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Very low serum adiponectin levels in patients with type 1 Gaucher disease without overt hyperglycemia

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Abstract

Gaucher disease (glucocerebrosidase deficiency) is characterized by massive accumulation of lipid-laden macrophages in various tissues. Patients with Gaucher disease show a hitherto unexplained increase in hepatic glucose output. Because adiponectin is thought to influence hepatic glucose output, we studied its serum concentration in a cohort of patients with Gaucher disease. Serum adiponectin was indeed found to be markedly reduced in patients (median value, 3.1 μg/mL; range, 1.4-6.3 μg/mL) as compared with healthy subjects (median value 5.6 μg/mL range, 1.9-14.0 μg/mL). Successful treatment of patients was accompanied by an increase in serum adiponectin, from 3.1 to 3.6 μg/mL ($P = .002$). In healthy individuals, low levels of circulating adiponectin are generally associated with obesity. In patients with Gaucher disease, however, adiponectin levels did not correlate with body mass index. The hypoadiponectinemia in Gaucher patients is most likely attributable to their low-grade chronic inflammation. The characteristic storage macrophages produce inflammatory cytokines such as tumor necrosis factor α that is known to suppress adiponectin production. It is of interest that the very low adiponectin levels in Gaucher patients are not accompanied by hyperglycemia, contrary to their effect in obese individuals. It is hypothesized that the excessive hepatic glucose production in these patients balances the assumed increased glucose consumption by the massive amounts of storage macrophages. Hypoadiponectemia may play a regulatory role in preventing hypoglycemia in this condition.

1. Introduction

Gaucher disease is caused by the deficiency of the lysosomal enzyme glucocerebrosidase (EC 3.2.1.45). In the most common nonneuronopathic (type 1) variant of Gaucher disease, clinical manifestations are restricted to the viscera. The disorder is characterized by massive accumulation of glucosylceramide in tissue macrophages. The characteristic lipid-laden storage cells (Gaucher cells) predominantly accumulate in the spleen, liver, and bone marrow. Their presence results in hepatosplenomegaly, cytopenia, and bone complications. Gaucher disease can be efficiently treated by long-term intravenous administration of recombinant glucocerebrosidase [1]. This so-called enzyme replacement therapy (ERT) results in fast removal of storage cells, as indicated by the prominent reduction of plasma markers for Gaucher cells, the hydrolase chitotriosidase and the chemokine CCL18 [2-5]. More recently, an alternative treatment based on inhibition of glycosphingolipid biosynthesis by oral administration of the iminosugar *N*-butyldeoxynojirimycin was shown to be effective in type I Gaucher disease [6]. This so-called substrate reduction therapy (SRT) also results in major clinical improvement and leads to reduction in storage macrophages [7].

The disappearance of storage cells upon therapy can also be visualized by monitoring of the triglyceride content of the lumbar bone marrow by Dixon quantitative chemical shift imaging (QCSI) [8]. In severely affected patients with Gaucher disease, the adipocyte content of the bone marrow is extremely low because of infiltration of Gaucher cells [9]. Successful ERT or SRT gradually normalizes the bone marrow adipocyte content.

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Patients with Gaucher disease show intriguing alterations in metabolism. Their resting energy expenditure is dramatically elevated [10,11]. The hepatic glucose output increased by about 30%, however, without concomitant abnormalities in blood glucose concentrations [10]. A simple hormonal explanation for the high glucose turnover in Gaucher patients is so far lacking. Glucagon, (nor)epinephrine, cortisol, and growth hormone levels do not differ between healthy control subjects and Gaucher patients after 16 hours of fasting. Insulin is significantly higher in Gaucher patients compared with healthy controls [10]. The role of the prominent macrophage storage cells in the abnormalities in glucose metabolism of Gaucher patients is so far unclear. The effect of removal of storage cells by ERT on metabolic abnormalities has been partly investigated. Clinical improvement of Gaucher patients coincides with a rapid and clear reduction in resting energy expenditure. Contrary to this, even after 6 months of treatment only a modest correction in excessive hepatic glucose output occurs [12].

In recent times, much attention has been paid to the importance of adiponectin in the control of glucose and whole-body metabolism. Adiponectin is an abundant circulating hormone produced by adipocytes. Plasma levels in healthy nondiabetic subjects are reported to be 7.9 ± 0.5 μg/mL in men and 11.7 ± 1.0 μg/mL in women [13]. Adiponectin consists of an N-terminal collagenous repeat and a C-terminal globular domain that resembles the structure of tumor necrosis factor α (TNF-α). In muscle cells, both the globular as well as the full-length adiponectin are able to stimulate fatty acid oxidation and glucose uptake, whereas in hepatocytes, only full-length adiponectin is active in inhibiting gluconeogenesis [14]. Adiponectin occurs in different complexes, including low molecular weight (LMW) trimers, middle molecular weight (MMW) multimers, and high molecular weight (HMW) multimers [15,16]. The biological importance of these different species is controversial. Most of the features activated by adiponectin seem to involve the AMP-activated protein kinase (AMPK) pathway. Low circulating levels of adiponectin are considered to constitute a risk factor for developing impaired glucose tolerance and eventually type II diabetes mellitus [17]. Low adiponectin levels are negatively correlated with increased hepatic glucose production [18]. It is conceivable that the increased hepatic glucose output of symptomatic Gaucher patients is caused by an abnormally low level of adiponectin. Therefore, we studied serum adiponectin in a cohort of patients with type I Gaucher disease before and during treatment with EST or SRT. This article reports and discusses the outcome of this investigation.

Table 1
Patient characteristics before and during ERT

Patient No.	Sex	Age at start of ERT (y)	BMI (kg/m^2)	Change in BMI	Adiponectin levels at start of ERT (μg/mL)	Liver volume at start of ERT (mL)	Spleen volume at start of ERT (mL)	Chitotriosidase activity at start of ERT (nmol/mL per hour)	Bone marrow fat fractions at start of ERT (%)	Months of ERT at second adiponectin measurement
1	M	53	25	−1.00	3.42	3424	Sx	[a]	NK	126
2	M	42	24	4.00	2.60	3351	2029	19.833	NK	120
3	F	34	21	2.00	2.50	4919	Sx	NK	NK	73
4	M	24	23	4.00	2.04	2911	3354	[a]	NK	114
5	M	51	23	6.00	3.91	2393	Sx	6.417	34	114
6	M	48	25	4.00	1.56	3334	3118	13.072	24	114
7	F	39	19	3.00	3.07	1797	535	6.886	22	89
8	F	55	25	−3.00	5.71	1528	470	9.205	NK	138
9	M	44	21	5.00	3.24	2014	885	5.644	40	102
10	M	39	25	4.00	3.14	1830	574	7.917	29	110
11	F	47	25	.00	3.84	2387	1905	[a]	NK	119
12	M	34	20	2.00	1.87	2108	501	11.765	NK	73
13	M	19	20	1.00	3.46	2281	1220	14.056[b]	9	53
14	M	30	22	3.00	2.56	6542	Sx	21.707	NK	120
15	M	37	22	−1.00	2.65	2257	Sx	20.349	NK	138
16	M	26	18	5.00	1.54	5814	Sx	16.857[b]	10	88
17	M	32	17	4.00	3.08	3691	Sx	55.377	11	120
18	M	45	22	.00	2.29	5005	Sx	62.122	NK	143
19	F	35	19	2.00	6.28	4139	Sx	80.009	11	103
20	F	45	22	1.00	5.36	3139	1042	25.398	22	132
21	M	47	27	1.00	1.44	3678	2002	12.853[b]	18	120
22	M	49	22	1.00	4.96	2269	855	11.864	18	96
23	M	30	23	4.00	1.69	3426	4379	42.260	8	108
24	F	32	22	4.00	5.32	2485	766	8.320	7	49
25	F	16	17	5.00	5.36	1597	864	10.639	NK	120
26	M	59	28	4.00	3.64	3195	Sx	14.774[b]	NK	120

Sx indicates splenectomy; NK, not known.

[a] Chitotriosidase deficiency.

[b] Carrier of chitotriosidase mutation.

2. Patients and methods

2.1. Patients

All consecutive patients that were referred to our hospital between 1993 and 2001 with symptomatic disease necessitating the initiation of treatment and of whom enough material was available for analysis were included in this study. Twenty-eight (18 men, 10 women) patients with type I Gaucher disease and 26 controls matched on age (±5 years), sex, and body mass index (BMI; ±1 kg/m^2) were investigated. In all patients, a diagnosis of Gaucher disease was confirmed on the basis of deficient glucocerebrosidase activity in leukocytes. None of the patients was known to have diabetes or impaired fasting glucose levels. Before the initiation of ERT, glucose and insulin levels in the post-absorptive state were available in 8 patients, of whom 7 have been reported earlier [10]. In addition, random glucose levels were available for 16 patients. Twenty-six patients received ERT (imiglucerase, Genzyme, Boston, MA), and 2 patients received SRT (*N*-butyldeoxynojirimycin, Zavesca, Actelion Pharmaceuticals, Allschwil, Switzerland). Samples were taken before initiation of treatment. A second serum sample was taken after several years of therapy (median, 114 months of treatment; range, 49 to 143 months). Samples were collected with the consent of the patients.

2.2. Disease severity assessment

Before the start of treatment and during follow-up, various disease parameters were assessed, as depicted in Table 1. Liver and spleen volume were measured by spiral computed tomography scan. Bone marrow fat fraction of the lumbar spine was measured by QCSI as described in detail by Maas et al [19] and Hollak et al [20]. Chitotriosidase was determined by the standard enzyme activity assay with 4 MU-chitotriose (4-methylumbelliferyl β-D-*N*,*N*′,*N*″-triacetylchitotriose; Sigma, St Louis, MO) as substrate as previously described [2].

2.3. Adiponectin measurements

Total serum adiponectin concentration was measured by using an enzyme-linked immunosorbent assay. Commercially available anti–human adiponectin capture and detection antibodies and recombinant adiponectin as standard were used (R&D Systems, Minneapolis, MN). The inter- and intra-assay coefficients of variation in our laboratory were less than 16% and less than 4%, respectively. If the adiponectin level was measured more than once, the mean of the measurements is presented.

2.4. Immunoblotting

Sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) was performed according to the standard Laemmli method. The sample buffer was 3% SDS, 50 mmol/L TRIS-HCl (pH 6.8), and 15% glycerol. The sample was diluted 1:10 with phosphate-buffered saline and then mixed with 3 × sample buffer and incubated for 1 hour at room temperature. For immunoblotting, proteins separated by SDS-PAGE were transferred to nitrocellulose membranes. The membranes were blocked with commercially available blocking buffer (Pierce, Rockford, IL) supplemented with 0.1% Triton X-100, followed by overnight incubation with the primary antigen (biotinylated anti–human adiponectin antibody, R&D Systems) diluted 1:500 in blocking buffer. After washing, the membranes were incubated with streptavidin-horseradish peroxidase antibody diluted 1:10 000 for 1 hour at room temperature and then washed and incubated with entry-level enhanced chemiluminescence (ECL) solution and exposed to x-ray film.

2.5. Statistical analysis

Results are given as median and range. For comparison of independent groups (eg, patients vs healthy control subjects), a Mann-Whitney test was used. For comparison between paired data (measurements before and after therapy), a Wilcoxon signed rank test was used. Correlations were calculated by using rank correlation (Spearman ρ). In all cases, a P value less than .05 was considered statistically significant.

3. Results

3.1. Adiponectin levels

Table 1 shows the characteristics of the studied patients at baseline and after the prolonged period of ERT. The control population was successfully matched for sex, BMI (P = .678), and age (P = .949) to the Gaucher patients (only the ERT-treated patients were matched).

Serum adiponectin levels were significantly lower (P < .001) in untreated patients compared with healthy controls.

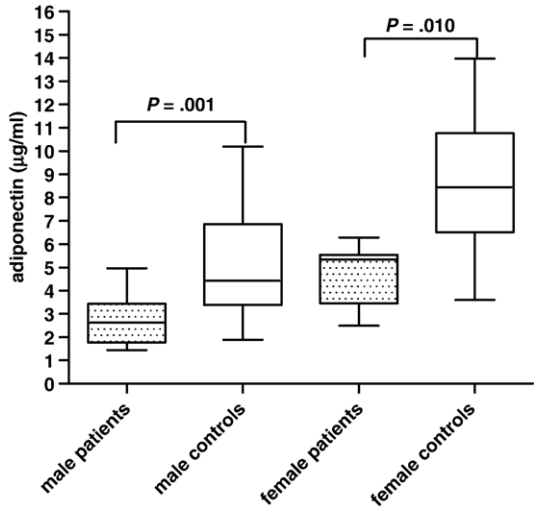

Fig. 1. Serum adiponectin in Gaucher patients. Adiponectin serum concentrations (μg/ml) in untreated male (n = 18) and female (n = 8) Gaucher patients and age and BMI matched male (n = 18) and female (n = 8) control subjects.

Median serum values were 3.1 μg/mL (range, 1.4-6.3 μg/mL) for patients vs 5.6 μg/mL (range, 1.9-14.0 μg/mL) for controls (Fig. 1). Adiponectin levels are known to be lower in men than in women. This difference was also observed in the Gaucher population: median plasma adiponectin level was 2.7 μg/mL (range, 1.4-5.0 μg/mL) in male patients and 5.3 μg/mL (range, 2.5-6.3 μg/mL) in female patients (Fig. 1) (P = .003). Both female and male patients showed lower adiponectin levels than matched controls.

The median BMI in the patient group was 22 kg/m^2 (range, 17-28 kg/m^2). The patient group included only 2 obese patients (BMI >25 kg/m^2). Adiponectin levels in untreated Gaucher patients did not correlate with their BMI (ρ = −0.11, P = .59) (Fig. 2). Glucose levels before the initiation of ERT were normal in all but 1 patient (median, 5.0 mmol/L; range, 4.4-6.9 mmol/L). For all patients in the postabsorptive state (n = 8), glucose levels were normal. In these 8 patients, insulin levels in the postabsorptive state were slightly elevated as previously reported (median, 51.8 pmol/L; range, 41.4-75.9 pmol/L) [10]. No correlation was found between glucose levels and adiponectin levels (ρ = 0.2, P = .37) and between insulin and adiponectin levels (ρ = 0.5, P = .2).

3.2. Relation between adiponectin levels and indicators of disease severity

There was no significant difference between adiponectin levels in patients who underwent splenectomy compared with nonsplenectomized patients (P = .4) (data not shown). Liver volume and spleen volume were not significantly correlated with plasma adiponectin levels (r = 0.134, P = .51, and r = 0.482, P = .06, respectively). Adiponectin levels did not correlate with plasma chitotriosidase activity (r = −0.032, P = .881). The triglyceride content of lumbar spine bone marrow as assessed by QCSI also did not correlate with the serum adiponectin levels of Gaucher patients (r = −0.13, P = .527).

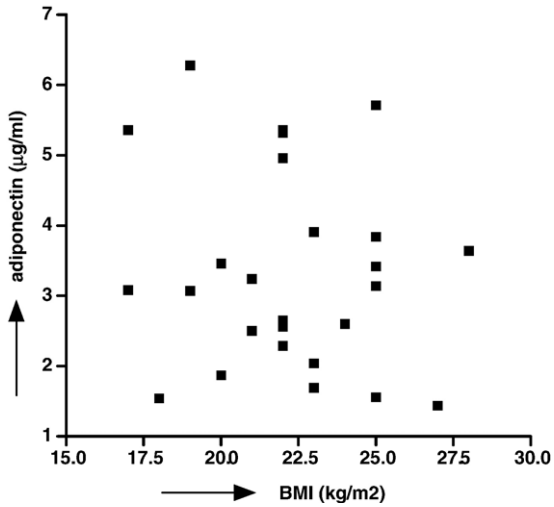

Fig. 2. BMI and serum adiponectin levels. Correlation between BMI (kg/m^2) and serum adiponectin level (μg/ml) in untreated Gaucher patients (ρ = −0.11, P = 0.59).

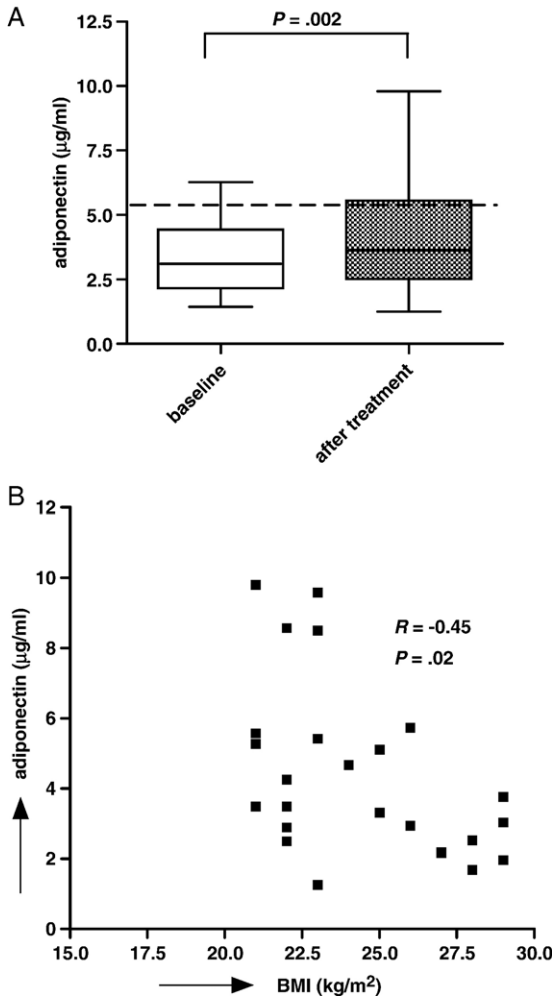

Fig. 3. Effect of therapy on serum adiponectin in Gaucher patients. Plasma adiponectin levels (μg/ml) in Gaucher patients before (n = 24) and after treatment with enzyme replacement therapy. The dotted line indicates the median control adiponectin level (A) correlation between BMI (kg/m^2) and plasma adiponectin level (μg/ml) in treated Gaucher patients (B).

3.3. Effects of treatment on adiponectin levels, BMI, and organomegaly

After several years of treatment with ERT (median, 114 months; range, 49 to 143 months), the adiponectin level in Gaucher patients increased marginally, but significantly (median serum adiponectin: 3.6 μg/mL; range, 1.3-9.8 μg/mL) compared with baseline (median, 3.1 μg/mL; range, 1.4-6.3 μg/mL). The adiponectin levels of Gaucher patients receiving ERT increased slightly but did not reach the level of those of BMI-matched controls (P = .022). BMI increased during therapy from a median of 22 kg/m^2 (range, 17-28 kg/m^2) to 23.5 kg/m^2 (range, 21-32 kg/m^2), which was highly significant (P < .0001). In treated patients, the normal negative correlation between body weight (BMI) and adiponectin levels was

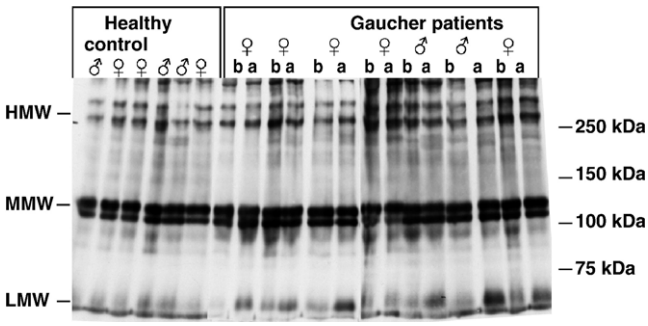

Fig. 4. Adiponectin isoforms in Gaucher and control serum samples. Separation of low molecular, middle molecular and high molecular forms of adiponectin by SDS_PAGE. Profile of adiponectin forms in six healthy control subjects (3 male, 3 female) and seven Gaucher patients (5 female and 2 male) before (b) and after (a) enzyme replacement therapy.

restored (Fig. 3). Serum adiponectin levels were also determined in 2 female Gaucher patients who received SRT. On therapy initiation, both had a normal BMI (<25 kg/m^2) and low adiponectin levels (7.3 and 4.5 μg/mL). In both patients, the serum adiponectin increased during therapy (in increments of 3.3 and 0.84 μg/mL, respectively). No correlation could be established between absolute or relative reductions in organomegaly, bone marrow fat fraction, or chitotriosidase and adiponectin levels (data not shown).

3.4. Adiponectin isoforms

Adiponectin circulates as the LMW, MMW, and HMW form. No striking differences could be detected by Western blot analysis in the distribution of adiponectin forms in serum samples of Gaucher patients as compared with corresponding healthy control subjects (Fig. 4). The treatment with ERT in Gaucher patients did not markedly change the distribution of adiponectin forms, although the increase in LMW adiponectin was prominent in some patients.

4. Discussion

Our investigation revealed that patients with type 1 Gaucher disease show remarkably low serum levels of adiponectin. Hypoadiponectinemia is common in obese individuals [21]. However, in Gaucher patients, low adiponectin levels are clearly not caused by the presence of excess adipose tissue. The body weight of Gaucher patients does not correlate with adiponectin levels. This is further emphasized by the fact that successful therapy of patients often results in an increase in adiponectin as well as in body weight. In addition, a negative correlation between circulating adiponectin levels and insulin resistance has been demonstrated, but preliminary results in our study do not indicate a relationship between adiponectin and insulin levels.

The cause of the lowering of adiponectin levels in symptomatic patients is not precisely known. Serum adiponectin levels in Gaucher patients do not strictly correlate with Gaucher cell burden as reflected by plasma chitotriosidase level, liver and spleen volume, or QCSI analysis of bone marrow infiltration by storage cells. Enhanced clearance of serum adiponectin by an increased mass of macrophages in Gaucher patients therefore offers no likely explanation for the observed low serum adipocytokine level. Low-grade systemic inflammation is a hallmark of Gaucher disease [22]. Massive storage of glucosylceramide in macrophages leads to specific activation of these Gaucher cells, manifested by the release of cytokines (TNF-α, interleukin [IL] 6, IL-10) and other factors [2,3,23-26]. In vitro, high concentrations of TNF-α and IL-6 are known to inhibit adiponectin production by isolated human adipose tissue [27]. It might be speculated that the (locally) altered cytokine profile in adipose tissue of Gaucher patients inhibits adiponectin production and causes the low serum adipocytokine levels. Obesity is another condition in which low adiponectin is associated with low-grade systemic inflammation and elevated circulating levels of TNF-α and IL-6, partially produced by macrophages residing in white adipose tissue [28].

Despite the impressive clinical improvement of Gaucher patients receiving ERT, this is accompanied by relatively modest corrections in adiponectin levels. No correlation could be established between decreases in organomegaly and increase in adiponectin levels. It has to be realized that ERT or SRT treatments result in only partial removal of Gaucher cells, without complete correction of low-grade systemic inflammation [22]. This may contribute to persistent suppression of adiponectin formation and prevent complete normalization of the serum adiponectin level. Our earlier observation that hepatic glucose production remains high in Gaucher patients receiving ERT for 6 months is consistent with the persistence of reduced adiponectin levels [10].

More recently, attention has been paid to the multimeric composition of adiponectin. Adiponectin may occur as the LMW or HMW form. The HMW multimer is specifically involved in the activation of AMPK in hepatocytes [15,16]. In contrast, only the LMW trimer is able to activate AMPK in muscle [29]. It has been proposed that the HMW adiponectin in particular suppresses hepatic glucose output [30].

We observed no abnormalities in the distribution of multimeric adiponectin isoforms. Moreover, therapy did not result in marked changes in the distribution of various isoforms.

Hypoadiponectinemia is generally considered an unfavorable condition associated with obesity, insulin resistance, and type II diabetes mellitus [21,31,32]. It is intriguing that symptomatic Gaucher patients, despite their very low adiponectin levels, do not develop apparent hyperglycemia. We hypothesize that in Gaucher disease, there is an increased glucose consumption by the massive amounts of storage macrophages and that the liver responds with an increase in glucose production. Hypoadiponectemia could therefore play a role by preventing hypoglycemia.

In conclusion, symptomatic patients with type 1 Gaucher disease show remarkably low serum adiponectin levels. Nevertheless, Gaucher patients are generally far from overweight and show no overt hyperglycemia. Consistent with

their low adiponectin levels, hepatic glucose output in Gaucher patients is high. Further investigations on insulin responsiveness of Gaucher patients and the factors mediating low adiponectin production are warranted. It is of interest to note in this connection that very recently, Vainio et al reported impaired insulin receptor activation in a mouse model for type C Niemann-Pick disease, another lysosomal storage disorder characterized by the presence of lipid-laden macrophages [33].

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