

Coagulation Parameters in Adult Patients With Type-1 Gaucher Disease

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Abstract

Background: Gaucher disease is a rare inborn error of lysosomal metabolism, characterized by lysosomal storage of the β -glucosylceramide. Bleedings observed in type-1 Gaucher disease (GD1) are commonly attributed to a low platelet count, but they can also occur when the platelet count is normal or slightly low. Abnormal platelet function has been described and deficiencies in coagulation factors too, such as factors II, V, VII, VIII, IX, X, XI, XII, and von Willebrand factor. However, studies are few in number, involving few patients and having varying conclusions. The aim of this study was to analyze clotting factor deficiencies in a larger cohort of French patients with GD1.

Methods: This is an observational national study. The coagulation parameters were collected during routine GD1 monitoring and described retrospectively.

Results: We highlighted low levels of various coagulation factors in

46% of the patients with GD1. The most frequent coagulation abnormalities encountered were factor V, X, XI, and XII deficiencies. Deficits were usually mild and coagulation abnormalities tended to be more frequent in non-splenectomized patients.

Conclusions: In conclusion, frequent and varied coagulation abnormalities were found in a high proportion of GD1 patients.

Keywords: Gaucher disease; Coagulation; Lysosomal storage disorder; Clotting factors

Introduction

Gaucher disease (GD) is a rare inborn error of lysosomal metabolism, characterized by lysosomal storage of the β -glucosylceramide sphingolipid [1]. Disease incidence is around 1/50,000 births in the general population, but 1/800 in the Ashkenazi Jewish population [2, 3]. GD is due to a deficiency in acid beta-glucosidase (a lysosomal enzyme also called glucocerebrosidase) or, in rare cases, in its activator, saposin C [4]. Detection of low glucocerebrosidase activity in peripheral leucocytes confirms the diagnosis of GD [5]. Three different types of GD have been described. Type-1 GD (GD1) is characterized by a combination of splenomegaly and/or hepatomegaly, cytopenia (thrombocytopenia, anemia, and more rarely leukopenia) of varying degrees, and/or severe bone involvement (Erlenmeyer flask deformity, bone infiltration, osteoporosis, fractures, lytic lesions, pathological and vertebral fractures, bone infarcts and avascular necrosis leading to degenerative arthropathy) [1]. GD1 represents 90% of all cases in Western countries. Bleeding observed in GD1 is commonly attributed to a low platelet count, but it can also occur when the platelet count is normal or slightly low. Abnormal platelet function has been described with GD, and although it seems unaffected by enzyme replacement therapy (ERT), it does seem improved by splenectomy [6]. Deficiencies in coagulation factors such as factors II, V, VII, VIII, IX, X, XI, XII, and von Willebrand factor (vWF) have been reported as causes of bleeding in clinical cases of GD1 [7]. Furthermore, four studies have investigated plasma coagulation factor deficiencies in GD, with various conclusions [8-11], including suggestions that coagulation abnormalities were due to coagulation factors

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Table 1. GD1 Patient's Characteristics

	Total (N = 43)	Splenectomized (N = 13)	Non-splenectomized (N = 30)
Male, n (%)	26 (60%)	7 (54%)	19 (63%)
Median age at diagnosis (min. - max.) (years)	29 (2 - 62)	29 (8 - 62)	30.5 (2 - 59)
Median age at inclusion (min. - max.) (years)	52 (18 - 83)	62 (18 - 83)	52 (25 - 80)
Splenectomy, n (%)	13 (30%)	13	0
Treatment, n (%)	38 (88%)	12 (92%)	26 (87%)
ERT	36	12	24
SRT	2	0	2
Genotype, n (%)	23 (53%)	4 (31%)	19 (63%)
Compound heterozygous (N370S/other)	16	3	13
N370S homozygous	6	0	6
L444P/R463C	1	1	0

GD1: type-1 Gaucher disease; ERT: enzyme replacement therapy; SRT: substrate reduction therapy.

consumption rather than impaired synthesis. The purpose of our study was to analyze clotting factor deficiencies in a larger cohort of French patients with GD1.

Patients and Methods

All the investigators were involved in the management of GD and worked in reference centers for lysosomal-storage diseases and/or metabolic diseases.

This is an observational national study. Clinical data were collected from the case report forms of a previous study about the diagnostic journey undergone by patients with GD1.

The coagulation parameters of GD1 patients were collected during routine GD1 monitoring and described retrospectively. Activated partial thromboplastin time (aPTT) and prothrombin time (PT) were measured using standard methods. The coagulation parameters assessed were: fibrin, factors II, V, VII, VIII, IX, X, XI, XII, protein C, protein S, and antithrombin (AT). Coagulation parameters in splenectomized and non-splenectomized patients were compared using a Fisher's exact test.

This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki declaration.

Results

The study included 43 patients (17 women and 26 men). Median age at inclusion was 52 years old (range: 18 - 83). Table 1 describes the patients' characteristics. Table 2 shows the median rate, range, and percentage of patients with results below normal values for the complete patient cohort as well as the non-splenectomized and splenectomized groups. Median time since splenectomy was 27 years (range, 6 - 44). None of the patients were treated with anticoagulant.

Seven patients suffered from a recurrent, moderate cutaneous or mucosal bleeding tendency before the introduction of

ERT. No deaths related to bleeding occurred. All these seven patients had thrombocytopenia, ranging from $34 \times 10^9/L$ to $136 \times 10^9/L$. At the time of the survey, one non-splenectomized, untreated patient suffered from nose and gingival bleedings; he had low platelets ($63 \times 10^9/L$) but no clotting factor deficiencies. Twenty (46%) patients had a deficiency in one or more clotting cofactors.

PT and aPTT were prolonged in 10% and 21% of patients, respectively. All the patients with abnormal PT were non-splenectomized. No hypofibrinogenemia was detected. The most frequent coagulation abnormalities encountered were factor V, X, XI, and XII deficiencies. Factor V was low in 31% of patients, principally in non-splenectomized patients; deficits were mild (minimum level 51%). Factor X was low in 11.5% of patients, mainly in splenectomized patients. Factor X was not very low, except for one patient with a level at 20%. This patient was splenectomized, treated with ERT, and had a deficiency in five different clotting cofactors. Factor XI was low in 20% of patients, mainly in non-splenectomized patients; their deficit was usually mild (minimum level 44%). Factor XII was low in 13% of patients, all of whom were non-splenectomized.

Fifteen patients had a single deficiency, and five had two or more clotting factor deficiencies. One splenectomized patient, with bone involvement (femoral osteonecrosis and fracture) and treated with ERT, had five clotting-factor deficiencies, although he has neither hemorrhagic features nor hepatocellular insufficiency: his results for factors II, VII, IX, and X were 42%, 19%, 53%, and 20%, respectively, and his protein C level was 28%.

Some deficiencies, such as hypofibrinogenemia and hemophilic factor VIII deficiency, were not observed among our GD1 patients, whether they were splenectomized or not.

Among the factor deficiencies which can lead to a prothrombotic state, we evidenced protein C deficiency and protein S deficiency in 12% and 16% of patients, respectively. No AT deficiencies were found. Two patients (from 25 tested) had anticardiolipin antibodies and two had circulating anticoagulant without any thrombosis. Overall, coagulation abnormalities were more frequent in non-splenectomized patients than in splenectomized ones.

Table 2. Coagulation Parameters in 43 GD1 Patients

	TP	Fib	II	V	VII	VIII	IX	X	XI	XII	AT	PC	PS
Normal value	70 - 100	1.5 - 4.0	70 - 140	70 - 140	70 - 120	60 - 150	60 - 120	70 - 150	60 - 120	60 - 160	80 - 120	70 - 140	70 - 140
Complete cohort (N = 43)													
N	33	38	26	29	29	25	22	26	25	23	26	26	26
% deficit	12	0	8	31	3.4	4	4.5	11.5	20	13	0	11.5	19
Median (min. - max.)	90 (58 - 146)	2.85 (1.9 - 11)	87 (42 - 112)	84 (51 - 116)	94 (19 - 118)	106 (58 - 239)	105 (53 - 151)	83 (20 - 151)	82 (45 - 155)	93 (33 - 210)	100 (83 - 142)	109 (28 - 151)	86 (83 - 148)
Splenectomized group (N = 13)													
N	10	11	5	8	8	5	5	7	6	5	6	6	6
% deficit	0	0	20	12.5	12.5	0	20	14.3	16.7	0	0	16.7	16.7
Median (min. - max.)	97 (76 - 146)	3.1 (2.1 - 5.2)	89 (42 - 96)	100 (64 - 116)	96 (19 - 118)	144 (75 - 239)	93 (53 - 117)	95 (20 - 151)	81 (56 - 155)	101 (68 - 210)	93 (83 - 110)	110 (28 - 118)	95 (88 - 148)
Non-splenectomized group (N = 30)													
N	23	27	21	21	21	20	17	19	19	18	20	20	20
% deficit	17.4	0	4.8	38	0	5	0	10.5	32	16.7	0	10	20
Median (min. - max.)	87 (58 - 114)	2.6 (1.9 - 11)	86 (50 - 112)	81 (51 - 111)	91 (72 - 108)	105 (58 - 220)	107 (76 - 159)	82 (49 - 122)	82 (45 - 120)	91 (33 - 149)	101 (90 - 142)	109 (58 - 142)	89 (43 - 151)
P	0.29	1	0.35	0.37	0.3	1	0.26	1	0.44	1	1	0.6	1

GD1: type-1 Gaucher disease; N: number of patients tested; P: difference in clotting factor deficit between splenectomized and non-splenectomized cohorts; AT: antithrombin; PC: protein C; PS: protein S.

Discussion

Low levels of various coagulation factors were found in 46% of the GD1 patients in the present study. This result is lower as compared to the data from Hollak et al, who reported clotting factor abnormalities in almost all their patients [8]. They described factor V deficiency in 87% of them, whereas we observed this abnormality in only 31% of our patients. Moreover, Mitrovic also reported hemostatic abnormalities in untreated GD patients [12]. The most frequently encountered clotting factor deficiency in his study was factor V in about 30% of cases, which is in accordance with our findings. We cannot exclude that this difference was only linked to an effect of treatment, as most of our patients were already undergoing ERT at the time of the survey. For some authors, even though controversy remains, ERT partly restores clotting factor levels [10, 11]. The severity of deficiencies in the present study was extremely variable and not always correlated with hemorrhagic syndrome. The lowest levels were recorded for factors VII and X, confirming previous results [8]. We observed variable but minor bleeding, including mucosal and cutaneous hemorrhages, but this was more related to thrombocytopenia than to clotting factor deficiencies. These data are in accordance with the literature [8, 9, 12].

Although all the coagulation abnormalities have been described in previous clinical studies or case reports, the most frequently observed among GD1 patients have been factor XI deficiency and factor II, V, VII, and X deficiencies [8]. A high frequency of factor XI deficiency has been highlighted among Ashkenazi patients with GD1, due to the common occurrence of both genetic disorders in this population [13].

Coagulation abnormalities in GD1 patients could be related to impaired factor production. Production of clotting factors by the liver may be deficient, due to Gaucher cell infiltration into that organ. However, we observed no liver enzyme abnormalities in our patients, and AT levels were normal in the 27 patients tested despite those levels usually being lower when liver function is impaired (Table 2).

The present study showed that coagulation abnormalities tended to be more frequent in non-splenectomized patients than in splenectomized ones, but the difference was not statistically significant (53% vs. 23%; P = 0.09). In particular, deficiencies in factors V and XI were more often observed in non-splenectomized patients. In the literature, the impact of splenectomy on clotting factors is controversial.

Conversely, one of our splenectomized patients, treated with high-dose imiglucerase, presented a multiple coagulation-factor deficiency (factor II, 42%; factor VII, 19%; factor IX, 53%; factor X, 20%) associated with both protein C and S deficiencies (28% and 38%, respectively), but without thrombocytopenia. This patient had no hepatocellular insufficiency, which is an argument for the absence of impaired synthesis.

Another particularity among our patients was the persistence of coagulation factor abnormalities despite long-term ERT. Some authors have observed that all lower coagulation factors returned to normal values after the start of ERT, with median times of 24 - 28 months [10, 11].

The present study had some limitations. Study size was

limited, and data were not exhaustive for all patients. Moreover, it is impossible to exclude a recruitment bias because only patients from the same country have been investigated. However, the study showed that a significant number of our GD1 population (20 of 43 tested patients) had at least one hemostatic abnormality. These results could justify a systematic, complete hemostasis assessment for every patient with GD1, especially in cases of planned surgery.

In conclusion, frequent and varied coagulation abnormalities were found in a high proportion of GD1 patients. Some patients had multiple coagulation factor deficiencies, but they were not always correlated with spontaneous bleeding conditions. However, a correlation with patients still having their spleens is probable.

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Conflict of Interest

We confirm that all authors have no conflict of interest to disclose either related to product or companies named in the article or to competing products or companies.

Informed Consent

Not applicable.

Author Contributions

Acquisition of data: CS and PC; drafting of the manuscript: CS and PC; critical proofreading: OL, EN, AM, VLS, RJ, CL, FM, IM.

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