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Gaucher Disease in Ontario, Canada: Clinical Manifestations, Natural Progression, and Treatment Response

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ABSTRACT

Gaucher disease (GD) is characterized by a deficiency in lysosomal glucocerebrosidase, resulting in a multisystemic disease with substantial variability in clinical manifestations, disease progression, and treatment response. This is the first study in Canada that examines the epidemiological profile of Gaucher patients, mapping out the GD clinical spectrum in the ethnically diverse province of Ontario.

Study found a prevalence of 1:155,367 (1:9,853 for Ashkenazi-Jews) type 1 GD adults in Ontario. Splenectomy was associated with improved thrombocytopenia, worsened hyperferritinemia and bone pain, but no effects on anemia, bone mineral density or bone crises. Compared to the non-treatment group, a higher proportion of patients who received enzyme replacement/substrate reduction therapy (ERT/SRT) presented with anemia, hepatomegaly, bone pain, and bone crises at baseline, suggesting that these presentations may be predictive of subsequent need for treatment. ERT/SRT were effective in improving all hematological, visceral, and skeletal manifestations (except bone mineral density), whereas the non-treatment group remained clinically stable over time (10.88 years) without significant disease progression – thus early use of ERT/SRT may not be necessary in all patients.

This comprehensive analysis summarizes the genotypic and phenotypic heterogeneity of GD, serving as a comparative resource for optimization of care for adult patients.

Introduction

Gaucher disease (GD) is an autosomal recessive disorder characterized by mutations in the glucocerebrosidase (*GBA*) gene, which results in the accumulation of undegraded glucocerebrosides in macrophages' lysosomes[1]. These macrophages predominantly infiltrate the liver, spleen, and bone marrow, leading to multisystemic manifestations such as anemia, thrombocytopenia, hepatosplenomegaly, and skeletal complications[2,3]. GD is categorized into three clinical subtypes based on the severity of neurological manifestations. Type 1 makes up 94%[4] of all occidental GD cases and is traditionally considered to be non-neuronopathic in contrast to the more severe type 2 (acute neuronopathic) and type 3 (subacute neuronopathic) phenotypes with early onset of central nervous system involvement[5]; however, there are also increasing reports of parkinsonism and peripheral neuropathy in type 1 patients[6,7].

Before enzyme replacement therapy (ERT) became available in 1991, splenectomy was the treatment of choice in patients with massive splenomegaly or severe thrombocytopenia and anemia. However, spleen removal was accompanied by a more aggressive

bone disease, and so such procedure is no longer justified since the emergence of ERT[8-10]. The first ERT, alglucerase (Ceredase; Genzyme Corporation)[11], was later replaced by a recombinant product, imiglucerase (Cerezyme; Genzyme Corporation)[12]. This was followed by velaglucerase in 2010 (V PRIV; Shire Human Genetics Company)[13]. Taliglucerase (Elelyso; Pfizer Inc)[14] currently is not approved in Canada outside of Quebec. Substrate reduction therapies (SRT) such as miglustat (Zavesca; Actelion)[15] and eliglustat (Cerdelga; Genzyme Corporation)[16] are usually used as second-line treatments in Canada, although the latter has been approved for first-line therapy in some jurisdictions.

Over 350 *GBA* mutations have been reported to cause GD[17], with marked variability in disease severity, clinical manifestations, natural progression, and treatment response[18-20]; there are also patients who are either asymptomatic or have clinically mild phenotypes that may never require treatment. GD has a low disease prevalence of 1:136,000-200,000[9,21,22], but a high prevalence in Ashkenazi-Jews (1:850-1,000)[23,24]; however, a high percentage of Jews are homozygous for the N370S genotype that is associated with a milder phenotype, and many of these may never come to medical attention[25-28].

There have been several studies examining the epidemiological profiles of GD in specific regions such as France[21], Brazil[29], Iberia[9], and South Florida[30], but none in Canada. Ontario is the highest populated province in Canada, consisting of 38.5% of the population[31], the largest share (53.3%) of immigrants[32], and more than half (57.9%) of Ashkenazi Jews[33]. Therefore, this study aims to explore the spectrum of variable GD phenotypes in ethnically diverse Ontario through the Ontario Gaucher disease referral centre (Mark Freedman and Judy Jacobs Program for Gaucher Disease), which opened in 1996. This is an epidemiological approach to examine the clinical pattern of disease manifestations, natural disease progression, and treatment response in adult Gaucher patients.

Material and methods

This is a retrospective chart review of adult GD patients in Ontario who had at least one consultation with a GD specialist between 1996 and August 2016, with patient medical records available as early as 1980. All patients in this study were identified through the Ontario Gaucher disease referral centre, and this comprises the great majority of known adult GD patients in Ontario. Patients' diagnoses were confirmed by the reduced glucocerebrosidase activity in leukocytes or fibroblasts[34]. The following demographic data were collected: gender, year of birth, ethnicity, GD type, *GBA* genotype, year of diagnosis, date of first consult, and year of death. Clinical information included: bloodwork (e.g. hemoglobin, platelets, chitotriosidase [CHITO], ferritin), treatment type and duration, spleen status, liver and spleen sizes, Parkinson disease, monoclonal gammopathy of undetermined significance (MGUS), and malignancies. Skeletal complications included: bone pain, bone crises, bone mineral density (BMD) status, and Erlenmeyer flask deformity.

For the purpose of data analysis, patients who had received at least one ERT/SRT were considered as the treatment group, whereas the non-treatment group refers to patients who had never been on treatment. To improve comparison methodology, as patients under study have varying follow-up timelines and treatment initiation points, baseline and end-points were standardized for patients (see Table 1 for definitions). This standardizes baseline for the "treatment group" patients, as some patients were already on treatment before first consult (treatment group 1), while others either initiated treatment around the first consult (treatment group 2) or were followed for a period before treatment initiation (treatment group 3).

Study cutoff date is August 31st, 2016

a. First consult is defined as first consultation with Dr. Dominick Amato (the physician responsible for all GD patients in the centre)

b. If pre-treatment data was not available, data on the date of treatment initiation was used instead

Follow-up durations (Table 2) are calculated as: follow-up before treatment initiation (first consult to first treatment date); treatment duration (very first treatment to very last treatment date or to study cutoff date for ongoing treatments. Midway treatment interruption < 1 year is still calculated as on-treatment); follow-up after treatment termination (last treatment date to study cutoff date). For the non-treatment group, patients are followed from first consult to study cutoff date.

Table 1. *Definitions for baseline and end-point clinical data*

Group	Baseline	End-Point
Non-treatment	Clinical data upon first consult[a]	Closest data to study cutoff date
Treatment	Most recent data before treatment initiation[b]	For ongoing treatments: closest data to study cutoff date If treatment terminated before study cutoff: first available data closest to treatment termination

Table 2. *Follow-up and treatment durations*

	Follow-up duration before treatment initiation (years)	Treatment duration (years)	Follow-up duration after treatment termination (years)
Treatment Group 1	N/A (Not Applicable)	16.54 [1.67-22.33] n=12	1 n=1
Treatment Group 2	N/A	5.42 [1.25-11.33] n=5	N/A
Treatment Group 3	2.25 [0.17-17.25] n=29	6.25 [1.50-23.50] n=29	0.92 [0.67-5.67] n=4
Non-treatment	10.88 [0.92-24.33] n=30	N/A	N/A

Median [range]

Abnormal hematological values were defined as: anemia (male: hemoglobin < 130 g/L, female: hemoglobin < 120 g/L), thrombocytopenia (platelets < 150 x 109/L), elevated ferritin (male: >500 µg/L, female: >300 µg/L), and elevated CHITO (>120 nmol/hr/ml). Spleen and liver volumes were measured in multiples of normal (MN), assuming normal spleen volume is 0.2 % of body weight and normal liver volume is 2.5 % of body weight35. MN>1 is defined as hepato/splenomegaly. If volumetric measurement was not available through either magnetic resonance imaging, computed tomography, or ultrasound, splenomegaly and hepatomegaly were alternatively defined as greater than 13cm or 15cm in length on imaging, respectively. If no imaging was available, palpation was used to identify splenomegaly (cm below the costal margin) and hepatomegaly (liver span > 12cm by percussion, or cm below right costal margin by palpation) instead.

As for the skeletal complications, Erlenmeyer flask deformity is characterized by the expansion of the distal lateral femur and proximal tibia[36]. Bone crisis, as previously described, is "pain with acute onset that requires immobilization of the affected area, narcotics for the relief of pain, and may be accompanied by one or more of the following: periosteal elevation: elevated white blood cell count, fever, or debilitation > 3 days[37]." Baseline bone crises are defined as any episodes prior to or on the day of baseline data collection. BMD was measured either radiographically or via dual-energy X-ray absorptiometry (DXA) and is categorized into normal, osteopenia, and osteoporosis.

Statistical Analysis

A total of 103 patients were screened for this study. According to the available data, 10 patients have died, 2 patients were not residents of Ontario, and 1 patient underwent bone marrow transplant and was cured of GD; these patients were excluded from all subsequent data analyses. The 5 patients with no detailed information available were included only in the total disease prevalence count; this leaves 85 patients for the rest of the data analyses. Patients who were lost to follow-up or treated for less than one year were excluded from analyses of treatment response, natural disease progression, and follow-up/treatment duration calculations.

Data were analyzed using IBM SPSS Statistics 20, and all analyses were done based on available data. Categorical variables are expressed as proportions; descriptive statistics such as mean and standard deviation are reported for continuous variables. Treatment and follow-up durations were calculated in months. To examine the differences between patients' baseline and most recent/during-treatment data, paired samples t-test was used to assess continuous variables, and Wilcoxon signed rank test was used for ordinal variables (e.g. BMD) or non-normal distributions of continuous variables. Pearson Chi-square and Fisher's exact tests, based on sample sizes, were used to compare the differences in the proportion of patients between different subgroups presenting with categorical baseline abnormalities; and Mann-Whitney U test was used for ordinal variables. The log of CHITO value was employed to address the inter-variability of CHITO levels between patients.

Results

Entire cohort

This study reported a total of 90 adult GD patients living in Ontario, leading to an estimated disease prevalence of 1: 155,367[38]. Twenty-three (27.1%) patients were known Ashkenazi-Jews, which corresponds to a disease prevalence

Table 3. *Glucocerebrosidase (GBA) genotype*

	Frequency	Percentage (%)
N370S/N370S	25	29.4
N370S/L444P	18	21.2
N370S/other	31	36.5
L444P/L444P*	1	1.2
L444P/other	6	7.1
Other/other	3	3.5
N370S/unidentified	1	1.2

of 1: 9,853 in the Ashkenazi-Jewish population in Ontario[33]. All patients were Type 1 GD, with 63.5% female, and a median age at GD diagnosis of 23 [birth-89]; 44.7% (38/85) of patients were diagnosed in childhood (56% in treatment, 28.6% in nontreatment group). The follow-up durations are noted in Table 2. Overall, 50 (58.8%) patients had received ERT/SRT, whereas 35 (41.2%) patients had never been on treatment. The most common *GBA* mutation was 31 (36.5%) N370S/other, followed by 25 (29.4%) homozygous N370S, then 18 (21.2%) N370S/L444P (Table 3).

*This patient has now reached her 7th decade, and has shown none of the typical neurological findings seen in type 3 disease. Her mutation analysis was done in two independent laboratories.

The most common abnormality at baseline was elevated CHITO (100% of patients with available data), followed by splenomegaly (90.9%), hepatomegaly (71.2%), thrombocytopenia (67.1%), hyperferritinemia (59.2%), reduced BMD (46.4%), anemia (42.7%), bone pain (30.1%), splenectomy (17.6%), and bone crises (9.6%) (Table 4).

In comparison to the non-treatment group, a higher proportion of patients in the treatment group presented with anemia (53.2% vs. 28.6%, p=0.026), hepatomegaly (80.9% vs. 57.6%, p=0.024), bone pain (42.9% vs. 11.8%, p=0.002), and bone crises (16.3% vs. 0.0%, p=0.019) at baseline. No significant differences were observed in the proportion of patients presenting with thrombocytopenia, hyperferritinemia, elevated CHITO, splenectomy, splenomegaly, and reduced BMD, as summarized in Table 4.

Other GD-associated complications include 62 (73.8%) Erlenmeyer flask deformity and 12 (14.1%) MGUS. In addition, 4 (4.7%) patients developed Parkinson disease, with a median age of 65.5 [51-68] at diagnosis (Table 5). A total of 12 (14.1%) patients were diagnosed with malignancies: 3 breast cancers, 3 colon cancers, 1 smoldering myeloma, 1 Hodgkin lymphoma, 1 non-Hodgkin lymphoma, 1 essential thrombocythemia, 1 prostate cancer, and 1 renal cancer. The total cancer rate (14.1%) was higher than the 10-year cancer prevalence (calculated to be 2.7%) in the Ontario population[39].

Treatment group

A total of 46 patients were available for the treatment group analyses. The median diagnosis-to-first-treatment interval was 11 years [0-46 years], and the overall median treatment duration was 7.83 [1.25-23.50] years. The most recent agents the patients were on were: 19 imiglucerase, 15 velaglucerase, 1 taliglucerase, 7 miglustat, 4 eliglustat.

The hemoglobin and platelet levels increased significantly after treatment, whereas significant reductions in ferritin, log CHITO, and spleen and liver sizes were observed (Table 6). Although no significant change in BMD was observed, the majority of patients (13 [72.2%]) with baseline bone pain are pain free after ERT/SRT; only 2/25 (8%) with no baseline pain developed pain by the end of the treatment. For bone crises, the patients who were crisis-free at baseline did not develop any episodes of bone crises post-treatment; 6 of the 8 patients (75%) with a

Table 4. *Baseline characteristics of the entire cohort, treatment group, and non-treatment group*

		Pearson Chi-Square Test			
	Entire cohort	Treatment group	Non-treatment group	p-value	Likelihood ratio
Anemia	42.7% (35/82)	53.2% (25/47)	28.6% (10/35)	**0.026**	5.07
Thrombocytopenia	67.1% (55/82)	70.2% (33/47)	62.9% (22/35)	0.483	0.49
Hyperferritinemia	59.2% (45/76)	61.0% (25/41)	57.1% (20/35)	0.735	0.12
Elevated Chitotriosidase	100% (58/58)	100% (28/28)	100% (30/30)	N/A	N/A
Splenectomy	17.6% (15/85)	18.0% (9/50)	17.1% (6/35)	0.919	0.01
Splenomegaly	90.9% (60/66)	97.4% (37/38)	82.1% (23/28)	0.076[a]	4.69
Hepatomegaly	71.2% (57/80)	80.9% (38/47)	57.6% (19/33)	**0.024**	5.09
Reduced bone mineral density (osteopenia or osteoporosis)	46.4% (32/69)	50.0% (18/36)	42.4% (14/33)	0.528	0.40
Bone pain	30.1% (25/83)	42.9% (21/49)	11.8% (4/34)	**0.002**	10.02
Bone crises	9.6% (8/83)	16.3% (8/49)	0% (0/34)	**0.019**[a]	9.02

Statistically significant

a. Fisher's exact test p-value

Table 5. *Gaucher disease associated complications*

	Prevalence (%)
Erlenmeyer flask deformity	62/84= 73.8%
Monoclonal gammopathy of undetermined significance (MGUS)	12/85 = 14.1%
Malignancies	12/85= 14.1%
Parkinson disease	4/85= 4.7%

Table 6. *Treatment response*

	Baseline (mean±S.D.)	End-Point (mean±S.D.)	Mean difference (mean±S.D.)	P-value	Confidence interval
Hemoglobin (g/L) (n=43)[a]	121.79±16.00	135.79±13.54	Not applicable (N/A)	**<0.001**	N/A
Platelets (x10^9/L) (n=43)	115.53±84.97	170.23±50.31	54.70±65.36	**<0.001**	34.58, 74.81
Ferritin (μg/L) (n=37)	651.62± 477.44	366.03±281.58	-285.59±438.65	**<0.001**	-431.85, -139.34
Log (Chitotriosidase) (n=24)	3.51±0.50	2.67 ±0.44	-0.83 ±0.44	**<0.001**	-1.02, -0.65
Spleen size (multiples of normal) (n=18)[a]	10.36±7.42	3.86±2.00	N/A	**<0.001**	N/A
Liver size (multiples of normal) (n=17)	1.18±0.25	0.94±0.15	-0.24±0.22	**<0.001**	-0.35, -0.13
Bone mineral density (normal, osteopenia, or osteoporosis) (n=31)	N/A	N/A	N/A	1.000	N/A

Statistically significant
S.D. = standard deviation
a. Wilcoxon signed rank test

history of bone crisis at baseline had no recurrence post-therapy.

Non-treatment group

The natural disease progression of GD was determined by analyzing the changes from baseline characteristics over time in the untreated cohort. Out of the 35 patients in the non-treatment group, 5 were lost to follow-up, so only 30 were included in the following analyses. Patients were followed for a median of 10.88 [0.92-24.33] years.

A mild but statistically significant decrease in hemoglobin level (-4.90 ±10.84 g/L, p=0.019) was observed over time, whereas platelets, ferritin, log CHITO, spleen and liver size, and BMD remained constant for the duration of the follow-up (Table 7). Skeletal symptoms also remained stable: all patients (4/4) with baseline bone pain still had bone pain at study termination; 24/25 (96%) patients with no baseline bone pain remained painless at the end of the study; no patient has experienced a bone crisis in the non-treatment group.

a. One patient developed essential thrombocythemia and was removed from the analysis as an outlier

b. Wilcoxon signed rank test

Table 7. *Natural progression of baseline characteristics in the non-treatment group*

	Baseline (mean±S.D.)	End-Point (mean±S.D.)	Mean difference (mean±S.D.)	P-value	Confidence interval
Hemoglobin (g/L) (n=30)	129.17±12.78	124.27±13.83	-4.90±10.84	**0.019**	-8.95, -0.85
Platelets (x10^9/L) (n=29)[a]	142.28±69.06	130.24±77.39	-12.03 ± 35.84	0.081	-25.67, 1.60
Ferritin (μg/L) (n=29)[b,c]	505.76±404.99	553.83±396.09	Not applicable (N/A)	0.681	N/A
Log (Chitotriosidase) (n=24)[b]	3.30±0.54	3.37 ±0.46	N/A	0.732	N/A
Spleen size (multiples of normal) (n=17)	6.11 ±5.15	6.22±5.21	0.12±1.13	0.679	-0.46, 0.69
Liver size (multiples of normal) (n=18)	1.10±0.34	1.08±0.31	-0.01±0.16	0.721	-0.09, 0.07
Bone mineral density (normal, osteopenia, or osteoporosis) (n=22)	N/A	N/A	N/A	0.132	N/A

Statistically significant
S.D. = standard deviation

Table 8. *Baseline characteristics: with-spleen vs. without-spleen cohort*

	In patients with intact spleen	In asplenic patients	Pearson-Chi Square test p-value	Likelihood ratio
Anemia	40.3% (27/67)	53.3% (8/15)	0.356	0.84
Thrombocytopenia	77.6% (52/67)	20.0% (3/15)	**<0.001**[a]	17.65
Hyperferritinemia	53.2% (33/62)	85.7% (12/14)	**0.025**	5.59
Bone mineral density (normal, osteopenia, or osteoporosis)	N/A	N/A	0.577[b]	N/A
Bone pain	24.6% (17/69)	57.1% (8/14)	**0.025**[a]	5.40
Bone crises	7.2% (5/69)	21.4% (3/14)	0.128[a]	2.21

Statistically significant

a. Fisher's exact test p-value

b. Mann-Whitney U test p-value

c. One extreme outlier with a 1563 µg/L reduction in ferritin level that was greater than 3xIQR was removed

Splenectomy

The median age at splenectomy was 11.5 [4-57] years, with a total of 15 patients (17.6%) splenectomized (6 in non-treatment and 9 in treatment group). All asplenic patients in the treatment group underwent splenectomy before treatment initiation. The association between splenectomy and patients' baseline characteristics is reported in Table 8. A higher proportion of asplenic patients presented with hyperferritinemia (85.7%) and bone pain (57.1%) compared to patients with intact spleen (53.2% and 24.6% respectively). In contrast, only 20.0% of asplenic patients presented with thrombocytopenia compared to 77.6% in patients with intact spleen. No correlations were observed between spleen status and anemia, BMD, or bone crises.

Discussion

This is the first epidemiological study to describe the Canadian GD spectrum, and comprises the majority of known adult GD patients in Ontario who have sought medical consults within the past 20 years. The reported prevalence of adult GD patients living in Ontario is 1: 155,367, similar to previous reports of 1: 136,000-200,000[9,21,22]. A disease prevalence of 1: 9,853 in the Ashkenazi-Jews in Ontario was also observed, higher than the general population, but lower than literature findings of 1: 850-1,000 Jews[23,24]. This suggests that there are likely Jewish persons in Ontario who either are undiagnosed or have not been referred to our centre. The most common ethnic origins in Ontario are Canadians, followed by English, Scottish, and Irish[40]. Accordingly, this patient cohort has similar genotype composition when compared to the United Kingdom/Ireland population: N370S/N370S (29.4% vs. 30.3%) and N370S/other 36.5% vs. 40.0%), except for N370S/L444P (21.2% vs. 3.3%)[30]. Similarities were also observed when compared to the World ICGG Registry, in N370S/N370S (29.4% vs. 24.0%) and N370S/L444P (21.2% vs. 18.1%), except for N370S/other (36.5% vs. 46.7%)[30].

Entire Cohort

Most of the overall baseline characteristics (Table 4) fell within the approximate ranges of previous literature findings[2,9,21,29,41-46], except that the proportion of splenectomized patients (17.6%) was slightly lower than literature values (22.5-30%) possibly due to this study's smaller sample size in comparison[2,47,48].

Comparison of the baseline characteristics between treatment and non-treatment groups shows a higher proportion of the treatment group having presented with anemia, hepatomegaly, bone pain, and bone crises. Similar skeletal symptoms have also been reported by Mekenian et al., but they found no differences in the hemoglobin levels or the proportions of hepatomegaly[42]. This is possibly due to the discrepancies in assessment criteria: their median hemoglobin values (12 g/dL [no ERT] and 12.5 g/dL [with ERT]) were close to our cutoff for anemia, and they defined hepatomegaly based on liver diameter, instead of the combination of methods used in the current study. Unlike the Wenstrup et al. study, where the treatment group presented with a lower Z-score at baseline[49], the current study did not observe a difference in baseline BMD. This may be due to the different analytical approaches, where the present study analyzed BMD in categories of normal vs. reduced (osteopenia/osteoporosis) instead of directly comparing Z-scores. Overall, our study reported a higher proportion of patients who subsequently received treatments presenting with anemia, hepatomegaly, bone pain and crises at baseline, suggesting that these clinical manifestations may be predictive of subsequent need for ERT/SRT.

In terms of the GD-associated complications, 14.1% of patients developed MGUS, suggesting a greater risk in Gaucher patients compared to the general population (1-7.5%)[50,51]. Furthermore, 4.7% of patients developed PD, a rate within the previously reported range (4-8%)[52,53]. This is higher than that of the general Canadian population living in private households (0.2%), but slightly lower than that

of residents in long-term care facilities (4.9%)[54], in keeping with the known increased risk of PD in GD patients. The observed median age of PD diagnosis was 65.5 [51-68], later than other studies [55-57.2 years][52,55], but close to that in the general population of 66.2 years[54]. GD also appeared to increase the risk of malignancies, as the reported total cancer prevalence was higher than the 10-year prevalence in the general Ontario population; other studies have also reported increased relative risks of overall cancers and hematological malignancies for GD patients[56,57].

Treatment group

The standard of care at this centre follows the Ontario treatment guidelines for ERT/SRT, and usually begins ERT with an initial dose of 30 units/kg/infusion every 2 weeks, then alters the dosage depending on response[58]. The majority (58.8%) of patients have received treatment, and ERT/SRT was noted to improve all baseline hematological, visceral, and skeletal parameters (except for BMD) in treatment-naive patients after a median treatment of 7.83 years. The reported clinical improvements were also seen in other studies with similar as well as shorter treatment durations[12,37,42,45,47,59-66]. Despite the relief of skeletal symptoms, ERT/SRT did not appear to improve BMD, contrary to other studies[12,37,49]. One limitation in this study is that rather than direct Z-score comparisons, BMD changes were evaluated semi-quantitatively in categories of normal, osteopenia, and osteoporosis. This might have resulted in a less accurate comparison and may be the cause of the discrepancies between this study and some literature findings. In summary, ERT/SRT appeared to be effective in improving the majority of the disease manifestations.

Natural disease progression

When examining the natural disease progression, we did not observe a change in platelet counts, ferritin, log CHITO, or spleen and liver volumes in most of the untreated patients over time. This stabilization was similarly reported by Beutler et al. and Piran et al.[67,68]; Zimran et al. also proposed that the progression of the disease tends to stabilize after early adulthood[18]. In contrast to literature findings, however, a mild but significant reduction in hemoglobin level was observed among the untreated patients; this was unexpected given that the present study was built upon the Piran et al. patient cohort. The discrepancy might be due to a longer follow-up duration in this study (10.88 years) compared to Piran et al. (9.5 years), Beutler et al. (around 5 years), and Zimran et al. (around 5 years); this suggests that a decrease in hemoglobin may be observed if patients are followed for an extended period. In contrast, Maaswinkel-Mooij et al. reported a progression in disease severity in 70% of their patients, possibly due to the lower proportion of N370S alleles and Askenazi Jews (both associated with a milder phenotype) in the Dutch cohort[69]. There are limited data in the literature on the natural progression of bone pain and crises. However, consistent with the observed bone pain, bone crises, and BMD stabilizations, other studies showed that skeletal lesions and BMD remained constant over time in most patients[49,67,68]. In sum, most of the GD complications in our untreated patients tend to remain stable over time; therefore, early use of ERT/SRT may not be needed in all GD patients, as suggested by previous literature[68].

Splenectomy

When patients' baseline characteristics are compared based on spleen status, a lower proportion of asplenic patients presented with thrombocytopenia, possibly due to the removal of enlarged spleens responsible for platelet sequestration[46]; this has been similarly reported in other studies[2,47,59,66,70] (Table 8). More asplenic patients were seen to present with hyperferritinemia at baseline; this was comparable to Stein et al.[66], whereas Mekinian et al. reported no differences based on spleen status[42]. It is currently unclear whether the hyperferritinemia reflects a more severe phenotype associated with the need for splenectomy or whether splenectomy is responsible for the ferritin build-up[66,71,72]. Contrary to the ICGG reports of a lower proportion of anemia in asplenic patients[2,47,59], our data did not show an association between anemia and spleen status, possibly due to a smaller patient sample size.

In terms of skeletal complications, although no correlations were observed between spleen status and BMD in the present cohort, a significantly lower BMD[73] and a higher proportion of osteoporosis[74] have been reported in splenectomized patients. Differences in methodology to evaluate BMD – semi-quantitative (current study) vs. direct comparison of Z-scores/prevalence of osteoporosis (previous literature) – may have led to the observed discrepancy. In comparison to literature findings of increased bone pain and crises in asplenic patients[2,59], a higher proportion of our asplenic patients presented with bone pain, but no differences were seen in bone crises. The increase in skeletal complications may be due to the acceleration of bone disease post-splenectomy[10]. Another, not mutually exclusive, hypothesis suggests that splenectomy may be an indication of more severe disease and greater bone involvement[22]. In summary, splenectomy appeared to be associated with improved thrombocytopenia, worsened hyperferritinemia and bone pain, but no effects on anemia, BMD or episodic bone crises. However, the impact of splenectomy is becoming less relevant in GD patients since the emergence of ERT/SRT, as these therapies help control for the majority of disease manifestations that would otherwise have led to splenectomy in the past.

Conclusions

Since more severe cases of GD tend to present earlier in childhood and require immediate ERT/SRT treatment, this paper focuses instead on optimizing the treatment guidelines in the adult population, where the decision to initiate treatment is less consistent. Overall findings suggest that the current guidelines for treatment initiation in adult patients are well-established since the treatment group patients experienced an improvement in most of the hematological, visceral, and skeletal parameters, and untreated patients' clinical manifestations remained relatively stable over time, indicating that the use of ERT/SRT may not be necessary in all patients.

This study highlights the overall genetic and phenotypic heterogeneity of GD in Ontario in relation to the variable patterns found across different demographic groups around the world. As GD is a rare condition affecting only a limited number of patients, a comprehensive analysis such as this provides a comparative resource for researchers and clinicians to evaluate their patient populations in order to optimize patient care and therapeutic regimens.

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