The Linkage of Tangier Disease with Premature Coronary Artery Disease: Relationship with Low Density Lipoproteins and Hypersplenism

Ernst J. Schaefer¹, Peter T. Klementowicz², Om Ganda³, Eliana Polisecchi¹, Bela F. Asztalos¹, Abhijit Pandya⁴, and Robert A. Hegele⁵

¹Boston Heart Diagnostics, Framingham, MA, ²Catholic Medical Center, Manchester, NH, ³Joslin Diabetes Clinic, Boston, MA, ⁴Florida Atlantic University, Boca Raton, FL, and ⁵University of Western Ontario, London, Canada

INTRODUCTION

Tangier disease is a rare disorder with very low plasma high density lipoprotein cholesterol (HDL-C) levels, mild hypertriglyceridemia, and decreased low density lipoprotein cholesterol (LDL-C) and non-HDL-C levels (1). Patients have cholesterol deposition in various tissues and mild corneal opacification (see figure) (2). They have marked hypercatabolism of HDL constituents, and often have premature cardiovascular disease (CVD) (3,4). They have a lack of cellular cholesterol efflux and defects in the ATP binding cassette A1 (ABCA1) gene. He died suddenly of muscle pain. Niacin and estrogen replacement had no effect on her HDL-C levels. Her TG levels were reduced by 41% on 4 capsules/day of fish oil. She was on coumadin because of atrial fibrillation, and also developed significant heart failure, which caused her death at age 56 years. At autopsy she had severe atherosclerosis in her coronary arteries and aorta and a very enlarged heart (7,8).

METHODS

We report the clinical, biochemical, and genetic features in four cases and review the results reported on 191 cases.

RESULTS

Case 1: A 63-year-old male had a tonsilllectomy at age 14 years, and underwent splenectomy at age 44 because of marked splenomegaly, anemia, and thrombocytopenia. His values in mg/dL were HDL-C 1, total cholesterol (TC) 30 to 45 prior to splenectomy, and 100 to 155 thereafter, with non-HDL-C consistently > 70 after splenectomy. At age 59 he developed angina and underwent coronary bypass for significant disease. At age 60 he was noted to have multiple orange omental masses (8). He died in his sleep of presumed coronary heart disease at age 73 years.

Case 2: A 54 year old male presented with an HDL-C of 3 mg/dL, triglycerides (TG) of 175 mg/dL, and non-HDL-C of 84 mg/dL, and had coronary bypass surgery at age 46. He had no neuropathy, anemia, or hepatitisplasmenogamy. His LDL apoB was < 50% of normal due to enhanced catabolism. He was a compound heterozygote for a splice site mutation in exon 7 and a premature stop codon in exon 40 of the ABCA1 gene. He died suddenly of presumed CVD at age 56 (10).

Case 3: A 48 year old female presented with a history of a tonsillectomy at age 6, peripheral neuropathy since age 25, and premature CHD since age 48, requiring bypass at age 47. Her lipids in mg/dL were: TC 137, TG 185, LDL-C 89, non-HDL-C 135, and HDL-C 2. Her apoA-1 level was 2.2 mg/dL, and HDL particle analysis showed apoA-1 only in preβ-1 HDL. She did not have significant hepatitisplasmenogamy or anemia. Her ABCA1 mutation was a homozogous replacement of asparagine for histidine at residue 1740 (2nd transmembrane domain). She was unable to tolerate statin treatment because of muscle pain. Niacin and estrogen replacement had no effect on her HDL-C levels. Her TG levels were reduced by 41% on 4 capsules/day of fish oil. She was on coumadin because of atrial fibrillation, and also developed significant heart failure, which caused her death at age 56 years. At autopsy she had severe atherosclerosis in her coronary arteries and aorta and a very enlarged heart (7,8).

Case 4: A 38 year old female presented with a long history of significant intermittent ataxia and neuropathy. Her lipid values in mg/dL were TC 124, TG 138, LDL-C 108, non-HDL-C 121, and HDL-C 3, with apoA-1 on 20 gels being found in preβ-1 HDL with some in very small α-4 HDL. She did have very mild corneal opacification, but no hepatitisplasmenogamy or anemia. She was found to be homozogous for an ABCA1 splice site mutation in exon 33 at the -1 position. She had a cardiac calcium score of 12 (> 98th percentile) and increased carotid intimal medial thickness. On atorvastatin her LDL-C values went to 50 mg/dL (11).

Case 5: A 56 year old male presented at age 35 with neuropathy, hepatitisplasmenogamy, and anemia. His lipid profile in mg/dL was: TG 312, LDL-C 7, HDL-C 2, non-HDL-C 38, and apoA-1 2.2. HDL particle analysis indicated apoA-1 only in preβ-1 HDL. On DNA analysis he was homozogous for a G851R amino acid substitution in the ABCA1 transportor. He had no evidence of coronary artery disease (CAD) on angiography.

Case 6: A 49 year old male, presented at age 43 years with angina and CAD requiring stents. He subsequently had more stenting, followed by coronary artery bypass surgery at age 49 years. He had no evidence of hepatitisplasmenogamy, neuropathy, or anemia. His values in mg/dL were: TC 115, TG 75, LDL-C 91, HDL-C 7, non-HDL-C 108, and apoA-1 21. HDL particle analysis indicated very low levels of apoA-1 in all particles, with a lack of very large α-1 HDL. On DNA analysis he was a compound heterozygote for two different amino acid substitutions in the ABCA1 transportor, W590L and W590C, the second of which was novel. His LDL-C level was reduced to 57 mg/dL with atorvastatin 80 mg/day.

CONCLUSIONS

In all 191 cases reviewed, about 50% have neuropathy, about 50% have significant hepatitisplasmenogamy, and about 50% over age 40 have CVD. Two main types of homozogous or compound heterozygous Tangier disease were noted: 1) Those with marked hepatitisplasmenogamy, low non-HDL-C levels (< 70 mg/dL), and lack of premature CVD; and 2) Those with no hepatitisplasmenogamy or anemia, premature CVD, and normal or near normal non-HDL-C levels (> 70 mg/dL). Our data indicate that optimizing the levels of atherogenic lipoproteins in these patients with lifestyle modification and statin therapy is warranted if their non-HDL-C is > 70 mg/dL.

REFERENCES