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ORIGINAL ARTICLE

Activated and Memory T Lymphocytes in Children with Gaucher Disease

Asmaa M. Zahran[1] · Azza A. Eltayeb[2] · Khalid I. Elsayh[2] · Khaled Saad[2] · Faisal-Alkhateeb Ahmad[2] · Ahmad I. M. Ibrahim[2]

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Abstract Gaucher disease (GD) is the most prevalent lysosomal storage disorder. Gaucher disease is associated with remarkable alterations in the immune system, and GD patients are more susceptible to infections and are at a higher risk of developing autoimmune disorders and malignancies. In a case–control study, we used three-color flow cytometric immunophenotyping for determination of the frequency of lymphocyte subpopulations and activated T lymphocytes among 18 children with GD1 under enzyme replacement therapy managed in Assiut University Hospitals. We found significant increases in the frequencies of total lymphocytes, $CD19^+$, $CD3^+$, $CD4^+$, and $CD8^+$ in children with GD1 when compared to healthy control. The frequencies of activated T lymphocytes ($CD3^+HLA\text{-}DR^+$), activated T-helper cells ($CD4^+HLA\text{-}DR^+$), and activated T-suppressor/cytotoxic cells ($CD8^+HLA\text{-}DR^+$) were significantly higher in GD1 as compared to healthy children. Our data show that the increased proportion of activated T lymphocytes in children with GD1 raises the issue of their possible involvement in the pathogenesis of the immune dysfunction seen in these patients. Our data suggested that the activated T lymphocytes could play a role in the clinical course of GD1. The relationship of these cells to immune disorders in GD1 children remains to be determined.

✉ Khaled Saad
ksaad8@yahoo.com; khaled.ali@med.au.edu.eg

[1] Clinical Pathology Department, South Egypt Cancer Institute, Assiut University, Assiut, Egypt

[2] Pediatric Department, Faculty of Medicine, Assiut University, Assiut 71516, Egypt

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Introduction

The most prevalent lysosomal storage disorder, Gaucher disease (GD), is an autosomal recessive hereditary disorder, resulting from an abnormal structure and/or impaired function of the enzyme glucocerebrosidase, which leads to insufficient cleavage of glucosylceramide to glucose and ceramide. Consequently, undigested glucosylceramide is accumulated in the macrophageal lysosomes of the reticuloendothelial system, leading to multi-organ dysfunction, which involves the bone marrow, liver, and spleen, resulting in cytopenia and hepatosplenomegaly (Bettman et al. 2015; Giraldo et al. 2016; Sotiropoulos et al. 2015). Gaucher disease has been classified into three subtypes according to the presence or absence of neurological features. Type 1 Gaucher disease (GD1) is the most common, and is characterized by the absence of neurological manifestations. GD2 and GD3 are characterized by acute and chronic neurologic symptoms, respectively (Bettman et al. 2015; Giraldo et al. 2016). Clinical and experimental studies have shown that GD patients exhibit various immunological abnormalities. Patients with GD, often experience slow resolution of infections, are more susceptible to infections and are at a higher risk of developing autoimmune disorders and malignancies. These phenomena may indicate a functional immune impairment in patients with GD (Bettman et al. 2015; Giraldo et al. 2016; Matta et al. 2016). Tissue distortion by foamy macrophages, resulting in extensive inflammation, was suggested to play a major role in the development of GD-related bone disease and organomegaly (Bettman et al. 2015). However,

the mechanisms responsible for the reported immune-related symptoms remain to be explained. To the best of our knowledge, the data on activated T lymphocytes cells in GD1 children are very limited. Therefore, the aim of this study was to describe the changes in lymphocyte subpopulations and activated T lymphocytes ($CD3^{+}HLA\text{-}DR^{+}$) in children with GD under enzyme replacement therapy (ERT) managed in Assiut University Hospitals.

Materials and Methods

Study Design and Population

This single-center prospective case–control study was carried out in Pediatric Hematology Unit, Children Hospital Assiut University. The study was approved by the Assiut University ethics committee and was conducted in accordance with the Declaration of Helsinki. An informed written consent in accordance with Assiut University Ethical Committee guidelines was taken from all guardians of patients and controls.

Patients

The study included 18 pediatric patients with GD1 aged 2–14 years (10 males and 8 females). All cases were recruited from Assiut University Pediatric Hematology Unit, Assiut University, Egypt. The study included 20 age and sex matched healthy children as a control group. In our center, all patients with GD received ERT, imiglucerase in a dose of 45 IU every two weeks by intravenous infusion.

Inclusion Criteria

1. Confirmed diagnosis of GD. Diagnosis of GD had been confirmed by the detection of low β-glucosidase activity in peripheral blood leukocytes. The assay is performed in blood leukocytes using a fluorescent substrate, 4-methyumbelliferone β-glucoside.
2. Subjects on ERT.

Exclusion Criteria

1. Unconfirmed diagnosis of GD.
2. Subject or guardian unable to provide consent.
3. Any chronic immunosuppressive state.
4. Any patient had recent infection or received any immunosuppressive medications, e.g., steroids, etc., during 1 month prior to enrollment that were excluded from the study.

Methods

Clinical and treatment records of all studied patients were reviewed. All clinical characteristics and current health status of GD1 patients managed in Assiut University Hospitals were collected. These included the patient's age, sex, and age at the start of ERT. We collected the details of all documented infections for all GD1 patients and controls in the previous 24 months before the study.

Baseline measurements included standard weight, height, complete blood count, abdominal ultrasonography, plain radiography of the chest and lower limbs, and two-dimensional echocardiography.

Flow Cytometric Detection of Activated and Memory T Lymphocytes

Blood was obtained during a scheduled appointment for patients' evaluation. All estimations were performed in the absence of a recent vaccination or any acute or chronic infection or any other known, active inflammatory condition. Fluoroisothiocyanate (FITC)-conjugated anti CD4, phycoerythrin (PE) conjugated anti CD8, peridinium-chlorophyll-protein (Per-CP)-conjugated anti HLA-DR, and allophycocyanin-conjugated anti CD3 were used to detect activated T lymphocytes. FITC-conjugated anti CD4, PE-conjugated anti CD8, and Per-CP-conjugated anti CD28 were used to detect memory T lymphocytes. All monoclonal antibodies were purchased from Becton–Dickinson (BD Biosciences, San Jose, CA, USA). Fifty microlitre of blood sample was incubated with 5 µl of CD4, CD8, HLA-DR, and CD3 in one tube and with CD4, CD8, and CD28 in another tube for 15 min at room temperature in the dark. Following incubation, red blood cell lysis, and washing with phosphate buffer saline (PBS) were done. The cells were resuspended in PBS, and were analyzed by FACSCalibur flow cytometry with CellQuest software (BD Biosciences, USA). An isotype-matched negative control was used with each sample. Forward and side scatter histogram was used to define the lymphocyte population (R1), and then, the percentage of activated T and memory T lymphocytes was detected, as shown in Fig. 1.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences, version 16.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as mean ± SD for continuous variables and percentages for categorical variables. Mann–Whitney test was used to analyze continuous variables, whereas Chi-square test was used to analyze

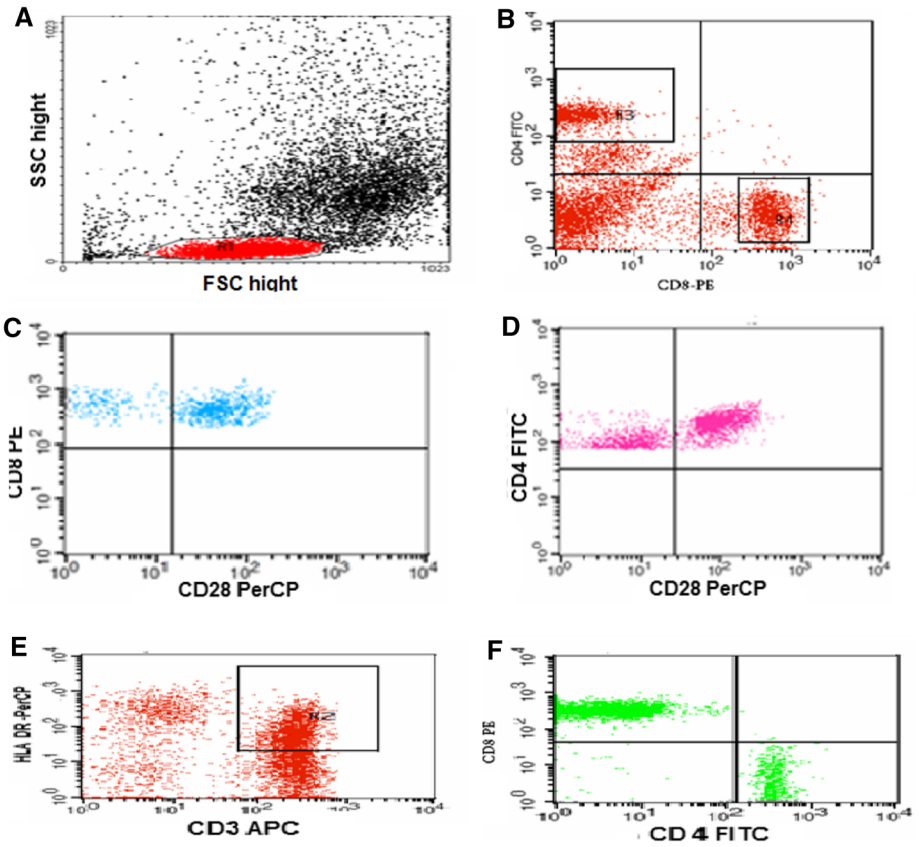

Fig. 1 Flow cytometric analysis of lymphocyte subsets in Gaucher patients. **a** Forward and side scatter histogram was used to define the lymphocytes population; **b** $CD4^+$ and $CD8^+$ cells were then gated for further analysis of memory T cells by detection of the expression of CD28 in $CD4^+$ and $CD8^+$ cells (**c**, **d**); **e** activated T lymphocytes were then gated (cells that positive for CD3 and HLA DR) within the lymphocyte population; **f** the expression of CD4 and CD8 within the activated T lymphocytes was then detected

categorical variables. The *p* value is considered statistically significant when less than 0.05. Spearman correlation coefficient was used to examine the correlation among different studied parameters.

Results

Patients' characteristics, including age, sex, weight, height, and body mass index (BMI), are shown in Tables 1 and 2. The median age of onset of GD1 symptoms was 2.7 years (range 1.2–11.5 years), with diagnosis occurring at a median age of 2.9 years (range 1.5–12 years). There were no significant differences in median age and sex distributions between GD1 patients and controls. The median weight, height, and BMI of patients were significantly lower than healthy age- and sex-matched controls. Seventy-two percent of our series with GD1 had weight for age between 5th and 25th percentile, and 28 % were between 25th and 50th percentile. Forty-four percent of children with GD1 had height for age between 5th and 25th percentile, 33 % were between 25th and 50th percentile, and 23 % of patient had height percentile between 50th and 75th. BMI was calculated for all patients. Nine patients (50 %) were underweight (<15th percentile of BMI), eight patients had normal BMI (15–85th percentile), and only one patient was overweight (BMI > 85–97th percentile). The median liver and spleen spans were significantly higher in children with GD1 as compared to controls. Skeletal abnormalities were found in 17 patients (94.4 %). Erlenmeyer flask deformity was found in 15 patients, kyphoscoliosis in one patient ,and avascular necrosis in one patient. Assessment of bone mineral density was done in six patients; osteopenia was found in only one of them.

As a summary, during the four-year period in which ERT has been used for GD patients in our center, we have observed the evolution of patients with different characteristics: (a) improvement of the mean weight *z* score from −1.28 to −0.3; (b) improvement of the mean height *z* score from −0.78 to 1.3; (c) improvement of the mean hemoglobin level 7.1–10.1, with elimination of blood transfusion dependency in all patients; (d) the mean platelet counts were raised 71.000–215.000/dl; (e) hepatic and splenic volumes were reduced 10 and 13 %, respectively. These improvements occurred mainly during the first 12–24 months of treatment.

Tables 3 and 4 show the hematological parameters and lymphocyte subsets in GD1 patients and controls. There were no statistically significant differences in platelet counts in the peripheral blood between GD1 group and the controls. Total leukocyte and neutrophil counts were significantly higher in children with GD1 as compared to

Table 1 Baseline characteristics of Gaucher patients and controls

Item	Gaucher patients ($n = 18$)	Controls ($n = 20$)	p value
Age (years)			
Range	2–14	2–13	–
Median ± SD	6.15 ± 2.9	6.40 ± 3.1	NS
Sex (male/female)	10/8	11/9	NS
Height (cm)			
Range	67–135	75–150	–
Median ± SD	98 ± 22.4	122 ± 30.1	0.001
Weight (kg)			
Range	7–30	10–36	–
Median ± SD	20 ± 3.4	24 ± 4.5	0.01
BMI	18.82 ± 7.2	20.34 ± 6.0	0.01
Liver span (cm)[a]			
Range	7–15	6–10	–
Median ± SD	9.1 ± 4.4	7 ± 1.2	0.004
Spleen span (cm)[a]			
Range	4–20	5–10	–
Median ± SD	9.9 ± 5.4	7 ± 0.9	0.01

Mann–Whitney U test. $p \leq 0.05$ is significant. Data represented as mean ± SD

NS non-significant

[a] Data were obtained at the time of flow cytometric assessment

Table 2 Details of all studied GD1 patients

Patient ID	Age (years)	Sex	ERT duration (months)	Age at flow cytometric analysis (months)
1	2	Male	7	22
2	4	Female	26	42
3	4	Male	13	40
4	3.5	Female	18	35
5	5	Female	20	48
6	4	Male	26	35
7	5	Male	24	52
8	3	Male	24	33
9	3	Female	29	33
10	3.5	Male	29	40
11	5	Male	21	54
12	10	Male	38	111
13	14	Male	42	160
14	7	Female	48	79
15	3	Female	23	31
16	4	Female	20	38
17	3	Male	28	32
18	2.5	Female	10	28

Table 3 Some hematological and laboratory parameters in Gaucher patients and controls

Cell type/subpopulation (unit) Mean ± SD	Gaucher patients ($n = 18$)	Controls ($n = 20$)	p value
White blood cell count ($\times 10^9$/L)	12.62 ± 3.40	9.49 ± 11.01	0.01
Hemoglobin (g/dl)	10.1 ± 1.35	12.5 ± 0.9	0.04
Platelets ($\times 10^9$/L)	215.75 ± 100.93	225.11 ± 116.23	NS
Neutrophil ($\times 10^9$/L)	5.4 ± 0.85	4.81 ± 0.31	0.021
Monocyte ($\times 10^5$/ml)	6.7 ± 1.5	7.2 ± 2.3	NS
Ferritin (ng/ml)	210 ± 85	78 ± 25	0.001
C-reactive protein	11.4 ± 2.5	1.1 ± 0.5	0.0001
Serum albumin (g/dl)	3.2 ± 1.2	3.4 ± 2.7	NS

Mann–Whitney U test. $p \leq 0.05$ is significant. Data represented as mean ± SD

NS non-significant

controls. The mean hemoglobin level was significantly lower in GD1 group when compared to controls ($p = 0.04$). No other causes of anemia, such as iron deficiency, thalassemia trait, and other hemoglobinopathies, were found in our series.

In GD1 patients, there were significant increases in the absolute numbers of lymphocytes ($p = 0.001$) and percentage of total lymphocytes ($p = 0.033$) when compared to controls. Moreover, the absolute numbers and percentages of B-lymphocyte ($CD19^+$) were significantly higher in GD1 group when compared to control (Table 4).

Three-color flow cytometric immunophenotyping of GD1 patients' peripheral blood showed that there were significant increases in the absolute numbers of T lymphocytes ($CD3^+$) ($p = 0.001$) and percentage of T lymphocytes ($p = 0.001$) when compared to healthy children (Table 2). The mean absolute numbers of helper T lymphocytes and cytotoxic T lymphocytes and percentage of cytotoxic T lymphocytes were significantly higher in GD1 group when compared to control; however, there was no significant difference between the two groups in the percentage of helper T lymphocytes and $CD4^+/CD8^+$ ratio (Table 2).

We found significant increases in the absolute numbers of activated T lymphocytes ($CD3^+HLA\text{-}DR^+$) ($p = 0.001$) and frequency of $CD3^+HLA\text{-}DR^+$ ($p = 0.001$) in children with GD1 as compared to healthy children. Furthermore, the frequencies of activated T-helper cells ($CD4^+HLA\text{-}DR^+$) ($p = 0.002$) and activated T-suppressor/cytotoxic cells ($CD8^+HLA\text{-}DR^+$) ($p = 0.0001$) were significantly higher in GD1 (Table 4). There was no significant difference between the patients and controls in the frequencies of $CD4^+CD28^+$ and $CD8^+CD28^+$.

Table 4 Lymphocytes subsets in Gaucher patients and controls

Cell type/subpopulation (unit)	Gaucher patients ($n = 18$)	Controls ($n = 20$)	p value
Total lymphocytes (%)	58.06 ± 12.37	49.36 ± 10.70	0.033
Total lymphocytes ($\times 10^9$/L)	7.22 ± 1.60	4.68 ± 1.01	0.001
B lymphocytes ($CD19^+$) (%)	15.13 ± 3.06	10.83 ± 1.12	0.02
B lymphocytes ($CD19^+$) ($\times 10^9$/L)	1.08 ± 0.22	0.48 ± 0.05	0.001
T lymphocytes ($CD3^+$) (%)	72.30 ± 9.02	60.09 ± 11.13	0.001
T lymphocytes ($CD3^+$) ($\times 10^9$/L)	5.31 ± 0.65	2.83 ± 0.52	0.001
Helper T lymphocytes ($CD4^+$) (%)	38.69 ± 8.42	40.27 ± 8.84	NS
Helper T lymphocytes ($CD4^+$) ($\times 10^9$/L)	2.07 ± 0.43	1.16 ± 0.27	0.01
Cytotoxic T lymphocytes ($CD8^+$) (%)	32.47 ± 8.42	24.50 ± 6.46	0.005
Cytotoxic T lymphocytes ($CD8^+$) ($\times 10^9$/L)	1.70 ± 0.42	0.71 ± 0.17	0.001
$CD4^+/CD8^+$ ratio	1.30 ± 0.58	1.56 ± 0.87	NS
Activated T lymphocytes ($CD3^+HLA\text{-}DR^+$) (%)	18.75 ± 8.64	12.16 ± 4.03	0.030
Activated T lymphocytes ($CD3^+$ $HLA\text{-}DR^+$) ($\times 10^9$/L)	0.95 ± 0.45	0.33 ± 0.11	0.001
Activated T-helper cells ($CD4^+HLA\text{-}DR^+$) (%)	9.81 ± 1.76	4.52 ± 2.37	0.002
Activated T-suppressor/cytotoxic cells ($CD8^+HLA\text{-}DR^+$) (%)	14.09 ± 8.16	9.68 ± 2.29	0.0001
$CD4^+CD28^+$ (%)	9.35 ± 4.16	8.89 ± 4.54	NS
$CD8^+CD28^+$ (%)	26.86 ± 8.62	25.52 ± 7.08	NS

Mann–Whitney U test. $p \leq 0.05$ is significant. Data represented as mean ± SD

CD cluster of differentiation, *NS* non-significant

Table 5 Comparison between GD1 patients and controls in frequency of infections

Variables[a]	GD1 patients ($n = 18$) %	Controls ($n = 20$) %	p value
Total number of infections	74.5	31.3	<0.01
Bacterial upper respiratory tract infections	56.8	42.3	<0.01
Viral upper respiratory tract infections	67.8	34.8	<0.05
Lower respiratory tract infections	32.3	6.6	<0.0001
Gastrointestinal infections	17.6	14.9	NS
Central nervous system infections	12.3	1.3	0.01

NS non-significant

[a] Each patient could appear in more than subcategory of infections

Table 5 shows the differences in rates of infection between GD1 patients and controls. GD1 patients had significantly higher percentages of all types of infections except gastrointestinal infections when compared to healthy control.

The frequencies of activated T lymphocytes had significant positive correlations with serum ferritin ($r = 0.53$; $p < 0.01$) and CRP ($r = 0.42$; $p = 0.01$). In addition, the frequencies of activated T lymphocytes had significant positive correlations with total rates of infections ($r = 0.46$; $p < 0.05$). There were no significant correlations between activated T lymphocytes percentages and patients age, sex, and age at onset of ERT.

Discussion

Gaucher disease is one of the lysosomal storage disorder with significant changes in the immune system, which is clinically manifested as an impairment in the host defense against microbial infections with an increase in the incidence of malignancies, hypergammaglobulinemia (i.e., monoclonal or polyclonal gammopathies) and the production of serum autoantibodies (Castaneda et al. 2008; Matta et al. 2016; Pandey and Grabowski 2013). In addition, numerous reports have shown several laboratory abnormalities leading to a systemic chronic proinflammatory response in patients with GD that may apparent clinically as autoimmune disorders and malignancy (Castaneda et al. 2008; Pandey and Grabowski 2013).

To the best of our knowledge, our study is the first study investigating changes in lymphocyte subpopulations and activated T lymphocytes ($CD3^+HLA\text{-}DR^+$) in children with GD under ERT. The analysis of data herein showed significant increases in the frequencies of total lymphocytes, $CD19^+$, $CD3^+$, $CD4^+$, and $CD8^+$ in children with GD1 when compared to healthy control. B cells are critical for humoral immune responses, and they have antigen presenting cells-like functions to generate T-cell-mediated immune responses (Pandey and Grabowski 2013). B

lymphocytes are classified into two subtypes: B-1 and B-2. B1 cells are present in the pleural cavities, peritoneal cavities, spleen, and Peyer's patches of the intestine, whereas B2 cells are present in spleen and lymph nodes (Arikan-Ayyildiz et al. 2011; de Fost et al. 2006; Pandey and Grabowski 2013). B1 cells can develop into B-cell chronic lymphocytic leukemia, and GD has been associated with B-cell and plasma cell malignancies. In addition, GD1 patients develop immunoglobulin abnormalities, IgG- and IgM-specific hypergammaglobulinemia, and plasmacytosis (Arikan-Ayyildiz et al. 2011; de Fost et al. 2006; Pandey and Grabowski 2013; Zahran et al. 2016). Sotiropoulos et al. (2015) investigated the peripheral blood lymphocyte subpopulations in 22 adult patients with GD1. Patients were compared with 19 sex- and age-matched controls. The total T-cell population ($CD3^+$ cells) was not significantly different between patient group and controls. Patients with GD showed decreased frequencies and absolute numbers of $CD3^+/CD4^+$ helper T lymphocytes and increased frequencies of $CD8^+$ suppressor T lymphocytes, resulting in a significantly decreased CD4/CD8 cell ratio (Sotiropoulos et al. 2015). In addition, GD patients have a significant numerical impairment of T-helper lymphocytes and a constitutive TH1 direction pattern of activation of both $CD4^+$ and $CD8^+$ cells, associated with a significant decrease in T-regulatory cells (Sotiropoulos et al. 2015).

In our cohort of GD1 children who received ERT, the frequencies of activated T lymphocytes ($CD3^+HLA\text{-}DR^+$; $p = 0.001$), activated CD4 ($CD4^+HLA\text{-}DR^+$; $p = 0.002$), and activated CD8 ($CD8^+HLA\text{-}DR^+$; $p = 0.0001$) were significantly higher in GD1 as compared to healthy children. The presence of activated T lymphocytes was determined by HLA-DR surface antigen expression. In line with our results, a recent study (Sotiropoulos et al. 2015) reported significantly higher percentages of $CD8^+HLA\text{-}DR^+$ cells in GD patients compared to healthy controls ($p = 0.019$), but HLA-DR expression on $CD8^+$ cells was not different, as was also absolute $CD8^+HLA\text{-}DR^+$ cell count. In addition, HLA-DR expression on both $CD4^+$ and $CD8^+$ cells was higher in splenectomized GD patients. The same was observed for the absolute $CD4^+HLA\text{-}DR^+$ lymphocyte count ($p = 0.003$) and the percentage and the absolute $CD8^+HLA\text{-}DR^+$ cell count. However, HLA-DR expression on $CD4^+$ cells did not differ significantly between patients and controls (Sotiropoulos et al. 2015).

Our series with GD1 had significantly higher frequencies of infections, when compared to control group (Table 3). Based on our findings in this study and the previous study (Sotiropoulos et al. 2015), an activation of the immune system of unknown nature occurs in patients with GD, as suggested by an increased number of activated T cells.

T lymphocytes are the main cells, involved in all immune processes, and they play an essential role in immune homeostasis (Pandey and Grabowski 2013; Sotiropoulos et al. 2015).

Ineffective T-cell control may explain the chronic inflammatory reaction and the increased incidence of lymphoid malignancies, which have been repeatedly reported among patients with GD (Sotiropoulos et al. 2015). T-cell lymphomas occur in patients with GD. The patients had increased expression of CD45, CD45R0, CD3, and CD15 indicating a disruption of the T- and B-cell networks (Sanchez et al. 2005). T-cell deficiency and poor T-cell response to lectins were found in spleen tissue and peripheral blood of patients with Gaucher disease (Burstein et al. 1987; Pandey and Grabowski 2013).

A deficiency of $CD4^+$ and $CD8^+$ T-cell subsets was found in the peripheral blood of 21 non-splenectomized and 10 splenectomized patients with GD (Lacerda et al. 1999). Balreira et al. (2005) reported that GD patients, either under ERT or not, have decreased proportion of $CD4^+$ cells and increased proportion of $CD8^+$ cells. They suggested that anomalies of sphingolipid metabolism in GD patients are linked to anomalies in the expression of molecules of the MHC family and to the existence of imbalances in T-cell subsets. Moreover, this study (Balreira et al. 2005) supported the notion that expression of CD1d and MHC-class II molecules by monocytes is influenced by the intracellular sphingolipid content. Because certain T-cell subsets are altered in GD patients, they suggested that the alterations in CD1d and MHC-class II as a result of sphingolipid accumulation may underlie imbalances in regulatory NKT and T cells, which may contribute to the clinical heterogeneity of the clinical manifestations in patients with GD (Balreira et al. 2005). In contrast, the thymus of mice with a conditionally deleted Gba1 gene showed increased percentages of the $CD4^+$ T-cell subsets (Mistry et al. 2010). In addition, Braudeau et al. (2013) demonstrated that GD patients display, low NK, and naive $CD4^+$ cells and high $CD4^+$ memory T-cell counts.

There were some limitations of this study. First, we investigated a low number of children with GD1 from a single center. Second, we were unable to investigate the impact of treatment on the immune abnormalities, since all patients in our study were under treatment long before their evaluation. Third, we did not investigate any functional assay of activated T lymphocytes in our patients. It is, therefore, important to confirm these data in a larger patient cohort exhibiting these features.

In conclusion, our data showed an increased proportion of activated T lymphocytes in children with GD1. Our data suggested that activated T lymphocytes might play a role in the clinical course of GD1. The relationship of these cells to immune disorders in GD1 children remains to be determined.

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Compliance with ethical standards

Conflict of Interest All authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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