Blood Cells, Molecules and Diseases xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Blood Cells, Molecules and Diseases

journal homepage: www.elsevier.com/locate/bcmd

The role of high density lipoprotein in Type 1 Gaucher disease

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ARTICLE INFO

Article history:
Submitted 3 November 2016
Revised 9 November 2016
Accepted 10 November 2016
Available online xxxx

Keywords:
Gaucher disease (GD)
Low density lipoprotein (LDL)
High density lipoprotein (HDL)
Biomarkers
Enzyme replacement therapy (ERT)

ABSTRACT

Type I Gaucher Disease (GD1) is known to be associated with hypocholesterolemia and reduced levels of low density lipoprotein (LDL) and high density lipoprotein (HDL). In this study we aimed to correlate disease severity with HDL levels and to evaluate the effect of enzyme replacement therapy (ERT) on HDL levels as well as estimating the frequency of cardiovascular events in GD. Two groups of GD1 patients were evaluated: 30 untreated and 36 patients on ERT. Disease severity, biomarkers of GD and lipid levels were evaluated in the two groups. The Zimran Severity Score Index (SSI) was used to estimate disease severity and the effect of ERT on HDL levels was evaluated, as well as the frequency of cardiovascular disease.

GD1 patients with more severe disease (SSI median 11) had significantly lower levels of HDL (median 23 mg/dL), compared to patients with milder (SSI median 4.5) disease (median 37 mg/dL $p = 0.001$). HDL levels increased after ERT. Despite lower HDL levels in patients with more severe disease, a low frequency of cardiovascular events was detected.

HDL level should be used in GD as a biomarker for diagnosis, monitoring and estimation of ERT effect.

1. Introduction

The clinical course of Type 1 Gaucher disease (GD1), the non-neuronopathic form of the disease, is characterized by hepatosplenomegaly, skeletal complications and pancytopenia caused by bone marrow infiltration by Gaucher cells and hypersplenism [1,2]. The gold standard for diagnosis of GD is a combination of the level of activity of leukocyte glucocerebrosidase and identification of relevant gene mutations [3,4]. GD1 is the most common form of GD with a global incidence of 1 per 50,000 to 100,000 population and with an incidence of 1 per 400–600 in Jews of Ashkenazi descent. The course and severity of the disease is variable and is influenced by the specific gene mutations present in individual patients. Some patients are asymptomatic or have mild symptoms, yet there are other forms of the disease characterized by hematologic, skeletal and pulmonary involvement with wide range of severity [1–3,5]. The severity of GD1 is evaluated according the Zimran Severity Score Index (SSI) [6]. The treatment of choice for patients with severe disease is Enzyme Replacement Therapy (ERT) which leads to significant improvement in most disease manifestations [7,8]. There are several biomarkers in use for the diagnosis and follow up of GD course and assessment of therapeutic goals achievement which, over time, have included tartrate resistant acid phosphatase (TRAP), angiotensin converting enzyme (ACE), and ferritin [9,10]. Abnormalities in lipoprotein metabolism in GD1 have been reported to include hypocholesterolemia, reduced levels of low density lipoprotein (LDL) and high density lipoprotein (HDL), which might be associated with increased catabolism of LDL and HDL due to impaired macrophage function [11–13]. Reduction in lipoprotein levels correlates inversely with the severity of disease manifestations and may identify a patient population at risk for irreversible complications requiring initiation of enzyme replacement therapy (ERT). Interestingly, there are studies which have shown that ERT resulted in significant increase in HDL-c plasma concentration [14], however there appears to be no higher incidence of atherosclerotic cardiovascular disease in GD1 patients with low HDL cholesterol [15].

In this study we evaluated the effect of ERT on HDL-c levels, determined guidelines for using HDL-c plasma levels in monitoring the efficacy of ERT in treated GD1 patients, and estimated the frequency of cardiovascular disease in the studied GD1 patient cohort.

2. Patients and methods

A cohort of 66 GD1 patients followed at the Gaucher clinic in the Rambam Medical Center, Haifa, Israel since 1990 was evaluated including 30 untreated patients and 36 receiving ERT. The study was approved by the local institutional review board.

The Zimran Severity Score Index (SSI) [6] was used to assess disease severity. Factors included in the SSI include cytopenia, splenomegaly, hepatomegaly, liver function, CNS involvement and skeletal involvement

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http://dx.doi.org/10.1016/j.bcmd.2016.11.005
1079-9796/

Table 1
Characteristics of untreated and enzyme replacement therapy-treated GD patients.

		Untreated patients	ERT patients	Total	*P* value
N		30	36	66	
Sex	F	17	18	35	0.63 (NS)
	M	13	18	31	
Age (years)	Median	59	52.5	52.5	0.449 (NS)
	Range	32–78	21–86	21–86	
Age at diagnosis (years)	Median	30	24	28	0.70 (NS)
	Range	6–59	1–80	1–80	

ERT: enzyme replacement therapy.

among other parameters, with a derived score in the range of 0–30 points where higher scores indicated more severe disease.

Levels of total cholesterol, LDL and HDL-c were measured and monitored in the untreated and ERT treated patients during follow-up for a two-year period before initiation of ERT and at several points during treatment.

The patients were evaluated for medical history of cardiovascular disease skeletal changes, liver and spleen size by ultrasound and/or magnetic resonance imaging, and biomarker measurements.

2.1. Statistical analysis

The data were analysed by SPSS, version 21 (SPSS Inc. Chicago, IL USA). Fishers Exact Test was used to detect the difference in the prevalence of low HDL-c between untreated and treated patients. Changes in HDL-c levels during ERT were demonstrated by Wilcoxon Signed Ranks Test or paired *t*-test. $P < 0.05$ was considered significant. Data are presented as medians and means ± SEM. Significance signs are displayed as following: NS for not significant, * for $P < 0.05$, ** for $P < 0.01$ and *** for $P < 0.0001$.

3. Results

Type I Gaucher patients were divided into two groups; GD untreated patients and patients on ERT. The characteristics of both groups are shown in Table 1. The cohort included 66 patients, of which 30 were untreated (13 males and 17 females) and 36 patients treated with ERT (18 men and 18 women). The median age of the whole group was 52.5 years (range 19–85 years), the untreated group 48.5 years (range 32.8–66.6 years), and the ERT treated group, 52.5 years (range 21 to 86 years). Median age at diagnosis was 28 years (range 1–81 years), 29.5 in untreated patients and 24 years in ERT treated patients (1–80 years).

The median SSI among the ERT-treated patients was 11 (11.8 ± 0.624), compared to 4 (4.48 ± 0.569) in untreated patients, $p < 0.0001$ confirming that treated patients had more severe disease than those for whom ERT was not deemed necessary.

Table 2
Lipid profile in mild and severe patient groups.

		Mild disease	Severe disease	*P* value
Severity score	Median	4	11	<0.0001***
	Mean	4.48 ± 0.569	11.65 ± 0.624	
Total cholesterol (mg/dL)	Median	169	140.5	0.38 (NS)
	Mean	153.48 ± 7.474	144.9 ± 6.38	
LDL (mg/dL)	Median	92	79.48	0.04*
	Mean	95.05 ± 6.3	77.48 ± 5.45	
HDL (mg/dL)	Median	38	24	<0.0001***
	Mean	39.7 ± 2.55	26.18 ± 1.6	
TG (mg/dL)	Median	130	138	0.164 (NS)
	Mean	138.95 ± 12.35	172.29 ± 18.4	

Total cholesterol: Desirable — <200 mg/dL, Borderline high — 200–239 mg/dL, High — >240 mg/dL.
LDL: Optimal for very high risk patients — <70 mg/dL, Optimal — <100 mg/dL, near optimal — 100–129 mg/dL, Borderline high — 130–159 mg/dL, High — 160–189 mg/dL, Very high — >190 mg/dL, HDL: Low — <40 mg/dL, High — >60 mg/dL, TG — 30–200 mg/dL.
LDL – Low Density Lipoprotein; HDL – High Density Lipoprotein; TG – Triglycerides.
NS P > 0.05.
* P < 0.05.
** P < 0.01.
*** P < 0.001.

Table 3
Lipid profile in severe patients before and after enzyme replacement therapy.

		Before treatment	After treatment	*P* value
Total cholesterol (mg/dL)	Median	141	158	0.0138*
	Mean	146.33 ± 6.46	161.59 ± 7.32	
LDL (mg/dL)	Median	81.96	90	0.0604 (NS)
	Mean	78.24 ± 5.69	88.93 ± 5.93	
HDL (mg/dL)	Median	24	36	<0.0001***
	Mean	26.6 ± 1.61	34.97 ± 2.37	
TG (mg/dL)	Median	147	143	0.216 (NS)
	Mean	178.31 ± 19.29	157.92 ± 15.78	

LDL — Low Density Lipoprotein; HDL — High Density Lipoprotein; TG — Triglycerides.
NS P > 0.05.
* P < 0.05.
** P < 0.01.
*** P < 0.001.

3.1. Lipid profile

Plasma levels of total cholesterol, LDL (Low Density Lipoprotein), HDL (High Density Lipoprotein) and TG (Triglycerides) were evaluated in the two groups of patients (Table 2). Treated patients had significantly lower HDL level of 24 mg/dL (26.18 ± 1.6 mg/dL) compared to untreated patients, of 38 mg/dL (39.7 ± 2.55 mg/dL), $p < 0.0001$. In addition, LDL reduction was observed in treated patients compared to the untreated group (77.5 ± 5.5 vs. 95.05 ± 6.3 mg/dL, $P < 0.05$). However, there was no statistically significant difference in TG and total cholesterol between the two groups.

Lipid profiles were evaluated in ERT treated patients, prior to treatment initiation and after 2 years of treatment (Table 3). ERT caused a statistically significant increase in HDL from 26.67 ± 1.61 mg/dL prior to ERT to 35 ± 2.37 mg/dL after treatment, $p < 0.0001$. There was no change in LDL levels (78.2 ± 5.7 pre treatment to 88.9 ± 5.9 mg/dL post treatment, $P = 0.0604$) or TG levels but there were significantly increased total cholesterol levels (from 146.3 ± 6.4 to 161.6 ± 7.3 mg/dL, $P < 0.05$).

Table 4
Gaucher Disease Biomarkers in mild and severe patient groups.

		Mild disease	Severe disease	*P* value
Severity score	Median	4	11	<0.0001***
	Mean	4.48 ± 0.569	11.65 ± 0.624	
TRAP (U/L)	Median	8	16	0.0017**
	Mean	8.82 ± 0.86	22.29 ± 3.19	
ACE (U/L)	Median	74.1	160	0.0016**
	Mean	74.65 ± 8.05	186.23 ± 23.3	
Chito (nm/mL/h)	Median	3450	5800	0.25 (NS)
	Mean	4226 ± 113.9	9067.4 ± 2590.5	
Ferritin (ng/mL)	Median	259.5	370	0.95 (NS)
	Mean	491.27 ± 137.15	482.68 ± 75.42	

TRAP — Tartrate-resistant Acid Phosphatase; ACE — Angiotensin Converting Enzyme, Chito — chitotriosidase.
NS P > 0.05.
* P < 0.05.
** P < 0.01.
*** P < 0.001.

Please cite this article as: S. Watad, et al., Blood Cells Mol. Diseases (2016), http://dx.doi.org/10.1016/j.bcmd.2016.11.005