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Low HDL cholesterol levels in type I Gaucher disease do not lead to an increased risk of cardiovascular disease

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ABSTRACT

Objective: A low plasma high-density lipoprotein cholesterol (HDL-c) concentration is an important risk factor for the development of atherosclerotic cardiovascular disease. HDL-c levels are abnormally low in type I Gaucher disease (GD) patients. The aim of this study was to determine whether GD is associated with premature atherosclerosis.
Methods: Lipid profiles, apolipoproteins, and carotid artery intima-media thickness (cIMT) were analyzed in 40 type I GD patients, 34 carriers and 41 control subjects. cIMT is a non-invasive validated biomarker for the status of atherosclerosis and present and future cardiovascular disease risk.
Results: Compared to control subjects, patients showed decreased HDL-c (1.1 ± 0.3 mmol/L) as well as mildly decreased low-density lipoprotein cholesterol (LDL-c) levels (2.8 ± 0.7 mmol/L), with an increased ApoB/ApoA1 ratio. In carriers, HDL-c levels were normal, but LDL-c levels were decreased (2.7 ± 0.8 mmol/L). Mean cIMT measurements were not different in the three study groups (patients: 0.63 ± 0.1 mm versus carriers: 0.64 ± 0.1 mm versus control subjects: 0.65 ± 0.1 mm).
Conclusion: In Gaucher disease low HDL-c levels do not lead to premature atherosclerosis as assessed by cIMT measurement. This indicates that the inverse relationship between levels of HDL-c and risk of cardiovascular disease in the general population may not be present in all conditions characterised by low HDL-c levels.

1. Introduction

Type 1 Gaucher disease (GD) is a lysosomal storage disorder, with a prevalence of 1:50,000 in most countries [1]. The disorder is characterized by a deficiency of the lysosomal enzyme glucocerebrosidase, which results in accumulation of glucocerebroside in macrophages, so called Gaucher cells. Type 1 GD is the most prevalent form and can manifest itself at any age [2]. The presence of Gaucher cells in liver, spleen and bone marrow results in hepatosplenomegaly, skeletal disease and cytopenia. In addition to these classical symptoms, GD is associated with several co-morbidities such as an increased prevalence of malignancies, hypergammaglobulinemias, pulmonary hypertension, polyneuropathies and an abnormal cholesterol profile [3–7]. In a study by Ginsberg et al. low levels of total plasma cholesterol (TC), low-density lipoprotein cholesterol (LDL-c) and high-density lipoprotein cholesterol (HDL-c) in GD patients were reported. The reductions of LDL-c and HDL-c were associated with reduced levels of their respective major protein components apolipoprotein B100 (ApoB) and apolipoprotein A1 (ApoA1), indicating reduced numbers of these particles, while apolipoprotein E (apoE) levels were reported to be high. The levels of LDL-c and HDL-c were inversely correlated with parameters of disease severity and splenectomy was associated with a subsequent increase of LDL-c and HDL-c [7]. In another study decreased levels of LDL-c and HDL-c were associated with enhanced fractional catabolism of LDL-c and HDL-c. Taken together with the increased level of apoE this suggests a central role for the macrophages in these abnormalities [8].

Interestingly, although carriers of a mutation in the GBA gene coding for glucocerebrosidase (carriers) do not exhibit any Gaucher

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symptoms, significantly lower HDL-c levels have also been found in these subjects [9].

Type I GD can be treated with enzyme replacement therapy (ERT) in which the intravenous administration of recombinant glucocerebrosidase leads to clearance of glucocerebroside and improvement of symptoms. Treatment with ERT for 18 months causes an increase in, but not normalization of HDL-c and ApoA1 concentrations while LDL-c and apoB levels remain unchanged [10].

In several epidemiologic studies it has been shown that low plasma HDL-c levels are associated with increased risk of cardiovascular disease (CVD) [11,12]. As a consequence, GD patients as well as carriers could be considered at risk for premature atherosclerosis. In our adult cohort of more than 70 GD patients followed for 20 years, the occurrence of cardiovascular disease does not appear to be increased. However, this is difficult to ascertain in such a small population, with relatively young patients.

A non-invasive validated biomarker for the status of atherosclerosis and present and future cardiovascular disease risk is ultrasonographically measured carotid intima-media thickness (cIMT) [13,14].

To determine whether the low HDL-c levels observed in GD patients and carriers are associated with premature atherosclerosis, cIMT was analyzed in a cross sectional study in GD patients, carriers and control subjects.

2. Methods

2.1. Study population

Consecutive patients were recruited at the national outpatient clinic for inherited metabolic diseases at the Academic Medical Center, Amsterdam (AMC). In all patients, the diagnosis of GD was previously confirmed by enzymatic assay as well as by mutation analysis. Patients who consented to the protocol were asked to recruit family members. These family members were either blood relatives (brothers, sisters, children) or family members sharing the same household (spouses), to control for genetic and environmental influences on lipid profiles and other determinants of CVD risk as much as possible. Subjects known with hereditary dyslipidemia were excluded ($n = 1$).

Medical history of CVD (myocardial infarction (MI), stroke), the presence of cardiovascular risk factors (smoking, diabetes, hypertension), and use of alcohol and medication were surveyed by questionnaires. Blood pressure, length and weight were measured. Hypertension was defined as a blood pressure >140/90 mmHg. In addition, in GD patients severity score index (SSI, as described by Zimran) [15], use and duration of use of substrate deprivation or enzyme replacement therapy and genotype were recorded from patient files.

The study was approved by the local Medical Ethical Committee and all participants provided written informed consent.

2.2. Laboratory analysis

In all subjects, blood samples were drawn after an overnight (12 h) fast. C-reactive protein (CRP) was determined. TC, HDL-c and triglycerides (TG) were measured by enzymatic colorimetric procedure. LDL-c was calculated by means of the Friedewald formula. ApoA1 and ApoB were determined by immunonephelometry. The concentration of apoE in plasma was determined by a turbidimetric immuno assay, as described by the manufacturer (Randox, Westburg, The Netherlands) using a Cobas Mirs auto analyzer (Roche, Basel Switzerland). Reference values were as follows: TC: 3.9–6.5 mmol/L; LDL-c: <4.49 mmol/L; HDL-c: male >1.1 mmol/L, female >1.2 mmol/L; TG: 0.5–2.0 mmol/L; ApoA1: male 1.1–1.8 g/L, female 1.1–2.1 g/L; ApoB: male 0.55–1.4 g/L, female 0.55–1.25 g/L.

In all non-Gaucher patients of whom the mutation status was unknown, mutation analysis of the GBA gene was performed. DNA was extracted from peripheral blood leukocytes and the familial GBA mutations (if applicable) and/or the six most prevalent Gaucher mutations in the Dutch population were determined (p.Asn409Ser (N370S), p.Leu483Pro (L444P), p.Arg159Trp (R120W), c.84dupG, RecNci combination (p.leu483Pro (L444P)), p.Ala495Pro (A456P) and p.Val499Val (V460V) and p.Leu363Pro (L324P)). Together, these six mutations account for >82% of the disease-causing alleles in the Dutch GD population [16].

To investigate a possible relation of the HDL-c levels with Gaucher cell burden, chitotriosidase activity was measured. This enzyme, produced by Gaucher cells, indicates the total Gaucher cell burden and the plasma activity is directly related to the amount of accumulated glycolipid in spleen [17]. Levels in carriers of the common chitotriosidase mutation were multiplied by two since heterozygocity for this mutation results in a 50% reduction in enzyme activity [18].

2.3. Carotid intima-media thickness

B-mode ultrasound images were acquired using an Acuson Aspen (Siemens/Acuson Corporation, Erlangen, Germany and Mountainview, CA, USA) using an L7 5–12 MHz broadband transducer. Bilaterally, images of predefined arterial far wall segments of the right and left common carotid artery, the carotid bulb and the internal carotid artery were acquired. Images were saved and IMT was measured by one image analyst, blinded for the clinical and genetic status of the patient. cIMT was defined as the average of the six IMT measurements.

2.4. Statistical analysis

ApoB/ApoA1 ratios were calculated. Descriptive statistics were used for exploration of the data. Correlation between HDL-c and chitotriosidase was calculated using a Spearman test. Differences in variables with a continuous or a dichotomous distribution between GD patients, carriers and control subjects were evaluated using linear or logistic regression analyses, respectively. These analyses were performed using the generalized estimating equations (GEE)-method in the SAS procedure GENMOD to account for correlations within families. The exchangeable correlation structure was used for these models. For differences in cIMT and the ApoB/ApoA1 ratio between the three groups, a stepwise backward multivariate regression analysis was used to adjust for potential confounders. Variables with a skewed distribution were log-transformed before statistical analyses. p-Values <0.05 were considered to indicate statistical significance. A p-value of <0.10 was considered indicative of a trend. The analyses were performed with the SAS package version 9.1 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. General characteristics

A total of 115 subjects (40 patients, 34 carriers and 41 control subjects) was investigated. Age, gender distribution, BMI, cigarette and alcohol use, CRP and the prevalence of hypertension were comparable in the three study groups (Table 1). Three patients, four carriers and two control subjects used lipid lowering drugs. The number of subjects with a cardiovascular event in the past was also not different between groups. Thirty-four of the patients