldorf.de

A 50-year-old woman was referred with a 6-month history of dyspnoea. She presented with obesity (body mass index: 40.9 kg/m²), blood pressures of 140/80 mmHg on the right arm and 100/70 mmHg on the left, a left subclavian bruit, and corneal clouding covering the pupil (Panel A). Laboratory tests were notable for haemoglobin of 9.9 g/dL (normal: 12–16), stomatocytes (Panel B) and a platelet count of 78 000/mL (normal: 150 000–400 000). C-reactive protein was normal. The total cholesterol was 189 mg/dL (normal: <200 mg/dL), triglycerides were 265 mg/dL (normal: <150), HDL was 3 mg/dL (normal: >35), and apolipoprotein-A1 was 11 mg/dL (normal: 105–205). Doppler-ultrasound and magnetic resonance angiography demonstrated moderate stenoses of the proximal left internal carotid and subclavian arteries (Panel C). Echocardiography showed normal pulmonary artery pressures and left ventricular function. Coronary angiography indicated mild left main stenosis and a collateralized total occlusion of the right coronary artery (Panel D); no inducible ischaemia was appreciated by dobutamine stress testing.

Based on the low HDL, diffuse atherosclerosis, and the stomatocytosis, we suspected an impairment of the ATP-binding cassette transporter 1 protein. ABCA1 responsible for the cellular cholesterol and phospholipid efflux and may lead to vascular foam cell accumulation. Genetic analysis (electropherogram) identified an undescribed single heterozygote splice mutation of G > A (Panel E: ‘r’; www.hgvs.org) at position 4274 of the cDNA (ABCA1 gene) targeting the donor splice site of the intron 30.

With no objective evidence of ischaemia to explain her dyspnoea and without neurological symptoms or exertional arm discomfort, we elected to manage her vascular lesions medically. We targeted non-HDL goals with statin therapy and encouraged our patient to lose weight and avoid drugs that may lower the HDL cholesterol. We arranged a familial genetic counselling and will follow her up carefully.

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