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LIVER STEATOSIS IS HIGHLY PREVALENT AND IS ASSOCIATED WITH METABOLIC RISK FACTORS AND LIVER FIBROSIS IN ADULT PATIENTS WITH TYPE 1 GAUCHER DISEASE

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The study was approved by the local ethics committee, and all participants gave written informed consent according to the Helsinki Declaration.

List of abbreviations:

ACE: angiotensin converting enzyme; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ATPIII: Adult Treatment Panel III; BMI: body mass index; CAP: controlled attenuation parameter; ERT: enzyme replacement therapy; GBA: glucocerebrosidase; GD: Gaucher disease; GD1 DS3: Disease Severity scoring system for type 1 Gaucher disease; GGT: gamma-glutamyltranspeptidase; HbA1c: glycated hemoglobin; HCC: hepatocellular carcinoma; HDL: high-density lipoprotein; HOMA-IR: homeostatic model assessment of insulin resistance; MAFLD: metabolic dysfunction-associated fatty liver disease; MetS: metabolic syndrome; MRI:

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magnetic resonance imaging; NAFLD: nonalcoholic fatty liver disease; SSI: Severity Scoring Index; VCTE: vibration controlled transient elastography.

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LAY SUMMARY

Gaucher disease, a rare lysosomal storage disorder, is characterized by peculiar metabolic abnormalities and variable liver involvement, ranging from hepatomegaly to liver fibrosis/cirrhosis and hepatocellular carcinoma.

The prevalence of and the factors associated with liver steatosis have not been systematically evaluated in previous cohorts of adult GD patients.

In this study, adult patients with GD showed a high prevalence of liver steatosis that was significantly associated with a worse metabolic profile and liver fibrosis.

ABSTRACT

Background and Aims: Gaucher disease (GD) is associated with peculiar metabolic abnormalities (i.e. hypermetabolic state, peripheral insulin resistance, dyslipidemia), partially reverted by enzyme replacement therapy (ERT) at the expense of weight gain. Such metabolic alterations together with an unhealthy lifestyle acquired by an aging GD population may favour the development of liver steatosis. We aimed at evaluating the prevalence of significant liver steatosis and at identifying the factors associated with liver steatosis in a cohort of patients with type 1 GD.

Methods: 20 adult type 1 GD patients from an Italian academic referral centre were prospectively submitted to vibration controlled transient elastography (Fibroscan®) with controlled attenuation parameter (CAP); significant steatosis was defined as CAP values ≥ 250 dB/min.

Results: Median CAP values were 234 [165-358] dB/min and 8 patients (40%) had significant steatosis. Significant steatosis was associated with indices of adiposity (weight, BMI and waist

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circumference), high blood pressure, insulin resistance and metabolic syndrome. GD-related variables and dose and duration of ERT were not associated with significant steatosis. In the subgroup of 16 patients on stable ERT for at least 24 months, CAP resulted significantly and positively associated with liver stiffness (rho 0.559, p=0.024).

Conclusions: Significant steatosis is highly prevalent in adult type 1 GD patients and is strongly associated with a worse metabolic profile, featuring metabolic dysfunction-associated fatty liver disease (MAFLD). MAFLD may determine liver fibrosis progression in GD patients on stable ERT and may be a risk factor for long-term liver-related complications.

EWC: 244

Key words: Controlled attenuation parameter, Enzyme replacement therapy, Glucocerebrosidase deficiency, Liver stiffness, Metabolic dysfunction-associated fatty liver disease

BACKGROUND

Gaucher disease (GD) is a lysosomal storage disorder due to biallelic loss-of-function mutations in the glucocerebrosidase (*GBA1*) gene leading to glycosphingolipid accumulation in cells of the reticulo-endothelial system [1, 2]. Hepatosplenomegaly, thrombocytopenia and bone disease are the major presenting features of type 1 GD, the most frequent chronic visceral variant [3, 4]. Liver involvement in type 1 GD is almost universal and ranges from hepatomegaly, with or without liver enzymes alterations, to liver fibrosis, cirrhosis, portal hypertension and

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hepatocellular carcinoma [2, 5-7]. GD is also characterized by peculiar metabolic abnormalities, including hypermetabolic state, peripheral insulin resistance, and dyslipidaemia with low plasma levels of high-density lipoprotein (HDL) cholesterol [8-11], owing to lysosomal dysfunction, alterations in sphingomyelin-ceramide-glycosphingolipid pathways and systemic chronic low-grade inflammation [12, 13]. These same pathophysiological mechanisms have been increasingly recognized in the pathogenesis of some common acquired conditions, such as obesity and metabolic syndrome (MetS) [12, 13]. Enzyme replacement therapy (ERT), very effective on visceral, haematological and skeletal complications of GD, has significantly improved expectancy and quality of life of type 1 GD patients [14], but a significant weight gain has been reported in several patients with time [8, 15]. Moreover, as for the general population, aging GD patients are increasingly exposed to unhealthy lifestyle, such as caloric intake excess, unbalanced diet, excessive alcohol consumption and sedentariness [8]. Due to this background, it could be expected that the prevalence of liver steatosis in adult type 1 GD patients is remarkable.

Liver steatosis is characterized by the ectopic storage of triglycerides in hepatocytes, and is mainly related to the components of the MetS, featuring metabolic dysfunction-associated fatty liver disease (MAFLD), formerly named non-alcoholic fatty liver disease (NAFLD) [16-18]. MAFLD is determined by an unbalance between the rate of hepatic triglycerides synthesis and catabolism due to an altered whole-body energetic homeostasis resulting from caloric intake exceeding caloric expenditure [19]. Paralleling the worldwide increase in obesity, diabetes and metabolic risk abnormalities, MAFLD is the most rapidly growing cause of chronic liver disease [20, 21], and is strongly associated with the risk of liver fibrosis/cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC), leading to increased liver-related morbidity and mortality [22]. Of note, MAFLD acts synergistically with concurrent chronic liver disease to further accelerate the progression of liver injury [23-26]. As a consequence, it could be hypothesized that GD patients with liver steatosis are at higher risk of developing advanced liver disease.

Controlled attenuation parameter (CAP) is a recently developed non-invasive tool for qualitative and quantitative assessment of liver steatosis [27]. CAP measures the degree of ultrasound attenuation due to hepatic fat based on signals acquired by a technology named vibration-controlled transient elastography (VCTE) implemented on Fibroscan® [28]. Several studies have

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clearly shown that CAP values are strongly associated with obesity, MetS and alcohol consumption, variables epidemiologically associated with liver steatosis [29, 30]. Moreover, large prospective studies including patients with chronic liver diseases of various etiologies consistently reported a good correlation of CAP values with the amount of steatosis assessed by liver biopsy [31-34]. Of note, since CAP is integrated in Fibroscan®, it is possible to have a one-shot reliable non-invasive assessment of both liver steatosis and fibrosis using the same equipment.

In this prospective study, we aimed to assess the prevalence of significant liver steatosis and to identify the factors associated with liver steatosis evaluated by VCTE with CAP in adult patients with type 1 GD from an Italian GD referral centre.

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PATIENTS AND METHODS

PATIENTS

In this study we recruited consecutive unrelated adult patients with type 1 GD confirmed by deficient GBA activity and defined mutations in the human *GBA1* gene, monitored at the Regional Referral Centre for Lysosomal Storage Diseases, Division of Internal Medicine and Metabolism, Civil Hospital of Baggiovara, AOU of Modena, Italy, between 2015 and 2017.

A complete medical assessment, including evaluation of GD severity, anthropometric and metabolic parameters and VCTE (Fibroscan®) with CAP, was performed. Concurrent causes of liver steatosis were evaluated through medical history, imaging and biochemical examinations. Dietary and lifestyle habits, including the amount of alcohol consumption, were also registered; significant alcohol consumption was defined as ≥20 g/day in women and ≥30 g/day in men.

The study was approved by the local ethics committee, and all participants gave written informed consent according to the Helsinki Declaration.

GAUCHER DISEASE SEVERITY EVALUATION

Several GD parameters, including age at diagnosis, GBA1 genotype, history of splenectomy, dose and duration of ERT, and GD severity, were assessed. GD severity at the time of evaluation was assessed using two validated scores: the Disease Severity scoring system for type 1 GD (GD1 DS3) [35] and the Severity Scoring Index (SSI) [36]. Moderate-marked GD was defined as DS3 ≥ 3 or SSI > 10, respectively. Liver and spleen volume were measured by magnetic resonance imaging (MRI). Serum angiotensin converting enzyme (ACE) was determined by a standard enzyme activity assay.

ANTHROPOMETRIC AND METABOLIC PARAMETERS

Weight, height, body mass index (BMI), waist circumference and blood pressure were measured in all GD patients at the time of evaluation. Central obesity was defined as waist circumference > 102 cm in men and > 88 cm in women; high blood pressure was defined as systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg and/or use of anti-hypertensive drugs. On the same day as the study visit a fasting blood sample was obtained from each patient for measurements of glucose, insulin, glycated haemoglobin (HbA1c), lipid profile,

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alanine and aspartate aminotransferases (ALT and AST), gamma-glutamyltranspeptidase (GGT), ferritin, platelets count and albumin. Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: [fasting insulin (mIU/L) x fasting glucose (mg/dl)] / 405. Patients with HOMA-IR ≥ 2 were considered as insulin-resistant individuals. Altered glucose homeostasis was defined as a fasting glucose ≥ 110 mg/dl, hypertriglyceridemia as fasting triglycerides levels ≥ 150 mg/dl and low HDL cholesterol as HDL cholesterol levels < 40 mg/dl in men and < 50 mg/dl in women. MetS was diagnosed according to Adult Treatment Panel III (ATPIII) criteria [37].

VIBRATION CONTROLLED TRANSIENT ELASTOGRAPHY

All patients were submitted to VCTE (Fibroscan®) with CAP on the same day as the study visit. VCTE with CAP measurements were performed by using the M probe after at least 3 hours of fasting by a single experienced operator who had previously executed more than 500 examinations in patients with chronic liver disease (F.N.). Significant steatosis (grade S2 or higher) was defined as CAP values ≥ 250 dB/min [30].

STATISTICAL ANALYSIS

Results were expressed as median [range] for numerical variables and frequencies (percentages) for categorical variables. Medians were compared by the Mann-Whitney U test and nominal variables by Paerson Chi-square and Fisher's exact test where appropriate. Spearman's rho was calculated for correlations between CAP values and other parameters. Because treatment with ERT may significantly affect GD progression over time, sensitivity analyses according to the length of ERT were conducted. A two-sided p value < 0.05 was considered significant. Statistical analyses were performed using the statistical software package SPSS, version 17.0 for Windows (SPSS Inc., Illinois, USA).

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RESULTS

GENERAL FEATURES OF THE OVERALL STUDY POPULATION

Twenty adult type 1 GD patients were enrolled in this study. The main clinical features of the overall study population are shown in **Table 1**. Males and females were equally represented; median age was 48 [18-78] years. The majority of patients were carriers of at least one N370S GBA1 mutant variant and had mainly mild disease according to DS3 and SSI. All but 2 patients were on ERT; 16 of these patients were on stable ERT for at least 24 months. Seven patients had a past history of splenectomy.

A significant proportion of patients had metabolic comorbidities: 40% were overweight or obese; 50% had high blood pressure; 10% showed an altered glucose homeostasis (1 patient with impaired fasting glucose and 1 patient with type 2 diabetes mellitus) and 15% were insulin-resistant according to HOMA-IR; 20% had full-blown MetS.

Median CAP values were 234 [165-358] dB/min; 8 patients (40%) showed CAP values ≥ 250 dB/min consistent with significant steatosis. 2 patients, both males, reported a significant alcohol consumption; 1 patient was a long-term responder to interferon-based therapy for post-transfusion chronic HCV infection; no other potential concurrent causes of liver steatosis were detected in the remaining patients.

FACTORS ASSOCIATED WITH CONTROLLED ATTENUATION PARAMETER

The correlations between CAP values and the main demographic, biochemical, GD-related and metabolic factors are shown in **Table 2**. CAP values were not associated with age and sex (p=0.226).

Several anthropometric and metabolic variables were significantly associated with CAP values. In particular, there were positive and significant correlations with all indices of increased adiposity,

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such as weight, BMI and waist circumference (**Fig. 1, Panels A and B**). Consistently, overweight/obese patients showed significantly higher CAP values than patients with a normal BMI (269 [221-358] dB/min vs. 211 [165-269] dB/min, p=0.004). Also patients with high blood pressure presented significantly higher CAP values than normotensive patients (262 [169-358] dB/min vs. 216 [165-261] dB/min, p=0.034); in parallel, we found a positive although not statistically significant association between diastolic blood pressure and CAP. Although we did not find significant associations between CAP values and glycaemia or HOMA-IR, patients with altered glucose homeostasis had significantly higher CAP values than normoglycemic patients (321 [284-358] dB/min vs. 226 [165-295] dB/min, p=0.032); similarly, CAP values were significantly higher in patients with insulin resistance according to HOMA-IR than in patients without (284 [251-295] dB/min vs. 225 [165-358] dB/min, p=0.050). As shown in **Fig. 1 Panel C**, CAP values were also positively and significantly associated with the number of factors of the MetS; as such, patients with the full-blown MetS presented significantly higher CAP values than those without (290 [251-358] dB/min vs. 223 [165-276] dB/min, p=0.008). Alcohol consumption was not significantly associated with CAP values; however, the 2 patients with significant alcohol consumption showed significantly higher CAP values than their counterpart (327 [295-358] dB/min vs. 226 [165-284] dB/min, p=0.023).

Concerning GD-related variables, we did not find any correlations between CAP values and GD severity as assessed either by scores (DS3 and SSI) or biomarkers (ACE, HDL cholesterol, ferritin, platelets). GBA1 genotype (p=0.217), splenectomy (p=0.721), and dose and duration of ERT were not associated with CAP values. Patients on stable ERT for at least 24 months did not show a significant difference in CAP values with respect to patients who have received ERT for < 24 months (p=0.156).

CAP values were not significantly associated with liver volume, liver enzymes and liver stiffness in the overall study population.

FACTORS ASSOCIATED WITH SIGNIFICANT STEATOSIS

Table 3 shows a comparison of the main features of GD patients with and without significant steatosis as evaluated by CAP. The factors associated with significant steatosis were fully consistent with the results obtained for CAP values. In particular, GD patients with significant

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steatosis clearly showed a worse metabolic profile than GD patients without significant steatosis. Indeed, patients with significant steatosis presented more frequently overweight/obesity, high blood pressure, insulin resistance and MetS, and had higher values of weight, BMI, waist circumference, diastolic blood pressure and glycaemia than their counterpart without significant steatosis. Moreover, there was a non-statistically significant overrepresentation of patients with significant alcohol consumption among those with significant steatosis. GD-related variables and ERT dose and duration were not significantly different between GD patients with and without significant steatosis. The prevalence of significant steatosis in GD patients on stable ERT for at least 24 months did not significantly differ from those who received ERT for < 24 months (44% vs. 25%, p=0.494). There were no significant differences between GD patients with and without liver steatosis with respect to liver volume, liver enzymes and liver stiffness in the overall study population.

SENSITIVITY ANALYSES ACCORDING TO THE LENGTH OF ERT

Analyses were repeated among the 16 patients who were on stable ERT for at least 24 months. BMI (rho=0.624, p=0.010), waist circumference (rho=0.531, p=0.034) and the number of factors of the MetS (rho=0.656, p=0.006), as well as overweight/obesity (p=0.049), insulin resistance (p=0.029), high blood pressure (p=0.006) and MetS (p=0.009), were all confirmed as factors significantly and positively associated with CAP or significant steatosis in this subgroup of patients. Of note, CAP was also significantly associated with liver stiffness (rho 0.559, p=0.024) (**Fig. 2**); consistently, GD patients with significant steatosis showed higher liver stiffness values than those without significant steatosis (6.8 [3-11.3] kPa vs. 4.3 [3-5.1] kPa, p=0.026).

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DISCUSSION

In this study, we assessed the prevalence of significant liver steatosis evaluated by CAP in a cohort of Italian adult patients with type 1 GD. Next, we evaluated which factors among metabolic features, GD-related variables and treatment with ERT, were associated with CAP values and significant liver steatosis. Finally, we investigated if liver steatosis by CAP was associated with liver fibrosis by VCTE. We showed that significant liver steatosis was highly prevalent in our cohort of adult type 1 GD patients, affecting 40% of individuals. Features of the MetS, including indices of adiposity, high blood pressure and insulin resistance, as well as significant alcohol consumption, were the main factors associated with CAP values and significant liver steatosis. Whereas, we did not find any significant association between liver steatosis by CAP, GD-related variables and treatment with ERT. We also demonstrated that liver steatosis by CAP was directly associated with liver stiffness assessed by VCTE, a parameter primarily related to the degree of liver fibrosis, in the subgroup of type 1 GD patients on stable ERT for at least 2 years.

There are several theoretical assumptions that support an association between GD and liver steatosis. Firstly, besides being a terminal catabolic station, the lysosome acts as a metabolic signalling hub that is involved in nutrient sensing and energy homeostasis [12]. Increasing data have shown that lysosomal dysfunction and subsequent metabolic derangements are associated

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with several pathological conditions in humans, including lysosomal storage diseases, GD being the prototype of these inherited metabolic disorders, as well as obesity, MetS and liver steatosis [12, 38]. Secondly, alterations in the balance between compounds of the sphingomyelin-ceramide-glycosphingolipid pathways play a key role in some metabolic abnormalities, such as insulin resistance, that have been described in GD patients and in subjects with liver steatosis [13, 39]. Moreover, GD-specific treatment, in particular ERT, has been associated with significant weight gain in adults [8, 15]. With regard to this aspect, it has been shown that GD is characterized by an increased resting energy expenditure, which is significantly reduced by ERT; however, if the energy intake remains unchanged, the decrease in hypermetabolism during ERT determines an increase in weight and in fat mass [8, 40]. Finally, unhealthy lifestyles characterized by overnutrition, unbalanced diet, alcohol misuse and sedentariness, are likely overlooked in the current treated and aging population of GD patients [8]. Despite these premises, the presence of liver steatosis has rarely been evaluated in previously published cohorts of GD patients. Webb et al. reported a prevalence of liver steatosis evaluated by abdominal ultrasound of 37% among 42 type 1 GD patients from Israel [41]. A very recent study from Poland found that liver steatosis defined by CAP values >250 dB/m was present in 22% of a mixed cohort of 59 adult and paediatric, type 1 and type 3 GD patients [42]. The prevalence of liver steatosis in our study (40%) is similar to that reported by Webb [41], but significantly higher than that found in the Polish cohort [42]. Since aging is a strong determinant of the development of liver steatosis, the difference in the mean or median age between the three GD cohorts may partly account for this discrepancy. Indeed, the mean age of the Israeli cohort (49.2 years) was the same to that of our GD population (49.2 years) [41], whereas the median age in Polish GD patients was significantly lower (35 years) [42]. These data collectively suggest that the prevalence of liver steatosis in GD patients is remarkable and even seems to be higher than that reported in the general population, which ranges from 14% in Africa to 31-32% in South America and the Middle East [20].

The high rates of metabolic abnormalities described in treated GD patients may easily justify the above-mentioned finding [8]. It is well known that GD is strongly associated with peripheral insulin resistance [10, 39]; moreover, many aging GD patients develop type 2 diabetes in parallel with increasing weight and occurrence of overweight/obesity and MetS [15]. However, the

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factors associated with liver steatosis in GD patients have not been extensively analysed so far. Lipinski et al. found a significant and independent association between CAP values and BMI in their cohort of Polish GD patients, but the potential associations with other relevant metabolic variables were not explored in detail [42]. Here, we have comprehensively evaluated the factors associated with liver steatosis in GD patients for the first time. As for the general population [29], we showed that all the major components of the MetS, including visceral adiposity, altered glucose homeostasis, and high blood pressure, were associated with CAP values and/or the presence of significant steatosis. On the contrary, we did not find any association between CAP/liver steatosis and GD-related variables or ERT. Moreover, alcohol misuse was also associated with steatosis, suggesting that unhealthy lifestyle may have a major contribution in metabolic disturbances found in our GD patients. Future studies are needed to carefully investigate dietary patterns and physical activity in adult GD subjects.

One may question if CAP actually reflects the accumulation of triglycerides in hepatocytes, i.e. liver steatosis, in GD patients, or rather represents the storage of other lipid species characteristic of GD, such as glycosphingolipids in liver macrophages and Kupffer cells. Since the factors we found to be associated with CAP in our GD cohort are the same factors identified in cohorts of biopsy-proven patients with liver steatosis of different etiologies [30], we may safely infer that CAP values are representative of liver steatosis also in GD patients.

A previous work of our group among that same cohort of GD patients showed that several components of the MetS, including BMI and arterial blood pressure, were significantly and positively associated with liver stiffness in the subgroup of subjects on stable long-term ERT [5]. In the current study, we were able to demonstrate that liver steatosis, mainly attributable to MAFLD, is a major driver of liver fibrosis in GD patients on ERT. MAFLD is the most common chronic liver disease and is the most rapidly growing cause of liver cirrhosis, end-stage liver disease and HCC [19, 22]. As a consequence, MAFLD-related fibrosis may be a neglected contributing factor for the high incidence of HCC reported in GD patients [6, 43].

Some limitations of the current study have to be acknowledged. Firstly, the cohort is relatively small, thus our findings need to be replicated in larger, multicentre studies. Secondly, liver biopsy or magnetic resonance spectroscopy, that are the gold-standard for liver fat detection and

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quantification, were not performed. However, it should be emphasized that this is the first study in which, besides undergoing a comprehensive metabolic assessment, GD patients were also systematically evaluated for the presence of liver steatosis and fibrosis.

In conclusion, significant liver steatosis as evaluated by CAP is highly prevalent in adult type 1 GD patients, is associated with the features of the MetS and unhealthy lifestyle, and correlates with liver fibrosis in ERT-treated subjects. Since MAFLD is a strong risk factor for long-term liver-related complications, including HCC, and cardiovascular morbidity and mortality, it seems appropriate to include the evaluation of liver steatosis in the overall assessment of all adult GD patients. Metabolic complications, including MAFLD, should be regularly monitored, and lifestyle advices and interventions promoting healthy dietary patterns, avoidance of alcohol misuse, and regular physical activity should be encouraged in all GD patients.

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FIGURES LEGEND:

Figure 1. Correlations between controlled attenuation parameter and metabolic risk factors in the overall cohort.

Correlations between controlled attenuation parameter and body mass index (Panel A), waist circumference (Panel B) and number of factors of the metabolic syndrome (Panel C).

Figure 2. Correlation between controlled attenuation parameter and liver stiffness in the subgroup of patients on stable enzyme replacement therapy for at least 24 months.

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Table 1. General characteristics of 20 adult patients with type 1 Gaucher Disease	
Demographic data	
Age (years)	48 [18-78]
Male Sex	10 (50)
Gaucher Disease-related data	
Age at diagnosis (years)	26.5 [2-62]
Genotype	
N370S/N370S	8 (40)
N370S/Other	9 (45)
Other/Other	3 (15)
Gaucher Disease severity	
DS3	1.7 [0-6.7]
Moderate-marked GD (DS3)	9 (45)
SSI	6 [1-16]
Moderate-marked GD (SSI)	5 (25)
Splenectomy	7 (35)
Liver volume (cc)	1450 [1106-2826]
Spleen volume (cc)	426 [203-975]
On ERT (imiglucerase)	18 (90)
Months of ERT	109 [0-275]
Dose of ERT (U/kg/month)	50 [0-120]
Cumulative dose of ERT (U/kg)	5145 [0-15860]
Anthropometric data	
Weight (kg)	69 [52-104]
BMI (kg/m^2)	24.3 [19.1-31.4]
BMI $\geq$25 kg/m^2	8 (40)
Waist Circumference (cm)	90 [69-113]
Metabolic features	
Central obesity	5 (25)
Altered glucose homeostasis	2 (10)
High blood pressure	10 (50)
Diastolic blood pressure (mmHg)	78 [70-90]
Systolic blood pressure (mmHg)	130 [100-150]
Hypertriglyceridemia	1 (5)
Low HDL cholesterol	9 (45)
N° of factors of metabolic syndrome	1 [0-4]
Metabolic syndrome (ATPIII)	4 (20)
Biochemical data	

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ACE (IU/L)	31 [5-191]
Ferritin (ng/ml)	93 [4-518]
Platelets (1000/mmc)	177 [88-453]
AST (IU/L)	21 [13-36]
ALT (IU/L)	21 [8-58]
GGT (IU/L)	34 [5-143]
Albumin (g/dl)	4.4 [3.5-5]
Glycemia (mg/dl)	90 [72-110]
Insulinemia (mIU/L)	5.7 [2.1-21.3]
HOMA-IR (%)	1.3 [0.5-5.7]
HOMA-IR ≥2	3 (15)
HbA1c (%)	5.2 [4.2-5.9]
Triglyceridemia (mg/dl)	117 [25-275]
Total cholesterol (mg/dl)	193 [95-282]
HDL cholesterol (mg/dl)	44 [30-67]
LDL cholesterol (mg/dl)	125 [53-208]
Transient elastography data	
CAP (dB/min)	234 [165-358]
Significant steatosis	8 (40)
Liver stiffness (kPa)	4.8 [3-11.3]
Other data	
Alcohol consumption (g/day)	0 [0-50]
Significant alcohol consumption	2 (10)

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Table 2. Correlation of Controlled Attenuation Parameter with other relevant variables		
	Spearman's rho	**p**
Demographic data		
Age (years)	0.176	0.457
Gaucher Disease-related data		
Age at diagnosis (years)	0.002	0.992
DS3	-0.140	0.557
SSI	0.207	0.382
Liver volume (cc)	0.154	0.516
Spleen volume (cc)	-0.137	0.655
Months of ERT	0.276	0.239
Dose of ERT (U/kg/month)	-0.406	0.076
Cumulative dose of ERT (U/kg)	0.164	0.490
Anthropometric data		
Weight (kg)	0.609	**0.004**
BMI (kg/m^2)	0.671	**0.001**
Waist Circumference (cm)	0.575	**0.008**
Metabolic features		
Diastolic blood pressure (mmHg)	0.436	0.055
Systolic blood pressure (mmHg)	0.185	0.436
N° of factors of metabolic syndrome	0.470	**0.037**
Biochemical data		
ACE (IU/L)	-0.050	0.835
Ferritin (ng/ml)	0.243	0.302
Platelets (1000/mmc)	0.192	0.416
AST (IU/L)	0.422	0.064
ALT (IU/L)	0.377	0.102
GGT (IU/L)	0.293	0.210
Albumin (g/dl)	-0.018	0.939
Glycemia (mg/dl)	0.347	0.134
Insulinemia (mIU/L)	0.043	0.858
HOMA-IR (%)	0.159	0.502
HbA1c (%)	0.262	0.265
Triglyceridemia (mg/dl)	0.285	0.224
Total cholesterol (mg/dl)	-0.260	0.268
HDL cholesterol (mg/dl)	-0.031	0.897
LDL cholesterol (mg/dl)	-0.190	0.423
Transient elastography data		
Liver stiffness (kPa)	0.224	0.342

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Other data		
Alcohol consumption (g/day)	0.352	0.127

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Table 3. Comparison between type 1 Gaucher Disease patients with and without significant steatosis

	Patients without significant steatosis (n=12)	Patients with significant steatosis (n=8)	p*
Demographic data			
Age (years)	43 [16-78]	52 [37-76]	0.189
Male Sex	6 (50)	4 (50)	1.000
Gaucher Disease-related data			
Age at diagnosis (years)	27 [2-62]	29 [4-51]	1.000
Genotype			0.067
N370S/N370S	6 (50)	2 (25)	
N370S/Other	6 (50)	3 (38)	
Other/Other	0 (0)	3 (38)	
Gaucher Disease severity			
DS3	1.4 [0-6.3]	2.5 [0-6.7]	0.726
Moderate-marked GD	5 (42)	4 (50)	1.000
(DS3)	4.5 [1-13]	7.5 [4-16]	0.096
SSI	2 (17)	3 (38)	0.347
Moderate-marked GD	3 (25)	4 (50)	0.356
(SSI)	1410 [1108-2826]	1494 [1106-2300]	0.938
Splenectomy	380 [203-975]	513 [216-723]	0.877
Liver volume (cc)	11 (92)	7 (88)	1.000
Spleen volume (cc)	75 [0-244]	130 [9-275]	0.203
On ERT (imiglucerase)	58 [0-120]	45 [30-120]	0.129
Months of ERT	4970 [0-12200]	5375 [1080-15860]	0.487
Dose of ERT (U/kg/month)			
Cumulative dose of ERT (U/kg)			
Anthropometric data			
Weight (kg)	64 [52-82]	77 [58-104]	**0.023**
BMI (kg/m^2)	23.2 [19.1-26]	27.1 [21.1-31.4]	**0.007**
BMI $\geq$25 kg/m^2	2 (17)	6 (75)	**0.009**
Waist Circumference (cm)	85 [69-98]	95 [78-113]	**0.034**
Metabolic features			
Central obesity	0 (0)	5 (63)	**0.004**
Altered glucose homeostasis	0 (0)	2 (25)	0.147
High blood pressure	3 (25)	7 (88)	**0.020**
Diastolic blood pressure (mmHg)	73 [70-90]	88 [75-90]	**0.010**
Systolic blood pressure (mmHg)	128 [100-150]	138 [115-140]	0.159
Hypertriglyceridemia	0 (0)	1 (13)	0.400

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Low HDL cholesterol	5 (42)	4 (50)	1.000
N° of factors of metabolic syndrome	1 [0-2]	3 [0-4]	0.058
Metabolic syndrome (ATPIII)	0 (0)	4 (50)	**0.014**
Biochemical data			
ACE (IU/L)	35 [8-191]	25 [5-113]	0.643
Ferritin (ng/ml)	93 [4-342]	93 [29-518]	0.817
Platelets (1000/mmc)	160 [88-453]	198 [121-374]	0.440
AST (IU/L)	19 [13-31]	22 [17-36]	0.202
ALT (IU/L)	16 [8-46]	22 [19-58]	0.053
GGT (IU/L)	24 [5-143]	36 [13-88]	0.315
Albumin (g/dl)	4.4 [3.6-5]	4.3 [3.5-4.5]	0.258
Glycemia (mg/dl)	87 [78-93]	94 [72-110]	**0.027**
Insulinemia (mIU/L)	5.3 [2.7-8.8]	6.2 [2.1-21.3]	0.563
HOMA-IR (%)	1.1 [0.5-2]	1.6 [0.5-5.7]	0.280
HOMA-IR ≥2	0 (0)	3 (38)	**0.049**
HbA1c (%)	5.2 [4.2-5.9]	5.6 [4.9-5.9]	0.093
Triglyceridemia (mg/dl)	113 [25-137]	119 [70-275]	0.354
Total cholesterol (mg/dl)	196 [95-240]	173 [127-282]	0.247
HDL cholesterol (mg/dl)	44 [30-64]	45 [30-67]	0.969
LDL cholesterol (mg/dl)	132 [53-191]	105 [72-208]	0.375
Transient elastography data			
CAP (dB/min)	211 [165-245]	273 [251-358]	**<0.001**
Liver stiffness (kPa)	4.4 [3-8.1]	6.7 [3-11.3]	0.132
Other data			
Alcohol consumption (g/day)	0 [0-25]	0 [0-50]	0.392
Significant alcohol consumption	0 (0)	2 (25)	0.068

* Paerson Chi-square, Fisher's exact test or Mann-Whitney U test, where appropriate.

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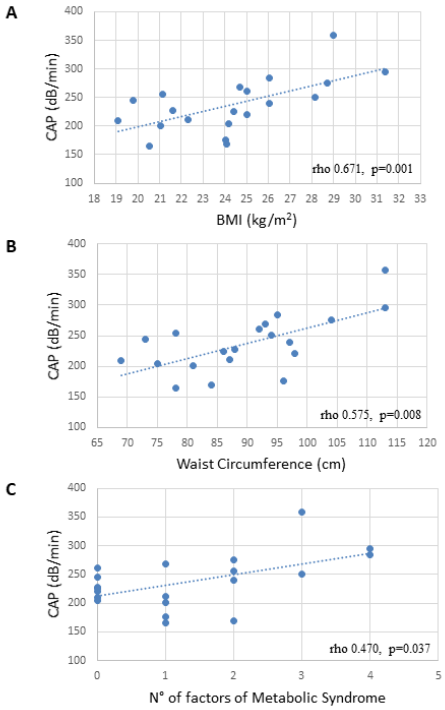

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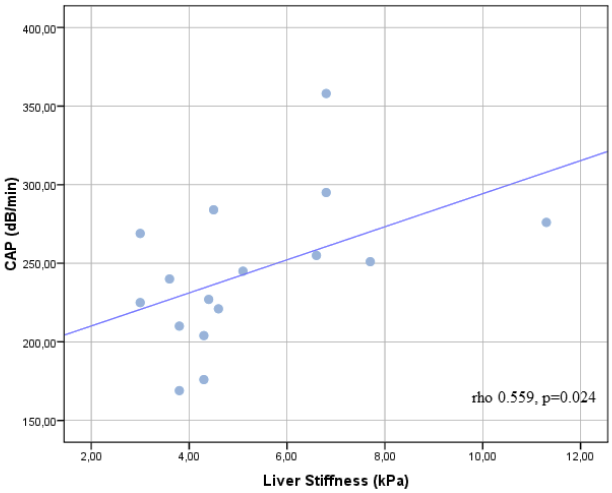

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