Infectious and digestive complications in glycogen storage disease type Ib: Study of a French cohort

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ABSTRACT

Glycogenosis type Ib (GSD1B) causes not only hypoglycemia but also infections and "Crohn's disease like" inflammatory bowel disease (IBD) that can significantly impair patient's quality of life. We retrospectively evaluated infectious and digestive complications in 9 French patients (3 girls, 6 boys) diagnosed at 0.8 years on average, with a mean follow-up of 19.1 years. Infections occurred earlier than IBD, at mean ages of 1.7 and 3.8 years, respectively. The number of acute hospitalizations was 0.7/year due to infectious (0.4/year) or digestive symptoms (0.4/year). Clinical presentations allowed separating patients into mild ($n = 5$) and severe ($n = 4$) intestinal involvement. Patients in the severe group had more serious digestive symptoms but also earlier neutropenia (median 0.3 vs. 1.5 years, $p = 0.046$) with a tendency to a lower neutrophil count (NC) during follow-up, and a higher number of acute hospitalizations (median 1.3/year vs. 0.2/year, $p = 0.014$) due to digestive symptoms (median 0.6/year vs. 0.05/year, $p = 0.012$) and infections (median 0.8/year vs. 0.2/year, $p = 0.014$). Treatments included G-CSF and cotrimoxazole ($n = 7$), 5-aminosalicylic acid ($n = 2$), and a polymeric solution enriched in the anti-inflammatory cytokine TGF-β ($n = 4$, "severe" group), and immunomodulatory treatment ($n = 1$). In conclusion, infections and IBD are rare but severe complications in GSD1B. Neutropenia tended to be more prevalent in the severe IBD group than in the mild IBD group. Dietetic treatment with specific anti-inflammatory solutions seems particularly appropriate in these patients.

1. Introduction

Glycogen storage disease type I (GSD1) is a rare disease that has two subtypes, GSD1A and GSD1B. The common metabolic phenotype includes hepatomegaly, short fasting hypoglycemia and hyperlactatemia, hyperlipidemia and hyperuricemia [1, 2, 3].

GSD1B is caused by a deficiency of glucose-6-phosphate translocase (G6PT), a ubiquitous enzyme encoded by the *SLC37A4* gene, which induces defects in the last step of both gluconeogenesis and glycogenolysis [1]. In addition to metabolic issues, GSD1B patients also present with neutropenia and neutrophil dysfunction [4]. The underlying mechanisms of neutrophil dysfunction are not well understood, but several

hypotheses have been proposed [5, 6, 7]. Patients have frequent bacterial infections and Crohn's disease-like inflammatory bowel disease (IBD), with bloody diarrhea, abdominal pains, histological inflammation of the intestinal mucosa, and mucocutaneous manifestations such as oral and perianal ulcerations [8, 9].

The treatment of GSD1B involves the limitation of fasting and galactose and fructose restricted diet to avoid hypoglycemia and limit hyperlactatemia [3, 10]. Granulocyte colony-stimulating factor (G-CSF) injections are used to correct neutropenia [11] and reduce the risk of infections and IBD activity [3, 12, 13, 14]. The biological monitoring of these patients includes thus metabolic parameters (glycemia, lactatemia, triglyceridemia, cholesterolemia and uricemia) but also the dosage of Absolute Neutrophil Count (ANC) at each hospitalization or consultation. The most serious complication of G-CSF is splenomegaly, which is dose-dependent [14]. Patients with severe intestinal disease evolution can require additional treatments, usually in analogy to patients with Crohn's disease (CD) [11]. In compliance with the consensus guidelines on the medical management of pediatric CD [15], nutritional therapy with a polymeric formula (Modulen IBD ®, Nestlé, Vevey, Switzerland) has been described as well as the administration of systemic corticosteroids and anti-TNFα immunosuppressive agents in patients with severe colitis [16, 17].

Here, we report the clinical and biological findings of non metabolic complications in a cohort of GSD1B patients. We also assessed the potential benefits of different treatments, including enteral nutrition with Modulen IBD ®.

2. Patients and methods

2.1. Patients

GSD1B patients diagnosed before 2016 and followed in two French National Reference Centers for Inherited Metabolic Diseases (Necker Enfants Malades Hospital, Paris and Antoine Béclère Hospital, Clamart) were included. The diagnosis was confirmed by the sequencing of the *SLC37A4* gene and/or by the level of G6PT enzyme activity found on liver biopsy. The follow-up of patients for this study was up to 21 years.

2.2. Methods

2.2.1. Assessment of digestive and infectious complications

Clinical features of IBD, including intestinal (abdominal pains, diarrhea, bloody diarrhea, abdominal mass), peri-anal (anal and perianal fissures, ulcerations or fistulas) and extraintestinal (including oral ulcers) symptoms, were noted at each follow-up time point, as well as infectious episodes. Acute hospitalizations to treat one of these events were classified as having occurred due to digestive symptoms or infections. A single hospitalization could be classified as having been due to both an infection and digestive complications. Patients were stratified according to the severity of their digestive phenotype using the Harvey Bradshaw score (validated score for the assessment of CD activity) [18], which was calculated for each patient at each follow-up time point. These scores allowed us to separate two groups of severity of digestive involvement in our cohort. Other infectious episodes treated at home were also reported, based on self-report by the patient.

2.2.2. Biological and radiologic findings

Hypoglycemia was noted at diagnosis and reported during the follow-up only if symptomatic (seizures, consciousness disorders). The mean values of lactatemia, triglyceridemia, cholesterolemia and uricemia were noted at each hospitalization.

Only the two extreme values (maximum {max} and minimum {min}) of the absolute neutrophil count (ANC), C-reactive protein (CRP) level, and erythrocyte sedimentation rate (ESR) were taken into account for each hospitalization (systematic follow-up and acute hospitalizations). Other inflammatory markers as albumin, ferritin, platelet

count and hemoglobin were also recorded. Neutropenia was defined when ANC was $\leq 1.5 \times 10^9/L$ and agranulocytosis when ANC was strictly $< 0.5 \times 10^9/L$.

Presence of liver adenomas (assessed by systematic abdominal ultrasound or hepatic Magnetic Resonance Imaging) was noted at each time of follow up.

2.2.3. Treatments

Nutrition modalities were noted at each follow-up time point. Patients could be fed by either Exclusive Enteral Nutrition (EEN) (continuous enteral nutrition 24/24 h without any oral feeding) or Partial Enteral Nutrition (PEN) (nocturnal enteral nutrition combined with frequent meals during the day). G-CSF doses were calculated in µg/kg/day, and the average dose was calculated from the beginning of chronic treatment (more than one uninterrupted month of treatment). Antibiotics and other IBD treatments were also reported.

2.2.4. Statistical analysis

The duration of treatments and duration under the thresholds of the biological parameters were recorded in months. Descriptive statistics such as percentage, min, max, arithmetic mean (SD), and median (25th and 75th percentiles) were used to summarize the patient characteristics. Due to the size of the study sample, comparisons were made with nonparametric tests. We compared the two severity groups ("mild" and "severe") using the Mann-Whitney test (for quantitative values), Fisher's exact test, and Chi^2 test (for qualitative values). We used the paired Wilcoxon test to compare variables before and after treatment. Statistical analyses were performed with STATA statistical software (release 13.1; Stata Corporation, College Station, TX, USA).

3. Results

3.1. Metabolic characteristics

Twelve patients (5 girls and 7 boys) with GSD1B were followed in the two centers. Three patients were excluded because of incomplete medical files. The average duration of follow-up was 19.1 years (and ranged from 14.3 to 21.1 years, SD: 2.6). The mean age at diagnosis was 0.8 years (and ranged from 1 month to 3.5 years, SD = 1.1). The referring symptoms were hepatomegaly (8 patients) and/or hypoglycemia (6 patients), sometimes associated with hyperlactatemia (> 1.95 mmol/L) or hypertriglyceridemia (Table 1).

3.2. Neutropenia characteristics

Neutropenia appeared at the mean age of 2.4 years (min-max: 0.2–8.8 years, SD 3.5), and patients spent approximately two-thirds of the follow-up time with neutropenia (69%, SD: 24.3) and more than one-third of the time with agranulocytosis (38.2%, SD: 27.7) (Fig. 1). Three patients were neutropenic at diagnosis.

3.3. Digestive and infectious complications

The average age at the onset of IBD was 3.8 years (ranging from 0.6 to 8.6 years, SD 3.4). The presenting symptoms were either oral ulcers (six patients) or diarrhea (three patients: 5,6 and 8).

The severity of IBD was variable, as 5 patients had mild symptoms (oral ulcers or mild abdominal pain) and the remaining 4 displayed serious symptoms, such as severe abdominal pain and bloody diarrhea for three of them (patients 7, 8 and 9). Ileocolonoscopy was performed in 5 patients and found patchy ulcerations in the ileon, the colon (patients 8 and 9) and the rectum (patient 8). Histology showed an increase of infiltrates from lymphocytes in all patients, and at worst distortion of the crypt architecture with dedifferentiation (patient 8) and crypt abscesses (patient 9).

The calculation of Harvey Bradshaw's score at each follow-up time

Table 1
Characteristics of GSD1B patients.

Patients	Hospital	Sex	Duration of follow-up (years)	Age at diagnosis (years)	Initial symptoms	Molecular analysis (when available)
1	A. Béclère	F	20.8	3.5	HMG, HTG	C.359_360insC c.1099G > A
2	A. Béclère	M	20.3	0.7	HMG, hgly (s)	c.352 T > C c.345_346insGG
3	A. Béclère	M	20.2	0.3	HMG, hgly, HTG, HL	c.59G > A (homozygous)
4	A. Béclère	M	21.1	0.6	HL, HTG	Not available: low enzymatic activity
5	Necker	M	14.3	1	HMG, HL, HTG, growth delay	c.345_346insGG c.686 T > C
6	Necker	F	14.8	0.7	HMG, hgly (s), HTG, HU	c.1016G > A (homozygous)
7	Necker	F	20.1	0.1	HMG, hgly, HL	c.1042_1043delCT (homozygous)
8	Necker	M	20.3	0.1	HMG, hlgy, HL	c.263G > A (homozygous)
9	Necker	M	20.2	0.2	HMG, hgly	Not available: low enzymatic activity

A. Béclère: Antoine Beclère Hospital in Clamart; Necker: Necker Hospital in Paris; F: female; M: male; HMG: hepatomegaly; HTG: hypertriglyceridemia; hgly: hypoglycemia; (s): hypoglycemia with seizures; HL: hyperlactatemia; HU: hyperuricemia.

point allowed us to arbitrarily distinguish two groups of patients: a "mild" group (patients 1, 2, 3, 4 and 5, who presented only mild symptoms like isolated oral ulcers or mild abdominal pain) and a "severe" group (patients 6, 7, 8 and 9, who showed severe abdominal pain with the need of hospitalization, many liquid stools per day, and even bloody diarrhea, with the need of blood cell transfusion for patient 8 because of severe acute anemia) with a mean score throughout follow up at 0,6 and 3,5, respectively ($p = 0.014$). Additionally, all calculated values in the mild group (100%) were less than 4 (inactive disease), compared to only 68.1% in the severe group ($p = 0.014$).

The average age at the onset of infections was 1.7 years (from 0.2 to 5.7 years, SD 1.7). The most frequently reported infections were ear, nose and throat (ENT) and skin. Patients had 1.8 infections/year on average (from 0.1 to 3.9/year, SD: 1.3). No severe sepsis was reported (as defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [19]).

The median values for the ESR and CRP levels during follow-up were high for all patients: 47.8 mm and 23.2 mg/L, respectively (See Table 2B.)

3.4. Number of acute hospitalizations due to infections or digestive symptoms

Patients had 0.7 acute hospitalization/year (from 0.05 to 1.6/year, SD: 0.6) on average, with 0.4/year (from 0.05 to 0.8/year, SD: 0.3) due to infections and 0.4/year (from 0 to 1.4/year, SD: 0.5) due to digestive symptoms (Table 2A). Two patients were never hospitalized for digestive reasons (patients 1 and 4).

3.5. Correlation of IBD score with other severity parameters of the disease

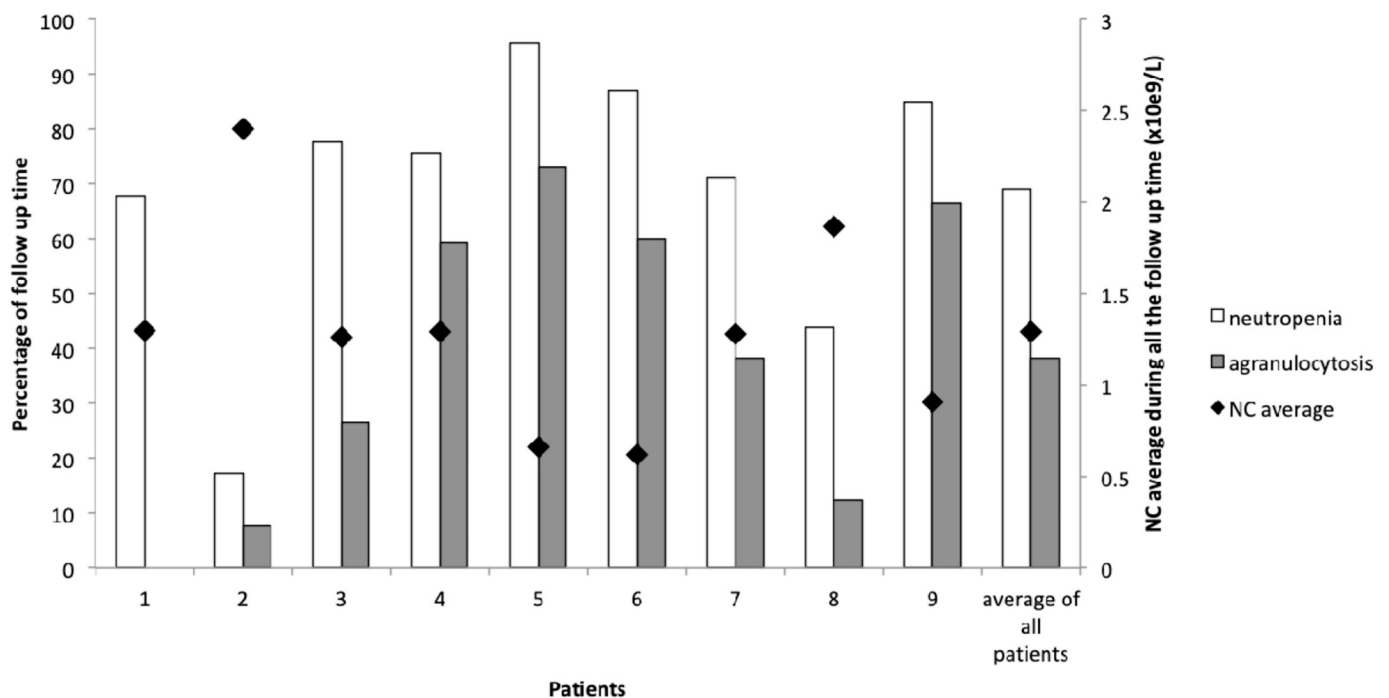Patients in the severe IBD group also had other parameters of the

Fig. 1. *Neutropenia.* Absolute Neutrophil count (ANC) for each patient and the whole cohort during follow-up: percentage of time spent with neutropenia in white columns, with agranulocytosis in grey columns (scale on the left of the figure), and mean values in black rhombs (scale on the right on the figure).

Table 2A

Clinical features and comparison between the 2 IBD severity groups with regard to infectious and digestive complications.

		All patients	Mild patients	Severe patients	p *
General parameters					
Duration of follow up (years)					0.323
	Mean (SD)	19.1 (2.6)	19.3 (2.8)	18.9 (2.7)	
	Median (P25;P75)	20.2 (20.1;20.3)	20.3 (20.2;20.8)	20.2 (18.8;20.2)	
Sex ratio		3F/6M	1F/4M	2F/2M	0.343
Age at onset (years)					
GSD1B diagnosis	Mean (SD)	0.8 (1.1)	1.2 (1.3)	0.3 (0.3)	0.064
	Median (P25;P75)	0.6 (0.2;0.7)	0.7 (0.6;1)	0.2 (0.1;0.3)	
Neutropenia	Mean (SD)	2.4 (3.5)	3.9 (4.2)	0.4 (0 0.2)	**0.046**
	Median (P25;P75)	0.7 (0.3;1.5)	1.5 (0.8;8.3)	0.3 (0.3;0.4)	
Digestive symptoms	Mean (SD)	3.8 (3.4)	6 (3.3)	1.2 (0.4)	**0.014**
	Median (P25;P75)	2.1 (1.3;8)	8 (2.7;8.5)	1.3 (1.1;1.4)	
First hospitalization	Mean (SD)	3 (3.6)	4.6 (4.2)	0.9 (0.6)	0.142
	Median (P25;P75)	1.3 (0.8;3.3)	3.3 (1;7.8)	1 (0.6;1.4)	
Number of hospitalizations (/year)					
Total	Mean (SD)	0.7 (0.6)	0.2 (0.2)	1.2 (0.4)	**0.014**
	Median (P25;P75)	0.5 (0.2;1.1)	0.2 (0.05;0.4)	1.3 (1;1.5)	
For digestive reasons	Mean (SD)	0.4 (0.5)	0.05 (0.05)	0.8 (0.4)	**0.012**
	Median (P25;P75)	0.1 (0.05;0.6)	0.05 (0;0.1)	0.6 (0.6;0.8)	
For infections	Mean (SD)	0.4 (0.3)	0.2 (0.2)	0.7 (0.1)	**0.014**
	Median (P25;P75)	0.4 (0.2;0.7)	0.2 (0.05;0.3)	0.8 (0.7;0.8)	
Number of infectious episodes (/year) (regardless if hospitalization needed or not)					0.142
	Mean (SD)	1.8 (1.3)	1.3 (1.5)	2.4 (0.8)	
	Median (P25;P75)	1.3 (0.7;2.7)	0.7 (0.6;1.1)	2.5 (2;2.8)	

overall GSD1B disease that ranked as severe. Compared to mild IBD patients, the age at the onset of the disease tended to be earlier (0.2 vs. 0.7 years, $p = 0.064$) as did the age at the onset of neutropenia (0.3 vs. 1.5 years, $p = 0.046$) and of symptoms of IBD (1.3 vs. 8 years, $p = 0.014$), such as oral ulcers, abdominal pain or diarrhea. The total number of acute hospitalizations was significantly higher in the severe IBD group than in the mild IBD patients (1.3/year vs. 0.2/year, $p = 0.014$), both for digestive reasons (0.6/year vs. 0.05/year, $p = 0.012$) and for infections (0.8/year vs. 0.2/year, $p = 0.014$). The first acute hospitalization also occurred earlier in the severe IBD group than in the mild IBD group (1 year vs. 3.3 years, $p = 0.142$) (Fig. 2 and Table 2A). Inflammatory syndrome and neutropenia tended to be more prevalent in the severe IBD group than in the mild IBD group, with significantly lower albumin and higher ferritin values (36.4 vs. 46.2 mg/L, p=0.028 and 140.5 vs 60.3 μg/L, p=0.021 respectively) (Table 2B).

We found no phenotype-genotype correlations (data not shown).

3.6. Treatment

G-CSF and cotrimoxazole were used in all patients with severe IBD presentation but only in 3 of the 5 patients with mild IBD. The median duration of treatments tended to be longer in the severe IBD group: 14.7 vs. 10.1 years ($p = 0.157$), and 72.5% of follow up time vs 50% ($p = 0.077$) for G-CSF and 8 vs. 6 years ($p = 0.348$) for cotrimoxazole, with a significantly earlier initiation (4.3 vs. 9.8 years, $p = 0.034$ for G-CSF; 0.3 vs. 5.6 years, $p = 0.06$ for cotrimoxazole). The initiation dose of G-CSF was 3.9 μg/kg/day on average (min: 2 max: 5 μg/kg/day, SD: 1.3) and the mean dose during follow-up was 2.72 μg/kg/day, for all patients (min: 1.1, max: 5 μg/kg/day, SD: 1.2). These doses did not differ between the groups (Table 3). The first indication for G-CSF initiation was severe (ANC < 0.5×10^9/L for 5 patients and < 1×10^9/L for one patient) and persistent neutropenia (ANC < 1.5×10^9/L found at least during 2 consecutive months). Other indications were frequent infections for 3 patients [3,7,8,and] and digestive symptoms (diarrhea or abdominal pains requiring hospitalizations) for two other patients [6 and 9]. Detailed parameters of G-CSF treatment for each patient are exposed in Table 3.

All patients in the severe IBD group were treated with Modulen IBD ® at a mean age of 8.3 years (min-max: 3.810.8years, SD: 3.1). The indications were chronic digestive symptoms for patients 6, 7 and 8,

with abnormal intestinal histology for patient 7, or unexplained growth retardation (patient 9), despite a well-conducted treatment with G-CSF. Exclusive enteral nutrition (EEN) was prescribed if severe digestive symptoms for a maximum duration of twelve days for patient 6, one month for patients 7 and 9, and four consecutive months during a severe episode of colitis for patient 8. The cumulative time receiving EEN ranged from 12 days (patient 6) to 10 months (patient 8) throughout follow-up. The rest of the time, partial enteral nutrition (PEN) was prescribed as a maintenance therapy. The mean duration of treatment by Modulen IBD ® (regardless of EEN or PEN), was 7.9 years (between 2 and 11 years, SD: 4).

Topical corticosteroids (patients 6, 7 and 8) and 5-ASA (patients 7 and 8) were administered as a second-line therapy in addition to Modulen IBD ®. Patient 8, in the severe IBD group, required systemic treatments: corticosteroids (intravenous then oral) and then intravenous biotherapy (infliximab) because of a loss of efficacy and corticosteroid side effects (severe hypertension). One patient (patient 9) achieved improvement of his digestive symptoms with sole nutritional therapy (in combination with G-CSF).

3.6.1. Efficacy of therapeutic management

With G-CSF, the median ANC tended to increase in all patients (from 1.05×10^9/L to 1.43×10^9/L, $p = 0.063$). The median time spent in agranulocytosis tended to decrease (from 53% to 29.1%, $p = 0.063$), and the median time spent in neutropenia decreased significantly (from 84.1% to 61.5%, $p = 0.043$) (Fig. 3).

The number of acute hospitalizations for digestive and/or infectious reasons tended to decrease with G-CSF treatment (from 1.1/year to 0.9/year, $p = 0.14$) as did the median number of infectious episodes (from 2.3/year to 1.4/year, $p = 0.091$). There was a significant decrease in the median CRP values with G-CSF treatment (from 38 to 20.1 mg/L, $p = 0.043$). (supplementary Table 3).

Splenomegaly was observed in all patients treated by G-CSF; it started on average 3.6 years after beginning treatment (SD: 3.6). No other known side effects from G-CSF were noted.

3.6.2. Metabolic balance according to the severity scores of the patients

Despite more severe digestive disease and a tendency towards more frequent and more serious infectious complications (Fig. 2), metabolic
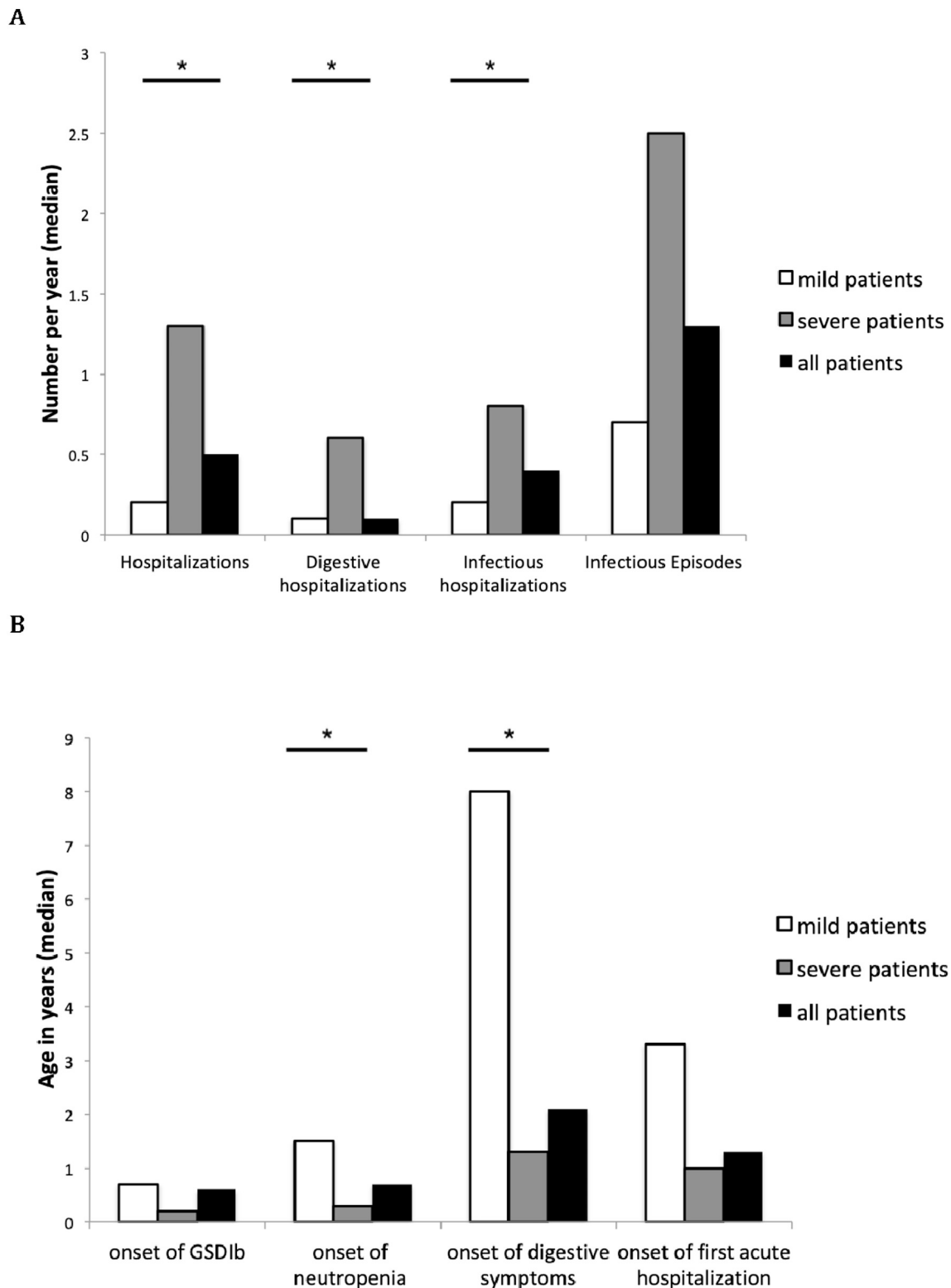
A

B

Fig. 2. Comparison of general clinical and biological parameters between the 2 IBD severity groups with regard to the natural history of the overall disease: age at the onset of GSD1B, neutropenia, digestive symptoms and acute hospitalizations (2A), and details of the type of acute hospitalizations and infectious episodes without hospitalizations (2B).

*: $p < 0.05$ (Mann–Whitney test). GSD1B: glycogen storage disease type Ib.

balance as well as growth seemed better in the severe IBD patients than in the mild IBD patients. Indeed, the median values for lactatemia, triglyceridemia and cholesterolemia throughout the follow-up were significantly lower in the severe IBD patients (2.1 vs. 3.7 mmol/L, $p = $ 0.014; 1,8 vs. 5 mmol/L, $p = 0,014$; and 3.1 vs. 4.4 mmol/L, $p = 0.028$, respectively) (Table 2B).

Six patients developed liver adenomas (one in the severe group and all of the patients from the mild group).

Table 2B

Biological, nutrition and growth features, and comparison between the 2 IBD severity groups with regard to biological inflammatory parameters, metabolic parameters, and growth and nutrition issues.

		All patients	Mild patients	Severe patients	p[a]
Biological parameters. Median values (P25;P75)					
ANC (x10^9/L)		1.28 (0.91;1.3)	1.29 (1.26;1.3)	1.09 (0.84;1.43)	0.462
ESR (mm)		47.8 (28.1;63.9)	31.5 (26.3;45.2)	60.7 (52.5;63.9)	0.387
CRP (mg/L)		23.2 (11.8;30.7)	15.5 (10;22.6)	30.2 (22.7;34.6)	0.149
Albumin (mg/L)		38,9 (36,6-46,2)	46,2 (40,2–46,3)	36,4 (35,4-37,2)	**0,028**
Ferritin (µg/L)		97,8 (76–136,4)	60,3 (27,7-92,2)	140,5(124,7–152)	**0,021**
Hemoglobin(g/dL)		10,9	11,1 (11 − 12)	10,4 (10–10,7)	0,086
		(10,1-11,1)			
Platelets (x10e9/L)		394 (356–407)	407 (403–409)	359 (325–370)	0,142
Metabolic parameters					
Lactates (mmol/L)	Mean (SD)	3 (1.2)	3.8 (1.1)	2 (0.4)	**0.014**
	Median (P25;P75)	2.5 (2.1;3.7)	3.7 (3.6;3.9)	2.1 (1.9;2.2)	
Triglycerides (mmol/L)	Mean (SD)	3.5 (2.4)	4.9 (2.3)	1.7 (0.3)	**0.014**
	Median (P25;P75)	1.9 (1.9;5)	5 (3.3;6.4)	1.8 (1.6;1.9)	
Cholesterol (mmol/l)	Mean (SD)	3,8 (1)	4,4 (0,8)	3 (0,5)	**0.028**
	Median (P25;P75)	3,4 (3,2-4,4)	4,4 (4,2-4,5)	3,1 (2,8-3,3)	
Uricemia (µmol/L)	Mean (SD)	388 (77)	406 (84)	365 (71)	0,462
	Median (P25;P75)	402 (329–442)	402 (366–477)	367 (318–414)	
Growth					
Final height (SD)	Mean (SD)	−1.7 (1.2)	−2.1 (1.5)	−1.2 (0.3)	0.289
	Median (P25;P75)	−1.5 (−2;-1.1)	−2 (−2.5;-1.5)	−1.2 (−1.4;-1.1)	
Enteral nutrition (percentage of follow-up duration)					
EEN	Mean (SD)	1.4 (2.5)	0 (0)	3.2 (3)	0.029
	Median (P25;P75)	0 (0;2.1)	0 (0)	2.9 (1.6;4.5)	
PEN	Mean (SD)	71.5 (40.8)	55.1 (50.6)	92.1 (4)	0.325
	Median (P25;P75)	89.2 (83.2;92.6)	83.2 (0;92.3)	90.9 (89.1;93.8)	

SD: standard deviation; P25-P75: 25th and 75th percentiles.

GSD1B: glycogen storage disease type Ib. ANC: absolute neutrophil count. ESR: erythrocyte sedimentation rate. CRP: C– reactive protein. Final height expressed as standard deviation (SD) compared to the height of the general population.

Diet: mean and median percentages of time during follow-up with different types of enteral nutrition: EEN: exclusive enteral nutrition, PEN: partial enteral nutrition.

[a] P value from Mann-Whitney test or Fisher's exact test for sex ratio.

4. Discussion

We described here the infectious and digestive complications of GSD1B in a cohort of nine patients; these complications significantly impacted their quality of life, which was already affected by the management of hypoglycemia. The diagnosis of the disease was reported in the first year of life for 90% of our patients ($n = 8$), and the referring symptoms were metabolic [1, 8]. All patients also presented with neutropenia. Infectious episodes were frequent, mostly ENT and cutaneous infections. Crohn's disease-like digestive symptoms were also noted, as previously described [8, 9, 16]. All of them had symptoms of IBD (even just oral ulcers in some mild patients), compared to only 77% of patients in the European study, but our follow-up duration was longer (19.1 years on average vs. a median of 8.6 years) [8].

Our report allowed to show that patients with severe IBD evolution showed earlier intestinal symptoms, and appeared to have a more severe global phenotype. Indeed, these patients were younger at the time of the diagnosis of GSD, presented earlier neutropenia with a tendency to lower absolute neutrophil count (ANC) during follow-up, and tended to present more infectious episodes, higher levels of inflammatory markers, requiring significantly more hospitalizations than mild IBD patients.

Although the associations between neutropenia, neutrophil dysfunction and the presence of CD was previously described in GSD1B [8, 9], the physiopathology underlying these digestive symptoms remains poorly understood. In CD, an impairment of neutrophil recruitment to the intestinal mucosa has been described, leading to persistence of bacteria within the tissues, phagocytose by macrophages and development of granulomas, with secondary systemic inflammation, fibrosis and fistulation [20]. Interestingly, Crohn's disease-like manifestations are observed in other pathologies involving neutrophil dysfunction,

such as chronic granulomatous disease [21] or G6PC3 deficiency [22]. Neutrophils in patients with GSD1B have the same pathological characteristics as those in patients with G6PC3 deficiency [3, 4]. Jun et al. described that GSD1B neutropenia is not a consequence of bone marrow primary dysfunction, but of apoptosis resulting in premature death [6]. Veiga-da-Cunha et al. (2019) reported that neutropenia in such patients was due to a failure to eliminate a phosphorylated glucose analog.

The majority of our patients were treated with G-CSF, with a mean dose of 2.72 µ/kg/day, and received antibioprophylaxis with cotrimoxazole, in accordance with the consensus guidelines for the treatment of GSD1B [2, 11, 23]. As reported [12, 14], intestinal symptoms improved in all of our patients treated with G-CSF, highlighting the closed link between digestive complications and neutrophil count and functions. The treatment with G-CSF tends to decrease the number of hospitalizations and infectious episodes and significantly decreases the mean level of CRP. Regarding the specific management of digestive manifestations, Modulen IBD ®, only described once in patients with GSD1B [16], was used in the severe group, mainly in those receiving PEN. The use of polymeric formulas is recommended for the management of pediatric CD: in those receiving EEN for the induction of remission and in those receiving PEN for maintenance therapy [15]. EEN seems to induce changes in the intestinal microbiota, which return to being protective [24]. It also has specific anti-inflammatory properties [25, 26, 27, 28]. The recommended duration of EEN is 6 to 8 weeks to obtain clinical remission and mucosal histological healing in CD and to decrease the risk of relapse [15, 25]. In our cohort, the efficacy of Modulen IBD ® on an exclusivity basis was difficult to demonstrate, probably because of the small number of patients treated and the short duration of EEN. Only one patient (patient 8) was treated for a long period (18 weeks) with EEN during an acute episode, compared to durations ranging between 12 days and one month for the other 3

Table 3

G-CSF Treatment for each patient and for the two groups: Indications to begin a long-term treatment by G-CSF; Age at onset for this long-term treatment; Initiation dose; Mean dose during all follow up; Duration of the treatment; Percentage of time of follow up with the treatment.

Patients	2	3	4	Mild group Median (P25;P75)	6	7	8	9	Severe Group median (P25;P75)	p[a]
Indication	Neutropenia	Neutropenia infections	Neutropenia		Neutropenia diarrhea	Neutropenia infections	Neutropenia infections	Neutropenia abdominal pain		
Age at onset (years)	8.8	9.8	11.7	9,8 (9,3;10,7)	6.4	5.6	0.3	3	4,3 (2,3;5,8)	**0,034**
Initiation dose (µg/kg/d)	5	5	4	4 (4.5;5)	2.4	5	2	4.1	3.25 (2.3;4.3)	0.271
Mean dose (µg/kg/d)	5	2.8	1.1	2,8 (1,9;3,9)	3	2.2	2.8	2.2	2,51 (2,2;2,9)	0.858
Duration of treatment (years)	10.1	12.3	7.9	10,1 (9;11,2)	8.3	14.5	18.9	14.8	14,7 (13;15,8)	0,157
Percentage of time under treatment	50%	61%	37%	50 (43.5;55.5)	56%	72%	93%	73%	72.5 (68;78)	0.077

(Patient 1 and 5 were not treated by G-CSF)

µg/kg/d: microgram per kilogram per day.

P25–P75: 25th and 75th percentiles.

[a] P value from Mann-Whitney test (comparison between mild and severe group).

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patients. Thus, relapses of intestinal symptoms could be favored by the absence of complete initial mucosal healing after a first inflammatory attack. Other treatments used in CD were immunosuppressors [15], and could be inappropriate in GSD1B patients who are immunocompromised due to their neutrophil dysfunction.

Combining EN with G-CSF may limit the doses of G-CSF and thus the dose-dependent side effects, such as hypersplenism [11, 23]. EN, already known to enhance growth and bone density in patients with CD [25, 27], also seems to improve metabolic parameters in our patients (higher values of lactatemia and triglyceridemia in mild patients). We already know that enteral nutrition improves metabolic balance in GSD1B by removing fasting periods, so a longer time spent with EN during follow up (because of digestive symptoms) could probably explain the better metabolic balance in severe patients. We then suggest that enteral nutrition has to be considered as a first-line treatment of digestive complications for these patients, because of its double metabolic and intestinal effects.

Finally, to limit the use of G-CSF and its potential side effects, other therapeutic approaches with encouraging results in the murine model [7] could be proposed, since neutrophil dysfunction could be related to an inhibition of glycolysis by accumulation of non-classical glucose analog.

5. Conclusion

GSD1B is a severe metabolic disorder with additional infectious and digestive complications. The severity of these symptoms varies among patients, and we identified two groups of patients, with a correlation between digestive and infectious complications, subtended by neutropenia. Dietary management with a polymeric formula such as Modulen IBD ®, in addition to G-CSF and antibioprophylaxis, improves digestive symptoms and seems to have also a positive effect on metabolic balance.

Author Contribution

Details of the contributions of individual authors: CW, CR, FR and PDL designed the study, followed the patients, analyzed data and wrote the manuscript. PL, FR and PDL supervised the work. CW, PHPL, JD, AB, MC, AS, JBA, JB, BP, PL, FR and PDL followed the patients. All authors helped write the manuscript.

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Informed patient consent statement

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Human and animal rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

Declaration of Competing Interest

FR has received speaker fees from: Shering-Plough, Nestlé, MeadJohnson, Ferring, MSD, Johnson & Johnson, Centocor, AbbVie; serves as a board member for: SAC:DEVELOP (Johnson & Johnson), and has been invited to MSD France, Nestlé Nutrition Institute, Nestlé
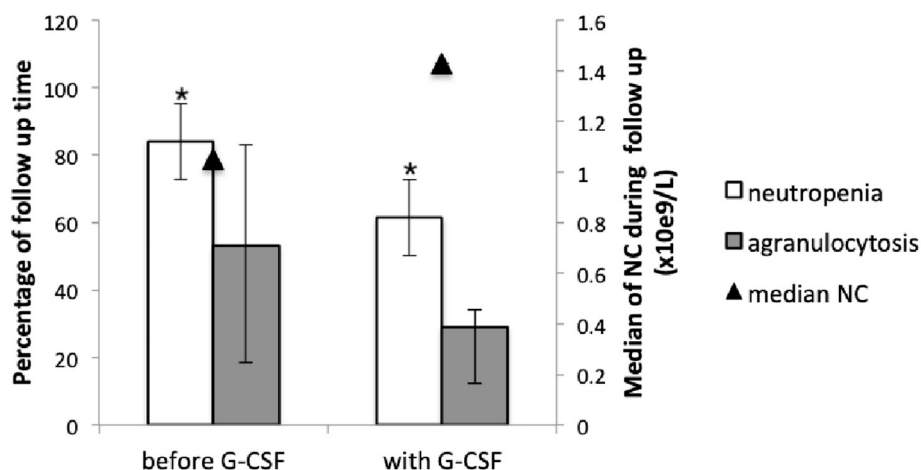
Fig. 3. Assessment of the efficacy of G-CSF: comparison of time spent in neutropenia and agranulocytosis, and neutrophil counts before and after treatment with G-CSF in all patients treated.
*: p < 0 .05 (paired Wilcoxon test).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2020.100581.

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