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Impact of imiglucerase on the serum glycosylated-ferritin level in Gaucher disease

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ABSTRACT

Gaucher disease (GD) is a lysosomal storage disorder, caused by deficient activity of the enzyme glucocerebrosidase, which can be treated by enzyme-replacement therapy (ERT). No prognostic marker can predict long-term complications of GD but several markers are used in therapeutic monitoring: chitotriosidase, total serum ferritin (TSF), angiotensin-converting enzyme (ACE) and tartrate-resistant acid phosphatase (TRAP). They all increase with disease progression and generally decrease under ERT. This study was undertaken to investigate ferritin glycoforms, i.e., glycosylated ferritin (GF) and non-glycosylated ferritin (NGF) concentrations, as potential markers for the follow-up of GD therapy.

GF and NGF determinations for GD patients followed in a single center between 1996 and 2007 were analyzed using two approaches: (1) the serum levels of 12 untreated patients were compared with those of 10 patients after 48 months on ERT; (2) the evolution of serum levels under ERT in 15 patients were analyzed using linear/logarithmic mixed models.

TSF and NGF levels did not differed significantly between untreated patients and those on ERT (TSF: 524.5 (range 221.0–2045.0) μg/L vs. 410.5 (range 115.0–1587.0) μg/L, respectively, $p=0.72$; NGF: 340.0 (range 182.8–1717.8) μg/L vs. 199.9 (range 77.1–649.8) μg/L, $p=0.09$). The percent GF was significantly lower in untreated patients than in those on ERT (27.0% (range 8.0–51.0) vs. 43.5% (range 22.0–80.0) respectively; $p=0.02$).

The percent GF increased significantly during ERT (slope = 0.156% [95% confidence interval (CI), 0.03; 0.29] per month, $p=0.01$) regardless of whether NGF and TSF significantly decreased during ERT (slope = −1.4% per month [95%CI, −1.9%; −1.0%], $p<0.0001$; slope = –1.1% [95%CI, −1.6%; −0.6%] per month, $p<0.0007$, respectively).

Thus, GF is low in untreated GD patients. GF and NGF changed significantly under ERT and might be of clinical value for GD management under treatment.

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Introduction

Gaucher's disease (GD), inherited as an autosomal recessive trait, is the most prevalent sphingolipid storage disorder. The metabolic defect of insufficient glucocerebrosidase activity is due to mutations in the gene encoding that lysosomal enzyme, leading to the accumulation of glucocerebroside within cells of the monocyte–macrophage lineage. The resulting chronically activated, long-lived "Gaucher cells" can progressively infiltrate a variety of tissues and organs, especially the spleen, liver and bone marrow [1]. The disease has traditionally been divided into three clinical subtypes based on the absence/presence of neurological features. The development of enzyme-replacement therapy (ERT) with imiglucerase, produced by genetic engineering, improved GD prognosis. No marker with prognostic value that can predict long-term complications of GD has been identified and few markers are used for therapeutic monitoring.

GD patients have numerous biological anomalies. Notable among them are increased chitotriosidase [2], angiotensin-converting enzyme (ACE) [3], ferritin [4–8] and tartrate-resistant acid phosphatase

Abbreviations: GD, Gaucher disease; ERT, enzyme-replacement therapy; ACE, angiotensin-converting enzyme; TRAP, tartrate-resistant acid phosphatases; ConA, Concanavalin A; TSF, total serum ferritin; GF, glycosylated ferritin; NGF, non-glycosylated ferritin; RCLD, Referral Center for Lysosomal Diseases.

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(TRAP) [9,10], which are used as GD markers [11] of GD progression of the disease and generally decline during ERT [12] and thrombopenia, anemia and/or disorders in hepatic function (cholestasis and/or cytolysis).

Ferritin is the major iron-storage glycoprotein found in all tissues but is predominantly located in reticuloendothelial cells [13]. It is made of a 24-subunit protein shell. The subunits are of two types, H (heavy, 21 kDa) and L (light, 19 kDa). Ferritin molecules are heteropolymers containing various proportions of the two subunits depending on the tissue type and physiological status of the cell, from predominantly L in tissues, like liver and spleen, to predominantly H in heart and kidney [13].

Intracellular ferritin is non-glycosylated (NGF). Carbohydrate residues are added to cytosolic L-ferritin during secretion from tissues into the plasma [14]. Circulating ferritin consists of L-ferritin and trace amounts of H-ferritin [15]. Only some of the L-ferritin is glycosylated. Ferritin glycosylation is assessed by the different affinities of ferritin for Concanavallin A (ConA), a vegetable lectin that interacts specifically with accessible mannosyl residues. In normal patients, a high percentage of circulating ferritin is glycosylated (GF) or sialoglycosylated (50–80% of "glycosylated" ferritin bind to ConA) [16,17]. Lower percentages of GF are recognized as a specific marker of active adult Still's disease [18,19] with <20% compared to the 20–40% in patients with acute and chronic inflammatory syndromes [20] and the 50–80% in normal adults.

The aim of this study was to investigate ferritin glycoforms: the commonly used GF percentage and NGF concentration as potential markers for follow-up of GD therapy in a monocenter cohort of patients untreated or under ERT.

Materials and methods

Patients and data collected

Our Referral Center for Lysosomal Diseases (RCLD) is specialized in GD follow-up. Adult GD patients followed in the RCLD (Beaujon Hospital) and having at least one ferritin-glycoform evaluation (i.e., total serum ferritin [TSF], GF and NGF) between 1996 and 2007, were enrolled. GD diagnosis was confirmed by low glucocerebrosidase activity in leukocytes from all patients [21]. Ferritin was measured when the patient had a systematic evaluation during follow-up, with or without ERT. Data collected were: demographic and diagnosis information (age, sex, phenotype, and genotype), splenectomy, treatment and biological data (TSF, GF percentage and NGF concentration).

TSF Concentration and GF-percentage assays

All biochemical analyses were performed in a single biochemistry laboratory. The TSF concentration was determined by immunoassay (Dimension RXL HM, Dade Behring, Paris-La Defense, France). GF was determined according to the method of Worwood et al. [14], with previously described minor modifications [19]. GF was separated using ConA-Sepharose 4B chromatography (Pharmacia Biotechnology Europe, Saclay, France). NGF not bound to ConA was recovered in the supernatant and quantified, and results are expressed as a percentage of TSF and NGF as absolute concentrations. Normal values were TSF, 10–250 μg/L; GF, 50–80%; and NGF, 50–125 μg/L.

Statistical analysis

All statistical analyses were performed with SAS software (version 9.1; SAS Institute, Cary, North Carolina). Significance was defined as $p<0.05$. Results are expressed as medians (range) for continuous variables and percentages for categorical variables.

Two approaches were used to explore GF in GD. First, we compared the serum TSF, GF and NGF values of 12 untreated patients with those of 10 treated patients after 48 (42–54) months on ERT, using a non-parametric Mann–Whitney–Wilcoxon test. Second, we analyzed the evolution of serum levels in 15 patients during ERT. For patients with two or more biological evaluations during ERT, the GF evolution was assessed using linear-mixed models and TSF and NGF evolutions using logarithmic mixed models for repeated measures with the MIXED procedure. The significance of the evolution slope under ERT was tested using a Wald test.

Results

Table 1 reports the number of TSF, GF and NGF measurements for each patient. A total of 274 samples were available (median 16 (1–35) per patient). Twenty-five patients (12 women) with ferritin-glycoform determinations were included: 12 were untreated, data were available for 10 patients after 48 months of ERT and 15 patients had at least two data during ERT.

Table 2 summarizes the characteristics of the cohort. All 25 patients had type 1 non-neuronopathic GD and genotypes were available for 20. Median age at the time of the first blood sample was 29.6 (19.3–59.9) years for untreated patients and 38.3 (19.6–67.1) years for patients receiving ERT. The duration of follow-up with GF samples was not available for untreated because only patients 4 and 12 had more than one sample (interval between first and last sample: 17.1 and 8.8 months, respectively). The median interval between ERT onset and last blood sample testing was 102.6 (16.9–174.1) months. Nine (36%) patients were splenectomized; all but patient 7 before the first GF determination.

Fig. 1 shows box plots of assay results of patients untreated or after 48 months of ERT. For all 12 untreated patients, TSF was high and, for 11 of them, the GF percentage was <50%. The TSF concentration did not differ significantly between untreated patients and after 48 months of ERT (524.5 (221.0–2045.0) μg/L versus 410.5 (115.0–1587.0) μg/L

Table 1
Description of the GF measurements in 25 Gaucher-disease patients before and/or after starting ERT.

Patients number	Number of assays		ERT at 1st assay	ERT duration at last assay (months)	Measurements after 48 (42–54) months of ERT
	Total	Under ERT			
1	1	0	no	–	no
2	1	0	no	–	no
3	3	2	no	17	no
4	2	0	no	–	no
5	1	0	no	–	no
6	1	0	no	–	no
7	1	0	no	–	no
8	1	0	no	–	no
9	1	0	no	–	no
10	1	0	no	–	no
11	16	15	no	40	no
12	29	24	no	53	yes
13	15	15	yes	126	yes
14	8	8	yes	110	no
15	31	31	yes	153	yes
16	3	3	yes	126	no
17	5	5	yes	111	yes
18	5	5	yes	28	no
19	28	28	yes	124	yes
20	35	35	yes	123	yes
21	23	23	yes	95	yes
22	28	28	yes	174	yes
23	18	18	yes	95	yes
24	1	1	yes	35	no
25	16	16	yes	52	yes
Total	274	257	13	102.6 (16.9–174.0)[a]	10

ERT = enzyme-replacement therapy; –: not available for patients not tested under ERT.
[a] Median (range).

Table 2
Summary of the characteristics of the 25 GD patients.

Characteristic	*n*	Value
Sex (female), *n* (%)	25	12 (48%)
Phenotype (type 1), *n* (%)	25	25 (100%)
Genotype, *n* (%)	20	
N370S/N370S		2 (10%)
N370S/L444P		6 (30%)
N370S/other		11 (55%)
R463C/K303I		1 (5%)
Splenectomy, *n* (%)	25	9 (36%)
Without treatment, median (range)		
GF (%)	12	27.0 (8.0–51.0)
TSF (μg/L)	12	524.5 (221.0–2045.0)
NGF (μg/L)	12	340.0 (182.8–1718.8)
At 48 months of ERT, median (range)		
GF (%)	10	43.5 (22.0–80.0)
TSF (μg/L)	10	410.5 (115.0–1587.0)
NGF (μg/L)	10	199.9 (77.1–649.8)

n = the number of patients with data available. GF = glycosylated ferritin. TSF = total serum ferritin. NGF = non-glycosylated ferritin. ERT = enzyme-replacement therapy.

respectively; $p=0.72$). By contrast, the GF percentage was significantly lower for untreated patients treatment than after 48 months of ERT (27.0% (8.0–51.0) vs. 43.5% (22.0–80.0) respectively; $p=0.02$), even though the NGF concentration was not significantly different for untreated and treated patients (340.0 (182.8–1717.8) μg/L vs. 199.9 (77.1–649.8) μg/L, respectively; $p=0.09$).

In addition, TSF, GF and NGF were comparable for splenectomized and non-splenectomized patients, untreated or after 48 months of ERT.

The evolutions of TSF, GF and NGF values during ERT (Fig. 2A, B and C, respectively) were analyzed with linear-mixed models for GF and with logarithmic mixed model for TSF and NGF for the 15 patients with at least two determinations during ERT. During ERT, TSF decreased significantly (slope = –1.1% [95% confidence interval (CI) −1.6%; −0.6%] per month, $p<0.0007$), GF increased significantly (slope = 0.156% [95% CI 0.03; 0.29] per month; $p=0.01$) and NGF declined sharply (slope = –1.4% [95% CI −1.9%; −1.0%] per month; $p<0.0001$). At ERT onset, and 4 and 8 years later, respectively, model predicted TSF means (percent of variation) (Fig. 2A) were 629.2, 374.5 (−40.5%) and 222.9 (−64.6%) μg/L; predicted GF means (Fig. 2B) were 33.8%, 41.4% (+22.7%) and 49.1% (+45.3%), and predicted NGF means were 425.5, 212.9 (−49.9%) and 106.5 (−74.9%) μg/L.

Discussion

The results of this study showed that, in GD patients: the GF percentage was low without treatment (<50% for 11/12 patients) and significantly higher under ERT; hyperferritinemia declined significantly with ERT; GF rose significantly under ERT; and the significant TSF decrease and percent GF increase during the course of ERT resulted in the highly significant diminution of absolute NGF concentrations (−74.9% at 8 years).

This is the first study to demonstrate low GF percentages and increased GF in GD patients under ERT. To our knowledge, only Morgan et al. analyzed GF in GD, reporting on 7 patients with type I GD; they found hyperferritinemia and GF percentages within the normal gender ranges, but the therapeutic status of their patients was not mentioned [6]. The mechanisms responsible for increased ferritin in GD patients are unknown. Interestingly, during ERT, our GD patients' NGF concentrations decreased significantly while GF concentrations did not significantly change (data not shown), thereby resulting in higher percentages of GF. Thus, their high serum ferritin concentrations mainly reflected increased NGF.

Ferritin that does not bind to ConA, the so-called non-glycoslylated form, could result from incomplete or abnormal glycosylation, or enhanced cell lysis. Serum ferritin is thought to be a consequence of the secretion of a small fraction of cellular ferritin, mostly L-ferritin in its glycosylated form. However, the mechanism by which L-ferritin, which has no known signal sequence, enters the secretory pathway is not known [22].

A similar example is that of plasminogen-activator–inhibitor type 2 that also exists in two forms: non-glycosylated cytoplasmic and glycosylated extracellular forms [23]. This dual localization was shown to result from a relatively inefficient routing into the secretory pathway. Kannengiesser et al. reported increased secretion of a mutated L-ferritin and suggested that the observed hyperferritinemia with high level glycosylation might simply reflect the enhanced proportion of mutated serum ferritin that is secreted, compared to the fraction that is released via cell lysis [24].

Hyperferritinemia, originating from liver necrosis, is also associated with less binding to ConA [25]. In our patients, liver cytolysis was unlikely because hepatic parameters were normal. In adult Still's disease and inflammatory syndromes, hyperferritinemia was associated with hypoglycosylation and reduced ferritin sialylation, in which led to lower GF percentages that are used as a marker [16]. In GD, elevated ferritinemia could mainly be of macrophage origin after

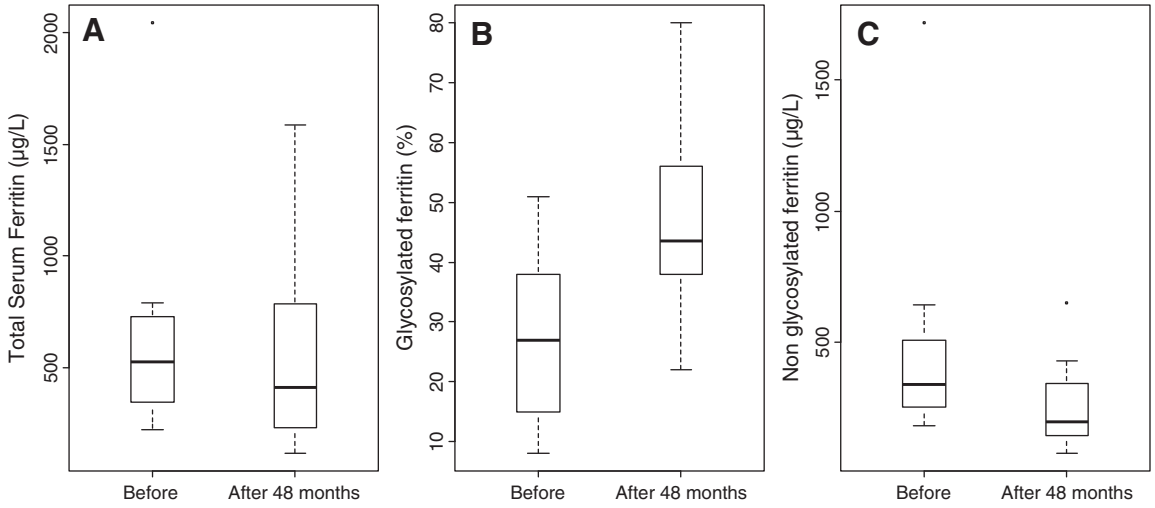

Fig. 1. Box plots of (A) total serum ferritin (TSF), (B) glycosylated ferritin (GF) and (C) non-glycosylated ferritin (NGF) concentrations before ($n=12$) and after 48 months of enzyme-replacement therapy (ERT) (N = 10). Differences were not significant for TSF ($p=0.7$) and NGF ($p=0.09$), but significant for GF ($p=0.02$). The bold line inside the box is the *median*; the lower and upper limits of the box are the 25th and 75th percentiles; and the T-bars represent the *range*.

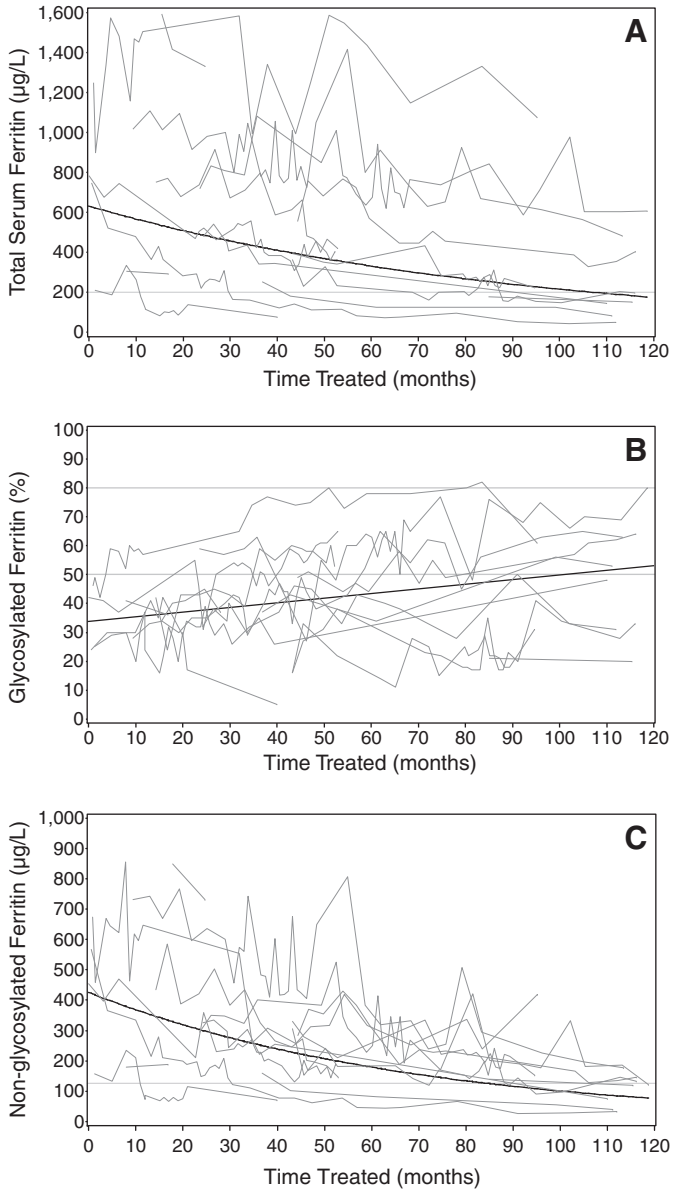

Fig. 2. Evolution of (A) total serum ferritin (slope = −1.1% per month [95% CI, −1.6; −0.6], $p = 0.0007$), (B) glycosylated ferritin (slope = 0.16% per month [95% CI, 0.03; 0.29], $p = 0.01$) and (C) non-glycosylated ferritin in 15 imiglucerase-treated GD patients (slope = −1.14% per month, [95%CI, −1.9; −1], $p = 0.0001$). The horizontal grey lines represent sent the upper limit of normal when only 1 is present or the normal range when both are given. ——: logarithmic mixed model; ——: each patient's evolution.

erythrophagocytosis, because iron overload in the form of ferritin was described in Gaucher cells [26]. However, the specific anomalies of ferritin metabolism, i.e., synthesis, secretion/lysis or decreased desialylated-ferritin clearance, remain to be investigated. Our patients' elevated NGF and low level of ferritin glycosylation might reflect enhanced release via cell lysis, compared to the fraction that is secreted.

Although patients' TSF, NGF and GF levels at ERT onset were highly variable, information could be obtained from the analysis of their variations under ERT. During ERT, the TSF decline mainly reflected less NGF, which might indicate diminished activation and/or burden of Gaucher cells infiltrating tissues and organs, especially the spleen, liver and bone marrow, as previously shown for plasma ACE, TRAP and chitotriosidase, which are secreted by Gaucher cells [27]. Cytokines are potent inducers of ferritin synthesis, and also affect ferritin glycosylation in and secretion by the liver and monocytes [13]. Barak et al. [28] reported enhanced production of interleukins 1 and 6 and tumor necrosis factor-α in GD patients that correlated with disease severity. None of our patients had signs of inflammation (erythrocyte sedimentation rate and C-reactive-protein were not elevated during follow-up). Our findings suggest that, among ferritin glycoforms, the absolute NGF concentration could be the best marker for ERT follow-up. As for adult Still's disease [19,29] and the hemophagocytosis syndrome, which is also associated with excessive macrophage activation [30–32], a low GF percentage was also reported to be a more specific, sensitive and predictive marker than hyperferritinemia.

ERT is a lifelong and expensive therapy that, when administered at an appropriate and individually tailored dose, can prevent severe complications. Although numerous methods are currently used, the ideal biomarker of GD, which would reflect Gaucher cell activity, correlate with clinical severity, disease progression, ERT efficacy and predict complications, remains unknown. Our results suggest that ferritin glycoforms (percent GF and especially NGF concentration) could be informative markers for monitoring GD progression and/or the response to ERT, along with the classical markers chitrotriosidase, TRAP and ACE, and possibly of excessive macrophage activation. Further validation in a large prospective study including evaluation of bone-marrow and visceral responses is required.

Authors' contributions

JS, AB, FM, CV, NB, BF and OF designed the research protocol; JS, AB, NB, AM, DH, BF and OF were involved in treating patients and collecting data; JS, CV and FM controlled the accuracy of collected data and conducted the statistical analyses; JS, AB, NB and FM wrote the draft of the paper, that was then corrected and approved by all authors.

Disclosure

Paris-Diderot University received a grant from Genzyme France. Beaujon Hospital received a grant from Shire.

Role of the funding source

Genzyme and Shire played no role in designing the study; collecting, analyzing and interpreting the data; writing the paper; or the decision to submit the manuscript for publication.

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References

[1] E. Beutler, Gaucher disease: new molecular approaches to diagnosis and treatment, Science 256 (1992) 794–799.
[2] C.E. Hollak, S. van Weely, M.H. van Oers, J.M. Aerts, Marked elevation of plasma chitotriosidase activity. A novel hallmark Gaucher disease, J. Clin. Invest. 93 (1994) 1288–1292.
[3] J. Lieberman, E. Beutler, Elevation of serum angiotensin-converting enzyme in Gaucher's disease, N Engl J. Med. 294 (1976) 1442–1444.
[4] A. Zimran, A. Kay, T. Gelbart, P. Garver, D. Thurston, A. Saven, E. Beutler, Gaucher disease. Clinical, laboratory, radiologic, and genetic features of 53 patients, Med. Baltim. 71 (1992) 337–353.
[5] E. Beutler, Gaucher disease, Blood Rev. 2 (1988) 59–70.
[6] M.A. Morgan, A.V. Hoffbrand, M. Laulicht, W. Luck, S. Knowles, Serum ferritin concentration in Gaucher's disease, Br. Med. J. (Clin. Res. Ed.) 286 (1983) 1864.

[7] L.W. Poll, J.A. Koch, R. Willers, H. Aerts, A. Scherer, D. Haussinger, U. Modder, S. vom Dahl, Correlation of bone marrow response with hematological, biochemical, and visceral responses to enzyme replacement therapy of nonneuronopathic (type 1) Gaucher disease in 30 adult patients, Blood Cells Mol. Dis. 28 (2002) 209–220.
[8] P. Stein, H. Yu, D. Jain, P. Mistry, Hyperferritinemia and iron overload in type 1 Gaucher disease, Am. J. Hematol. 85 (2010) 472–476.
[9] L.R. Tuchman, H. Suna, J.J. Carr, Elevation of serum acid phosphatase in Gaucher's disease, J. Mt. Sinai Hosp. 23 (1956) 227–229.
[10] K. Troy, J. Cuttner, M. Reilly, G. Grabowski, R. Desnick, Tartrate-resistant acid phosphatase staining of monocytes in Gaucher disease, Am. J. Hematol. 19 (1985) 237–244.
[11] P.B. Deegan, M.T. Moran, I. McFarlane, J.P. Schofield, R.G. Boot, J.M. Aerts, T.M. Cox, Clinical evaluation of chemokine and enzymatic biomarkers of Gaucher disease, Blood Cells Mol. Dis. 35 (2005) 259–267.
[12] M.A. Cabrera-Salazar, E. O'Rourke, N. Henderson, H. Wessel, J.A. Barranger, Correlation of surrogate markers of Gaucher disease. Implications for long-term follow-up of enzyme replacement therapy, Clin. Chim. Acta 344 (2004) 101–107.
[13] F.M. Torti, S.V. Torti, Regulation of ferritin genes and protein, Blood 99 (2002) 3505–3516.
[14] M. Worwood, S.J. Cragg, M. Wagstaff, A. Jacobs, Binding of human serum ferritin to concanavalin A, Clin. Sci. (Lond.) 56 (1979) 83–87.
[15] M. Worwood, S. Dawkins, M. Wagstaff, A. Jacobs, The purification and properties of ferritin from human serum, Biochem. J. 157 (1976) 97–103.
[16] C. van Reeth, G. Le Moël, Y. Lasne, M.C. Revenant, J. Agneray, M.F. Kahn, P. Bourgeois, Serum ferritin and isoferritins are tools for diagnosis of active adult Still's disease, J. Rheumatol. 21 (1994) 890–895.
[17] M. Cazzola, G. Bergamaschi, L. Tonon, E. Arbustini, M. Grasso, E. Vercesi, G. Barosi, P.E. Bianchi, G. Cairo, P. Arosio, Hereditary hyperferritinemia-cataract syndrome: relationship between phenotypes and specific mutations in the iron-responsive element of ferritin light-chain mRNA, Blood 90 (1997) 814–821.
[18] S. Higashi, T. Ota, S. Eto, Biochemical analysis of ferritin subunits in sera from adult Still's disease patients, Rheumatol. Int. 15 (1995) 45–50.
[19] S. Vignes, G. Le Moël, B. Fautrel, B. Wechsler, P. Godeau, J.C. Piette, Percentage of glycosylated serum ferritin remains low throughout the course of adult onset Still's disease, Ann. Rheum. Dis. 59 (2000) 347–350.
[20] T. Ota, I. Katsuki, Ferritin subunits in sera and synovial fluids from patients with rheumatoid arthritis, J. Rheumatol. 25 (1998) 2315–2318.
[21] L.B. Daniels, R.H. Glew, Beta-glucosidase assays in the diagnosis of Gaucher's disease, Clin. Chem. 28 (1982) 569–577.
[22] S. Ghosh, S. Hevi, S.L. Chuck, Regulated secretion of glycosylated human ferritin from hepatocytes, Blood 103 (2004) 2369–2376.
[23] G. von Heijne, P. Liljestrom, P. Mikus, H. Andersson, T. Ny, The efficiency of the uncleaved secretion signal in the plasminogen activator inhibitor type 2 protein can be enhanced by point mutations that increase its hydrophobicity, J. Biol. Chem. 266 (1991) 15240–15243.
[24] C. Kannengiesser, A.M. Jouanolle, G. Hetet, A. Mosser, F. Muzeau, D. Henry, E. Bardou-Jacquet, M. Mornet, P. Brissot, Y. Deugnier, B. Grandchamp, C. Beaumont, A new missense mutation in the L ferritin-coding sequence associated with elevated levels of glycosylated ferritin in serum and absence of iron overload, Haematologica 94 (2009) 335–339.
[25] M. Worwood, Ferritin, Blood Rev. 4 (1990) 259–269.
[26] M. Lorber, Letter: iron distribution in adult-type Gaucher's disease, N Engl J. Med. 292 (1975) 110.
[27] J.M. Aerts, C.E. Hollak, Plasma and metabolic abnormalities in Gaucher's disease, Baillières Clin. Haematol. 10 (1997) 691–709.
[28] V. Barak, M. Acker, B. Nisman, I. Kalickman, A. Abrahamov, A. Zimran, S. Yatziv, Cytokines in Gaucher's disease, Eur. Cytokine Netw. 10 (1999) 205–210.
[29] B. Fautrel, G. Le Moël, B. Saint-Marcoux, P. Taupin, S. Vignes, S. Rozenberg, A.C. Koeger, O. Meyer, L. Guillevin, J.C. Piette, P. Bourgeois, Diagnostic value of ferritin and glycosylated ferritin in adult onset Still's disease, J. Rheumatol. 28 (2001) 322–329.
[30] L. Fardet, P. Coppo, A. Kettaneh, M. Dehoux, J. Cabane, O. Lambotte, Low glycosylated ferritin, a good marker for the diagnosis of hemophagocytic syndrome, Arthritis Rheum. 58 (2008) 1521–1527.
[31] O. Lambotte, P. Cacoub, N. Costedoat, G. Le Moël, Z. Amoura, J.C. Piette, High ferritin and low glycosylated ferritin may also be a marker of excessive macrophage activation, J. Rheumatol. 30 (2003) 1027–1028.
[32] Z. Wang, Y. Wang, J. Wang, C. Feng, L. Tian, L. Wu, Early diagnostic value of low percentage of glycosylated ferritin in secondary hemophagocytic lymphohistiocytosis, Int. J. Hematol. 90 (2009) 501–505.