Short Communication

Serum $\beta_2$-microglobulin is frequently elevated in type 1 Gaucher patients

Tiago Koppe a,b, Filippo Vairo b,c, Matheus Camargo a, Livia Paskulin a, Liane Dautd,e, Ida V. Schwartz b,c,f,g,*

a School of Medicine, Universidade Federal do Rio Grande do Sul — UFRGS, Porto Alegre, Brazil
b Postgraduate Program in Genetics and Molecular Biology, UFRGS, Porto Alegre, Brazil
c Medical Genetics Service, Hospital de Clínicas de Porto Alegre - HCPA, Porto Alegre, Brazil
d Department of Pediatrics and Puericulture, UFRGS, Porto Alegre, Brazil
e Clinical Hematology Service, HCPA, Porto Alegre, Brazil
f Postgraduate Program in Genetics and Molecular Biology, UFRGS, Porto Alegre, Brazil
*g BRAIN (Basic Research and Advanced Investigations in Neurosciences) Laboratory, Porto Alegre, Brazil

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ABSTRACT

$\beta_2$-Microglobulin is the major prognostic factor in multiple myeloma, a known comorbidity of Gaucher disease. We evaluated herein serum $\beta_2$-microglobulin levels of 31 type 1 Gaucher patients; for 8/31 patients, pre- and post-treatment comparisons were made. Thirteen patients (on treatment $= 6$) had high levels of $\beta_2$-microglobulin, and showed higher chitotriosidase activity and Severity Score Index, and lower concentration of platelets, than patients with normal levels. Levels of $\beta_2$-microglobulin correlated with chitotriosidase activity ($\rho = 0.65; p < 0.01$), platelets ($\rho = -0.42; p = 0.02$) and $\alpha_1$- ($\rho = 0.43; p = 0.02$) and $\alpha_2$-protein bands ($\rho = -0.40; p = 0.03$). Regarding pre- and post-treatment values, median $\beta_2$-microglobulin levels decreased after treatment [(pre- = 2931 ng/mL; post- = 1970 ng/mL; $p < 0.01$). Our data suggest that levels of serum $\beta_2$-microglobulin are frequently elevated in type 1 Gaucher patients, correlate with severity of the disease and decrease after treatment.

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1. Introduction

Several epidemiological studies have been reporting an increased prevalence of multiple myeloma (MM) in type 1 Gaucher disease (GD) (OMIM #230800). Using the Gaucher Registry database, Rosenbloom et al. [6] found a relative risk of 5.9 [95% CI: 2.8–10.8] for GD patients showing MM. Putative explanation for these observations arises from the hypothesis of chronic stimulation of the immune system by Gaucher cells [8,9]. In fact, individuals with chronic inflammation are susceptible to develop MM as well as several lymphoproliferative disorders and malignancies [5]. There is an intense research field in this regard and a constellation of humoral and cellular surface molecules has been found to be abnormal in GD.

$\beta_2$-Microglobulin (beta2) is a non-covalently attached-component of class I HLA (human leukocyte antigen) molecules, which is required for the proper functioning of this entire structure on the cell surface [3] and is released on extracellular fluid [1]. Beta2 is the core of the International Staging System for MM [4], being higher levels associated with higher mortality in these patients. However, apart from the paper by Deibener et al. [2], who described a type 1 GD patient with raised serum levels of beta2 which became normal after 24 months on treatment with Alglucerase (Ceredase®, Genzyme Co, Cambridge, MA, USA), we were not able to find any other study on beta2 and Gaucher disease. We hypothesized that beta2 would be found in higher levels in GD patients and could be used as a marker for the follow-up.

2. Methods

In order to prove such hypothesis we enrolled type 1 GD patients followed at the local Reference Center for GD (Rio Grande do Sul state—Brazil) who had no evidence of malignancy (e.g., MM) in a prospective study. For patients who were receiving any kind of specific treatment for GD at inclusion (enzyme replacement therapy — ERT, or substrate reduction therapy — SRT; group 1) only one measurement of beta2 was performed. For patients receiving no treatment at inclusion (group 2), beta2 levels were evaluated just before the onset of treatment and after a mean of 20 months, or just at inclusion if the patient remained untreated. Beta2 values at inclusion were correlated with age at inclusion, age at onset of treatment, time on treatment, ERT dosage, chitotriosidase activity, Severity Score Index (SSI) [10], hemoglobin, serum ferritin, platelets, immunoglobulins (IgA, IgE, IgG, and IgM), and concentrations of $\alpha_1$, $\alpha_2$, $\beta$ and $\gamma$
proteins (blood serum gel electrophoresis), which were obtained retrospectively through chart review (values considered for analysis were those obtained closest to the beta2 measurement). Patients with high and normal beta2 levels at inclusion were also evaluated to these variables, as well as patients on treatment presenting high and normal beta2 levels.

Statistical analyses were performed on SPSS 18 (IBM®). Pearson chisquare tests were run to compare categorical data. For quantitative data, nonparametric tests were used (Wilcoxon-signed rank and Mann-Whitney tests, and Spearman correlation). Values were expressed as median [25th–75th percentiles] or absolute count. Alpha accepted was 0.05.

3. Results

Thirty-one type 1 GD patients (group 1 = 21; group 2 = 10) were included in the study (Table 1). For the whole sample, beta2 level was

3.1 Patients included in the study (Table 1).

| Characterization of type 1 Gaucher patients included in the study (n = 31). |
|-----------------------------------------------|
| **Group 1 (n = 21)**                          |
| On treatment at inclusion                   |
| Male:female                                  | 9:12 |
| GBA1 genotype                                |
| -N370S/L444P                                 | 14 |
| -N370S/N370S                                 | 3 |
| -Other                                       | 4 |
| Age at inclusion (yrs)                       | 32.5 [18–56.1] |
| Age at onset of treatment (yrs)              | 22.8 [7.6–35.4] |
| Time on treatment (mo)                       | 108.5 [30–120] |
| Type of treatment                            |
| -Imiglucerase                                | 21 |
| -T-alglucerase alpha                         | 0 |
| -Miglustat                                   | 2 |
| Dosage of ERT (IU/kg/inf)                    | 15 [15–30] |
| SSI score                                    | 4 [3–6.5] |
| SSL                                         | 2.5 [1–4.2] |
| **Group 2 (n = 10)**                         |
| No treatment at inclusion                    |
| Male:female                                  | 5:5  |
| GBA1 genotype                                |
| -N370S/L444P                                 | 2 |
| -N370S/N370S                                 | 2 |
| -Other                                       | 4 |
| Age at inclusion (yrs)                       | 39.9 [18.6–57] |
| Age at onset of treatment (yrs)              | 41.7 [10.2–32.3] |
| Time on treatment (mo)                       | 20.4 [12–30] |
| Type of treatment                            |
| -Imiglucerase                                | 4 |
| -T-alglucerase alpha                         | 2 |
| -Miglustat                                   | 2 |
| Dosage of ERT (IU/kg/inf)                    | 15 [15–18.7] |
| SSI score                                    | 3 [1–4] |
| SSL                                         | 4 [3–5.5] |

Values expressed as median [25th–75th percentiles] or absolute count. GD: Gaucher disease; ERT: enzyme replacement therapy; IU: International Unit; inf: infusion; --: not applicable.

3.2 Comparison between type 1 Gaucher disease patients with elevated and normal serum β2-microglobulin at inclusion.

| Elevated (n = 13) | Normal (n = 18) | p-Value |
|------------------|-----------------|---------|
| Male:female      | 5:8             | 9:9     | 0.524 |
| Age at inclusion (yrs) | 32.5 [18–56.1] | 29.4 [20.5–42.6] | 0.779 |
| Spleenectomy     | 2               | 3       | 0.924 |
| SSI              | 4 [3–6.5]       | 2.5 [1–4.2] | 0.045* |
| Patients receiving treatment                  | 6               | 15      | 0.029* |
| -Age at onset of treatment (yrs)              | 22.8 [7.6–35.4] | 14.5 [10.4–34.7] | 0.938 |
| -Time on treatment (mo)                       | 74.4 [30–134.4] | 108 [264–1248] | 0.015 |
| -Dosage of ERT (IU/kg/inf)                    | 17.5 [15–33.8] | 15 [15–30] | 0.502 |
| Chitotriosidase (nmol/h/mL)                   | 6996 [5130–17,113] | 3476 [2073.5–7038] | 0.004* |
| Hemoglobin (g/dL)                             | 12.7 [11.5–13.5] | 13.3 [12–15] | 0.128 |
| Platelets (x 10^12)/μL                       | 82 [62.5–143.5] | 138.5 [111.5–172] | 0.031* |
| Ferritin (ng/mL)                              | 2433 [2073–10427] | 3927 [167–630] | 0.401 |
| Serum immunoglobulins (mg/dL)                 | 3               | 2/16    | 0.347 |
| -IgG                                         | 1464 [1243–1722] | 1262 [953.5–1635.5] | 0.186 |
| -IgA                                         | 240 [191–375.5] | 285.5 [197.7–444] | 0.337 |
| -IgE                                         | 65.5 [28–213] (n = 11) | 136.5 [13.5–334.7] | 0.369 |
| -IgM                                         | 244.5 [145–286.7] (n = 12) | 162.5 [129.7–2242] (n = 16) | 0.228 |
| Blood serum protein electrophoresis (g/dL)    | 7.9 [7.3–8.2] | 7.6 [7.3–8] | 0.367 |
| -Total protein                               | 4.5 [4.1–4.9] | 4.3 [4.1–4.6] | 0.677 |
| -α1                                          | 0.24 [0.22–0.31] | 0.21 [0.16–0.25] | 0.031* |
| -α2                                          | 0.66 [0.59–0.76] | 0.77 [0.65–0.88] | 0.032* |
| -β                                          | 0.7 [0.63–0.77] | 0.76 [0.62–0.84] | 0.334 |
| -γ                                           | 1.61 [1.35–1.73] | 1.48 [1.01–1.8] | 0.525 |

Values expressed as median [25th–75th percentiles] or absolute count. GD: Gaucher disease; ERT: enzyme replacement therapy; IU: International Unit; inf: infusion; --: not applicable.

* In bold, statistically significant results.
on imiglucerase 15 IU/kg/inf; and patient E, on imiglucerase 30 IU/kg/inf for 5 months and taliglucerase alpha 15 IU/kg/inf after that. Patient F received imiglucerase 15 IU/kg/inf for 10 months and miglustat after that; patient H received imiglucerase 15 IU/kg/inf for 9 months and taliglucerase alpha 15 IU/kg/inf after that. Patients A to G are treatment-naïve. Patient H received ERT for a year and had ERT interrupted for 4 months before the inclusion in the study.

4. Discussion/conclusions

To the best of our knowledge, this is the first study to report increased levels of beta2 in a cohort of GD patients. Our data is in accordance to that by Deibener et al. [2] and suggests that higher levels of beta2 arise from untreated patients, decrease after a short period of treatment and are associated with improvement of chitotriosidase. SSI, IgE, IgM and hemoglobin. Therefore, ERT/SRT appears to decrease the chronic antigenic stimulation commonly found in GD. In addition, our data showed that patients with higher beta2 levels had SSI, platelet levels, and chitotriosidase activity worse than patients with normal levels of beta2, which suggests that it may be a biomarker of the severity of the disease.

The moderate positive correlation found between beta2 and chitotriosidase values may reflect increased coexpression of both proteins in macrophages, or the chitotriosidase secreted by macrophages may stimulate other cells at distance, expressing MHC-I molecules, and secondarily increasing beta2. Still, α serum proteins are a heterogeneous group of proteins secreted by different sources. Therefore, the true meaning of the correlation found between beta2 and these proteins needs to be further studied.

Beta2 may be not only a putative GD biomarker but also it may have potential therapeutic utility, because new therapies have emerged from beta2 targeting. For example, specific antibodies to beta2 have remarkable tumoricidal activity for both solid tumors and blood malignancies with no toxicity to normal cells [7].

However, the correlation of beta2 levels with clinical endpoints of GD, such as the risk to develop MM and mortality, needs to be addressed by further studies, with larger sample sizes and periods of follow-up as well as focusing in specific α serum proteins and other biomarkers.

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