Molecular Genetics and Metabolism Reports 2 (2015) 38–40

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: http://www.journals.elsevier.com/molecular-genetics-and-metabolism-reports/

Short Communication

Serum β_2-microglobulin is frequently elevated in type 1 Gaucher patients

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ARTICLE INFO

Article history:
Received 1 September 2014
Received in revised form 28 November 2014
Accepted 28 November 2014
Available online 15 December 2014

Keywords:
Serum β_2-microglobulin
Gaucher disease
Multiple myeloma
Chitotriosidase
Biomarkers

ABSTRACT

β_2-Microglobulin is the major prognostic factor in multiple myeloma, a known comorbidity of Gaucher disease. We evaluated herein serum β_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 β_2-microglobulin, and showed higher chitotriosidase activity and Severity Score Index, and lower concentration of platelets, than patients with normal levels. Levels of β_2-microglobulin correlated with chitotriosidase activity ($\rho = 0.65$; $p < 0.01$), platelets ($\rho = -0.42$; $p = 0.02$) and α1- ($\rho = 0.43$; $p = 0.02$) and α2-protein bands ($\rho = -0.40$; $p = 0.03$). Regarding pre- and post-treatment values, median β_2-microglobulin levels decreased after treatment (pre- = 2931 ng/mL; post- = 1970 ng/mL; $p < 0.01$). Our data suggest that levels of serum β_2-microglobulin are frequently elevated in type 1 Gaucher patients, correlate with severity of the disease and decrease after treatment.

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.

β_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 α1, α2, β and γ

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http://dx.doi.org/10.1016/j.ymgmr.2014.11.009

Table 1
Characterization of type 1 Gaucher patients included in the study (n = 31).

	Group 1 (n = 21)	Group 2 (n = 10)	
	On treatment at inclusion	No treatment at inclusion	On treatment at follow-up (n = 8)
Male:female	9:12	5:5	4:4
GBA1 genotype			
-N370S/L444P	14	2	2
-N370S/N370S	3	2	2
-Other	4	6	4
Age at inclusion (yrs)	28.7 [19.9–41.2]	39.9 [18.6–57]	43.9 [32.3–57.1]
Age at onset of treatment (yrs)	16.7 [10.2–32.3]	–	44.4 [37.1–56.1]
Time on treatment (mo)	108.5 [30–120]	–	20.4 [12–30]
Type of treatment			
-Imiglucerase	21	–	4
-Taliglucerase alpha	0	–	2
-Miglustat	0	–	2
Dosage of ERT (IU/kg/inf)	15 [15–30]	–	15 [15–18.7] (n = 6)
SSI score	3 [1.5–4.5]	4 [3–5.5]	3 [1–4]

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

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 chi-square 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 2180 ng/mL [1880–2919] (range = 1465–4630). Significant Spearman correlations were observed only between beta2 and chitotriosidase activity ($\rho = 0.65$; $p < 0.01$; n = 31), platelets ($\rho = -0.42$; $p = 0.02$; n = 31), and α1 ($\rho = 0.43$; $p = 0.02$; n = 29) and α2 protein bands ($\rho = -0.40$; $p = 0.03$; n = 29) of blood serum gel electrophoresis. We did not find any correlation between beta2 and age at inclusion ($\rho = 0.21$; $p = 0.913$; n = 31) nor differences between sexes (male beta2 median = 2191 ng/mL [1993–2500.5]; female = 2180 ng/mL [1801–3062]; $p = 0.52$).

Thirteen patients had beta2 above the reference range (600–2450 ng/mL); they are found to be less frequently on treatment, and to present higher chitotriosidase activity, α1 concentration and SSI, and lower levels of platelets and α2, than patients presenting normal beta 2 (Table 2).

Regarding group 2, eight patients (patients A to H) started to receive treatment soon after the inclusion in the study (Table 1, Fig. 1). For the whole period of treatment, patient A is on miglustat; patients B, D and G,

Table 2
Comparison between type 1 Gaucher disease patients with elevated and normal serum β_2-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
Splenectomy	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 [26.4–124.8]	0.815
-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 [2075.5–7038.7]**	**0.004***
Hemoglobin (g/dL)	12.7 [11.5–13.5]	13.3 [12–15]	0.128
Platelets ($\times 10^3$/μL)	**82 [62.5–143.5]**	**138.5 [111.5–172]**	**0.031***
Ferritin (ng/mL)	343.3 [207.3–1042.7]	349.7 [167–630.9]	0.401
Polyclonal gammopathy	3	2/16	0.347
Serum immunoglobulins (mg/dL)			
-IgG	1464 [1243–1722]	1262 [953.5–1635.5]	0.186
-IgA	240 [191–375.5]	295.5 [197.7–444]	0.337
-IgE	65 [28–213] (n = 11)	136.5 [33.5–334.7]	0.369
-IgM	244.5 [145–286.7] (n = 12)	162.5 [129.7–224.2] (n = 16)	0.228
Blood serum protein electrophoresis (g/dL)			
-Total protein	7.9 [7.3–8.2]	7.6 [7.3–8]	0.367
-Albumin	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. Comparisons made by Pearson chi-square or Mann–Whitney U test.
* In bold, statistically significant results.

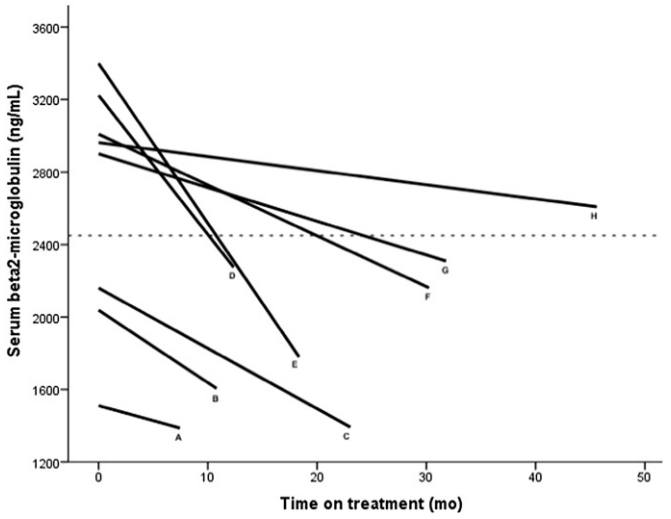

Fig. 1. Serum β_2-microglobulin levels in eight type 1 Gaucher disease patients just before and after onset of treatment. Each line represents one patient. Dashed line represents the upper limit of normality (2450 ng/mL). Patients A and F are on miglustat; patients B, D and G are on imiglucerase 15 IU/kg/inf; patient E is on imiglucerase 30 IU/kg/inf; and patients C and H are on taliglucerase alpha 15 IU/kg/inf at follow-up. Patients A to G are treatment-naïve. Patient H has received ERT for a year and had ERT interrupted for 4 months before the inclusion in the study.

on imiglucerase 15 IU/kg/inf; and patient E, on imiglucerase 30 IU/kg/inf. Patient C received imiglucerase 15 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 has been previously treated for a year and had ERT interrupted for 4 months before the inclusion in the study. Out of the patients who started treatment, five had beta2 levels above the reference range at inclusion and only one at follow-up (Fig. 1). Treatment was associated with a significant reduction of beta2 levels (median levels of beta2 at inclusion = 2931 ng/mL [2068–3169]; median levels of beta2 at follow-up = 1970 ng/mL [1446–2300]; $p < 0.01$) (Fig. 1), and improvement of chitotriosidase levels (8302.5 nmol/mL/h [6728.2–11,044.2] vs. 2343 nmol/mL/h [1681.2–5817.7]; $p < 0.02$), SSI (4 [3–6.5] vs. 3 [1–3.7]; $p < 0.02$), hemoglobin (13.2 g/dL [11.8–13.8] vs. 14.1 g/dL [12.4–14.7]; $p < 0.02$), IgE (139 mg/dL [111–273] vs. 70.9 mg/dL [21.9–183.2]; n = 7, $p = 0.028$) and IgM (266.5 mg/dL [167.2–394.2] vs. 174.5 mg/dL [123.2–306.7]; $p = 0.012$).

When we compared all patients on treatment (n = 29; group 1 = 21; group 2 = 8), we did not find any difference between the variables analyzed (data not shown).

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.

Acknowledgments

Financial support for this study was provided by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazil), Fundo de Incentivo à Pesquisa e Eventos do Hospital de Clínicas de Porto Alegre (FIPE/HCPA, Brazil) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES, Brazil).

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