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CLINICAL STUDY

APOC3 and *ABCA1* variants in unusual combined hypolipidaemia showing premature peripheral vascular disease

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ABSTRACT:
BACKGROUND: Familial combined hypolipidaemia is a condition characterised by very low concentrations of circulating very-low-density lipoprotein (VLDL), low-density lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL). It is thought that low LDL/combined hypolipidaemia can protect from cardiovascular disease (CVD), but this is not what we found in a case we present.
OBJECTIVE: We report on a 57-years-old male patient with combined hypolipidaemia who presented with premature peripheral vascular disease. We investigated also his two sons, 32- and 27-years-old, who manifested a tendency to low lipid levels.
METHODS AND RESULTS: We used Illumina exome analysis in all three individuals and in all of them we could exclude the major effect of the variants within the genes most frequently mutated in hypolipidaemia, including recently reported LIPC gene variant. Instead, in all three individuals we identified a novel *ABCA1* variant, possibly responsible for the decreased HDL levels. The proband and one of his sons also share the splicing *APOC3* variant rs138326449, known to be associated with decreased TG levels.
CONCLUSION: The heterogeneous nature and the risk of atherosclerosis in combined hypolipidaemia seems to be variable, based on an interplay between low HDL and LDL levels, and it depends on the combination of variants that cause it *(Tab. 2, Ref. 38).* Text in PDF *www.elis.sk*
KEY WORDS: hypolipidaemia, atherosclerosis, coronary artery calcium score, hypoalphalipoproteinaemia, hypobetalipoproteinaemia, *ABCA1, APOC3.*

Introduction

Marked hypocholesterolaemia is relatively uncommon in general population. In the absence of secondary causes (such as malignancy, severe chronic liver disease and end-stage chronic failure), hereditary causes should be suspected. As recently reviewed by Jakubowski et al (1), low (< 1.3 mM or < 50 mg/dL) or extremely low (< 0.5 mM or < 20 mg/dL) levels of serum LDL-C have been associated with variants in five genes (2–4): *i*) familial hypobetalipoproteinaemia due to variants in apolipoprotein B (*APOB*); *ii)* hypocholesterolaemia due to variants in proprotein convertase subtilisin/kexin type 9 (*PCSK9*); *iii)* abetalipoproteinaemia due to variants in microsomal triglyceride transfer protein (*MTTP*); *iv)* chylomicron retention disease caused by variants in secretion-associated *ras*-related GTPase 1B (*SAR1B*); and *v)* combined hypolipidaemia due to variants in angiopoietin-like 3 (*ANGPTL3*).

Heterozygous familial hypolipoproteinaemia is usually characterised by low LDL-C and ApoB levels below the 5th percentile for age and sex and normal HDL – cholesterol (HDL-C) level (5). Instead, familial combined hypolipidaemia is characterised by very low concentrations of circulating very-low-density lipoprotein (VLDL), LDL, and HDL. This condition is usually caused by variants in the *ANGPLT3* gene and is thought to carry a reduced cardiovascular risk (6, 7). Recently, in a family with dominant familial combined hypocholesterolaemia, a gain-of-function *LIPC* (hepatic lipase C) *v*ariants have been identified (8). The proband from this family showed extremely low values of circulating TC, LDL-C, HDL-C, phospholipids, and ApoA1 (below the fifth percentile for age and sex). In contrast, circulating TGs and ApoB levels were within the low but normal range.

There are also many unexplained cases of extremely elevated or reduced LDL-C concentrations, in which a polygenic origin

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is suspected, however, polygenic risk scores have so far yielded lower effect sizes compared with the effect of monogenic variants (9, 10). This might suggest that additional monogenic variants that cause very low plasma LDL-C concentrations or combined hypolipidaemia remain to be characterised (1).

It is generally believed that low LDL/combined hypolipidaemia can protect from cardiovascular disease (CVD), but this is not what we found in the unusual case presented in this paper, i.e., in a case of combined hypolipidaemia associated with premature atherosclerosis (at the age of 51).

Subjects and methods

Subjects

A fifty-seven-year-old man (PID1, British Caucasian) was referred by his family doctor, to the lipid clinic at the Royal Liverpool University Hospital, United Kingdom, for further assessment of his abnormally low lipid profile: TC 1.5 mmol/l, LDL 0.8 mmol/l, HDL 0.4 mmol/l, and TG 0.6 mmol/l (Tab. 1). Measurements were confirmed on repeated testing by enzymatic colorimetric as well as by ultra-centrifugation, while the patient was off a lipid-lowering therapy. Venepuncture was performed at fasting. At the age of 51, he started experiencing claudication in his right leg and was subsequently diagnosed with right external iliac artery occlusion for which he underwent an angioplasty procedure. His other medical problems included mild anaemia, and stage 3 chronic kidney disease (CKD3b) due to obstructive uropathy and hypertension. Physical examination revealed a BMI of 21 kg/m^2, blood pressure of 121/76 mm Hg, and heart rate of 70 beats/min. Cardiac examination revealed a regular rhythm and soft aortic systolic murmur. He was not diabetic. The remainder of his examination was unremarkable.

Further analysis showed biochemical parameters as follows: ApoA: 0.50 g/L (reference range 1.04–2.02 g/L), ApoB: 0.34 g/L (reference range 0.66–1.33 g/L) (measured by ultra-centrifugation) and Lp(a) concentration was 9.0 mg/dL (< 30.0 mg/dL is normal range). Liver function tests (LFTs) and thyroid function tests (TFTs) were normal; HbA1C was 33 mmol/mol. Thrombophilia screening was negative. Plasma homocysteine was normal. Abdomen ultrasound examination showed the liver to be in normal size, echo-bright with no focal lesion, and with no splenomegaly. Echocardiography showed a normal left ventricular function and traces of tricuspid and mitral regurgitation. Coronary artery calcium score (CAC), obtained through cardiac CT, was zero. Contrast-enhanced cardiac CT scan was not performed because of the reduced eGFR (31 ml/min/1.73 m^2) and absence of cardiac symptoms. He quit smoking more than 25 years ago, consumed alcohol only very occasionally, and was a physically active man.

He had no eye symptoms. His weight was stable, and he was not malnourished. He suffered with irritable bowel syndrome but had no steatorrhea. There was no history of autoimmune diathesis. He was not known to have deficiency of vitamin B12 or folate (serum B12 482 ng/L (200–770 ng/L) and serum folate > 20.0 ug/L (3.9–26.8 ug/L)).

The proband had a 56-year-old healthy brother. His sister died at age of 50 years because of colorectal carcinoma. His mother died aged 78 years because of heart failure due to mitral valve disease. His father was still alive at the age of 80 years and was treated with a statin following a transient ischemic attack. Lipid concentrations in his siblings and parents were not available, due to the lack of will to collaborate.

The proband has two sons aged 32 (PID2, BMI 40 kg/m^2) and 27 years (PID3, BMI 35 kg/m^2), who showed a tendency to lower lipid levels (Tab. 1). Their mother, proband's wife, has normal TGs and HDL-C concentrations and slightly increased TC and LDL-C values. Both sons were fit and well. Mother was diagnosed with multiple sclerosis.

Exome sequencing and analysis

Sequencing libraries were prepared using SureSelectXT Library Prep Kit (Agilent) and exome sequencing was performed in PID1, 2 and 3 using HiSeq 4000 sequencer (Illumina). In total, 33,561 variants spanning 12,910 genes were identified. For annotation and filtering of the variants we used QIAGEN Clinical Insight Interpret (QCI version 8.1.20220121, "confidence" filter 20.0). The first filtering approach was based on the selected dyslipidaemia-associated genes, the second one on "biological-clinical features" and the third one on "predicted deleterious" variants (details available in Supplementary Methods).

Results

Exome sequencing was performed in 3 individuals, PID1-PID3. We used three filtering approaches based on three factors, namely dyslipidaemia genes, biological features and all variants predicted deleterious, altogether 53, 108 and 457 variants were individuated, respectively. However, no *pathogenic* or *likely pathogenic* variants within the main hypocholesterolaemia/dyslipidaemia candidate genes (*ANGPTL3, SAR1B, APOB, PCSK9* or *MTTP,* recently reviewed in ref.) (1) were found in any of the individuals. The list of benign non-pathogenic variants within *APOB*, *PCSK9* and *MTTP* genes is provided in Supplementary Table 1.

Instead, two other possibly clinically relevant variants were identified (Tabs 1 and 2). The first one is a novel variant within *ABCA1* gene (ATP-binding cassette transporters A1) gene NM_005502.4:c.1857_1858delinsAT. This variant is not listed in the Human Gene Mutation Database (HGMD) [11] and ClinVar database (12), but it meets two of the American College of Medical Genetics and Genomics (ACMG) criteria (Tab. 2) (13). It causes serious truncation of the ABCA1 protein, namely NP_005493.2: p.(Met619_Val2261delinsIleTer), which would lead to no functional protein being produced and is predicted as highly deleterious (Mutalyzer 3 Beta (14) and VariantValidator (15)). This variant is shared by all three family members PID1-PID3, confirming its segregation in the family, and being in line with dominant inheritance of primary hypoalphalipoproteinemia. The second variant, a splicing variant affecting intron 2 of *APOC3* gene NM_000040.3:c.55+1G>A (rs138326449) (Tab. 2), found in PID1 and PID2, has been previously associated with low TG

Tab. 1. Lipid profile and other clinical features in proband PID1, his two sons, PID2 and PID3, and their mother, proband's wife.

ID	Age (years)	BMI (kg/m^2)	TC (mg/dL)	TC centile	TGs (mg/dL)	TG centile	HDL (mg/dL)	HDL centile	LDL (mg/dL) calculated	LDL centile	ABCA1 and APOC3 variants
PID1; father	57	21	58	Below 1st centile	53	Between 5th and 10th centile	15	Below 1st centile	31	below 1st centile	ABCA1 +/wt APOC3 +/wt
PID2; son1	32	40	120	Between 1st and 2.5th	62	Between 10th and 25th centile	35	5th centile	73	between 5th and 10th centiles	ABCA1 +/wt APOC3 +/wt
PID3; son2	27	35	97	Below 1st centile	142	Between 75th and 90th centile	27	1st centile	43	below 1st centile	ABCA1 +/wt APOC3 wt/wt
Mother of PID1&2	56	n.a.	259	90th centile	177	Between 75th and 90th centile	66	Between 75th and 90th centile	159	between 75th and 90th centile	n.a.

Reference ranges are shown. Percentiles for lipid values were calculated based on the data from Balder et al.[37] TC, TG, HDL and LDL values were measured by EC= enzymatic colorimetric. *ABCA1* and *APOC3* variants are APOC3: NM_000040.3: c.55+1G>A and ABCA1: NM_005502.4:c.1857_1858delinsAT. + indicates the presence of the variant, wt= means wild type, and n.a. = not available

Tab. 2. Details on the identified *ABCA1* and *APOC3* variants.

Gene	Nucleotide change (cDNA)	Protein change	Reference SNP	HGMD database	Variant effect	Clin Var	Varsome	ACMG
ABCA1	NM_005502.4: c.1857_1858delinsAT	NP_005493.2: p.(Met619_Val2261delinsIleTer)	novel	n.p.	Truncated protein	n.p.	Uncertain Significance LP	PM2 strong, PP3 supporting
APOC3	NM_000040.3: c.55+1G>A	p.(?)	rs138326449	CS138510 (DM)	Aberrant splicing	Conflicting interpretations of pathogenicity	Uncertain Significance	PP3 supporting, BS2 Strong

The dbSNP ID (rs) and HGMD code[11] are indicated for an already known *APOC3* variant. We list the fulfilled ACMG classification criteria[13] for both variants, together with the interpretation/verdict of the effect of the variant from the ClinVar database [12] and Varsome [38]. N.p. = not present

concentrations and reduced risk of ischemic vascular disease and ischemic heart disease (16, 17).

PID1 and PID2 are carriers of the *SLCO1B1* (Solute-carrier organic anion transporter family member 1B1) gene variant c.521T>C (p.(Val174Ala)), rs4149056) known to be associated with statin-related myopathy risk (SRM) (18).

Discussion

It has been estimated that plasma LDL-C concentrations are strongly affected by genetics, with heritability explaining about 4 0% to 60 % of plasma levels (19). Combined hypolipidaemia can also be seen in the context of critical illness, anaemia, chronic liver disease, infection, inflammation and hyperthyroidism (20). Primary causes of hypolipidaemia include abetalipoproteinaemia, hypobetalipoproteinaemia and chylomicrons retention disease. Our patient had no features to suggest any of these primary or secondary causes.

His low LDL-C and TG levels did not protect him from atherosclerosis, while the low HDL-C concentration does not explain it sufficiently. In general, the risk of atherosclerosis in combined hypolipidaemia seems to be variable and it depends on the combination of variants that cause it. However, the presence of premature atherosclerosis in our patient is difficult to explain.

After exome analysis we could exclude the major effect of the variants within the genes most frequently mutated in hypolipidemia, including recently reported LIPC gene variants. However, we believe that the lipid profile in our proband may be resulting from a combination of mainly two independent pathogenic variants affecting *APOC3* and *ABCA1* genes.

Residual CVD risk can result from elevated TGs, markers of remnant particles (17) but our proband had low triglycerides concentrations, likely caused by a splice-site variant (c.55+1G>A) in the *APOC3* gene. APOC3 is secreted by the liver and small intestine and is found on TG-rich lipoproteins (TRLs) such as VLDL and chylomicrons, as well as on HDLs (21). In biochemical studies and in those conducted on experimental animals, it has been shown that APOC3 increases plasma TG levels by both direct inhibition of the activity of lipoprotein lipase and hepatic lipase on TRLs, and by inhibition of the clearance of TRLs by the liver (22). The loss-of-function variants in this gene are associated with a reduced risk of ischemic cardiovascular disease (16, 17) and their carriers show low plasma TG levels, reduced levels of APOC3 and ApoB (17), as well as hyperalphalipoproteinaemia (increased ApoA1), which is characterised by elevated levels of HDL-C in human patients (23). On the contrary, in addition to low TG due to the *APOC3* splicing variant, our patient showed low levels of HDL and ApoA, which we believe could be caused by the novel pathogenic variant within *ABCA1* gene. Thus, our proband phenotypically differs also from the recently published case with familial combined hypocholesterolaemia caused by the gain-of-function LIPC variant. This individual showed extremely low values of circulating cholesterol, LDL-C, HDL-C, phospholipids, and ApoA1 levels

(below the fifth percentile for age and sex), but his circulating TGs and ApoB levels were within the low but normal range (8).

Low HDL-C is associated with an increased risk of CVD although no proof of causation has been found in the MESA cohort (24). Tangier disease (TD), an autosomal recessive condition characterised by a near absence of HDL cholesterol (25), is caused by variants in *ABCA1* (26). In familial hypoalphalipoproteinaemia (FHA), an allelic condition to TD that results from heterozygosity for variants in the *ABCA1* gene (26), cholesterol efflux is decreased. FHA patients manifest also decreased ApoAI levels, mild decrease in ApoAII, as well as TG increase by 40 % and no significant decrease in either TC or LDL (27). ABCA1 transporter is also known as the cholesterol efflux regulatory protein (CERP) (28) and it is a major regulator of cellular cholesterol and phospholipid homeostasis (29, 30).

In general, atherosclerosis is a chronic disease characterised by the deposition of excessive cholesterol in the arterial intima. It has been shown that macrophage foam cells play a critical role in the occurrence and development of atherosclerosis and that the generation of these cells is associated with an imbalance of cholesterol influx, esterification, and efflux (31, 32). ABCA1, ABCG1 and scavenger receptor BI (SR-BI, or SCARB1) play crucial roles in macrophage cholesterol export (33). When inflow and esterification of cholesterol increases and/or its outflow decreases, the macrophages are ultimately transformed into lipid-laden foam cells, the prototypical cells in the atherosclerotic plaque (31, 32).

Taken together, we can hypothesize that in our patient, despite his low TGs concentration obtained owing to the presence of the protective *APOC3* variant, atherosclerosis developed due to the impaired cholesterol efflux caused by *ABCA1* variant c.1857_1858delinsAT and possibly by increased foam cell formation.

The liver can obtain cholesterol necessary for its function from *de novo* synthesis, from HDL carrying cholesterol from the periphery, as well as through receptor-mediated uptake of cholesterol-enriched remnants including LDL. If HDL cholesterol delivery to the liver is decreased due to low HDL concentrations, the liver can obtain the cholesterol it requires through increased *de novo* synthesis as well as increased hepatic clearance of LDL and remnants (34, 35). We believe that low LDL-cholesterol in our proband might be due to a better clearance of LDL by the liver to adapt to the decreased reverse cholesterol transport by HDL.

ABCA1 variant is present also in both sons, confirmed by their tendency to low HDL, whereas *APOC3* variant is only in one of them, although both show lower levels of TGs and a tendency to lower LDL. Regular check-ups can be relevant for clinical follow-up for both since it has been shown that subjects heterozygous for *ABCA1* variants manifest age-modulated decrease in HDL and more than a three-fold increase in coronary artery disease (27).

Proband PID1 and his first son PID2 were both heterozygous also for the c.521T>C variant (p.(Val174Ala)) within the *SLCO1B1* gene. This SNP has been associated with statin-related myopathy risk (SRM) ($p = 0.010$) (18). Irrespective of the type of statin used, carriers of the minor C allele (heterozygotes and homozygotes) were present in a significantly higher proportion in the case group compared to the controls (18). In the HGMD (11), this variant is associated with an increased rate of cholesterol synthesis.

Recently, an association of epigenetic mechanisms and risk of coronary artery disease (CAD) was investigated in the Chinese Han population (36). The authors showed that methylation status of *APOC3, APOA5, LIPC, CETP* and *APOC1*, but not of *APOB* and *PCSK9* gene promoters, may be involved in the regulation of CAD development. It might be interesting to further investigate these genes in our family. This might indicate that also some epigenetic mechanisms contributed to the early atherosclerosis in our proband. Generally, the heterogeneous nature of atherosclerosis and interplay between low HDL and LDL levels in the development of premature atherosclerosis requires further research.

Conclusion

We presented a patient with combined hypolipidemia, premature peripheral vascular disease and negative CAC score, who carried variants in *ABCA1* and *APOC3* genes. His low LDL-C and TG levels did not protect him from atherosclerosis and the low level of HDL-C is insufficient to explain it either. In general, the risk of atherosclerosis in combined hypolipidaemia seems to be variable and it depends on the combination of variants that cause it. After excluding the major effect of the variants within these most frequently mutated gene, we believe that the lipid profile in the proband appears to result from a combination of mainly two independent pathogenic variants; one affecting *APOC3* a splice-site variant (c.55+1G>A) and causing low TG, and the other affecting *ABCA1* gene and possibly causing low HDL.

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