Journal of Inherited Metabolic Disease

WILEY

JIMD SSIEM

ORIGINAL ARTICLE OPEN ACCESS

Epidemiology of Gaucher Disease in France: Trends in Incidence, Mortality, Management, and Complications Over Three Decades

Yann Nguyen[1,2] | Maxime Beydon[1] | Karima Yousfi[1] | Samira Zebiche[1] | Dalil Hamroun[3] | Anaïs Brassier[4] | Samia Pichard[4] | Laure Swiader[5] | Thierry Billette de Villemeur[6] | Bénédicte Héron[6] | Florence Dalbies[7] | Bérengère Cador[8] | Anne-Sophie Guemann[9] | Francis Gaches[10] | Bénédicte Hivert[11] | Vanessa Leguy-Seguin[12] | Agathe Masseau[13] | Robin Deshayes[13] | Yves-Marie Pers[14] | Magali Pettazzoni[15] | Soumeya Bekri[16] | Catherine Caillaud[17] | Edouard Le Guillou[17] | Marie Szymanowski[18] | Leonardo Astudillo[19] | Wladimir Mauhin[20] | Yann Nadjar[21] | Christine Serratrice[22] | Marc G. Berger[23,24] | Fabrice Camou[25] | Nadia Belmatoug[1] | Jérôme Stirnemann[26] | French Evaluation of Gaucher Disease Treatment Committee

[1]Service de Médecine Interne, Centre de référence des maladies lysosomales, Hôpital Beaujon, AP-HP.Nord, Université Paris Cité, Clichy, France | [2]Centre de Recherche en Epidémiologie et Statistiques (CRESS), Unité Inserm 1153, Université Paris Cité, Paris, France | [3]Pôle Recherche & Innovation, CHU de Montpellier, Montpellier, France | [4]Centre de Référence des Maladies Lysosomales, Hôpital Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, IHU Institut Imagine, Paris, France | [5]Service de Médecine Interne, Hôpital La Timone, Assistance Publique-Hôpitaux de Marseille, Marseille, France | [6]Service de Neurologie Pédiatrique, Centre de Référence des Maladies Lysosomales, Hôpital Armand Trousseau-La Roche Guyon, Fédération Hospitalo-Universitaire I2-D2, APHP.Sorbonne Université, Paris, France | [7]Institut de Cancéro-Hématologie, CHRU Morvan, Brest, France | [8]Service de Médecine Interne, CHU Pontchaillou, Rennes, France | [9]Centre de Référence des maladies héréditaires du métabolisme de l'enfant et de l'adulte, CHRU de Lille, Lille, France | [10]Service de Médecine Interne, Clinique Monié, Villefranche-de-Lauragais, France | [11]Service d'Hématologie, Hopital Saint-Vincent-de-Paul, Lille, France | [12]Service de Médecine Interne et Immunologie Clinique, CHU Bocage Central, Dijon, France | [13]Service de Médecine Interne, CHU Hôtel Dieu, Nantes, France | [14]IRMB, Université de Montpellier, Inserm U1183, CHU Montpellier, Montpellier, France | [15]Département de Biochimie Métabolique, Centre de Biologie et de Pathologie Est, Hospices Civils de Lyon, Bron, France | [16]Département de Biochimie Métabolique, UNIROUEN, INSERM U1245, CHU Rouen, Rouen, France | [17]Laboratoire de Biochimie, Métabolomique et Protéomique, AP-HP.Centre Université Paris Cité, Hôpital Necker-Enfants Malades, Paris, France | [18]Service de Pédiatrie, CHU Estaing, Clermont-Ferrand, France | [19]Service de Médecine Interne, CHU Toulouse, Toulouse, France | [20]Service de Médecine Interne, Centre de Référence des Maladies Lysosomales, Hôpital La Croix Saint-Simon, Paris, France | [21]Service de Neurologie, Centre de Référence des Maladies Lysosomales, Hôpital Pitié-Salpêtrière, Paris, France | [22]Service de Médecine interne de l'âgé, Hôpitaux Universitaires de Genève, Thonex, Switzerland | [23]Service d'Hématologie Biologique et service d'Hématologie Clinique Adulte, CHU Estaing, Clermont-Ferrand, France | [24]EA 7453 CHELTER, Université Clermont Auvergne, Clermont-Ferrand, France | [25]Service de Médecine Interne et Maladies Infectieuses, Hôpitaux Haut-Lévêque, CHU de Bordeaux, Pessac, France | [26]Service de Médecine Interne Générale, Hôpitaux Universitaires de Genève, Genève, Switzerland

Correspondence: Yann Nguyen (yann.nguyen2@aphp.fr)

Received: 30 January 2025 | **Revised:** 27 March 2025 | **Accepted:** 22 April 2025

Communicating Editor: Nicola Brunetti-Pierri

Funding: The FDGR received a research grant from Sanofi and Takeda. The present article reflects only the authors view and Sanofi and Takeda had no link with the design of the study and had no access to the data.

Keywords: enzyme replacement therapy | epidemiology | Gaucher disease | lysosomal disorder | registry | substrate reduction therapy

ABSTRACT

Gaucher disease (GD) is a rare autosomal-recessive lysosomal disorder caused by glucocerebrosidase deficiency. In this study, we described the epidemiology of GD in France over more than three decades. The French GD registry (FGDR) includes all known

Nadia Belmatoug and Jérôme Stirnemann contributed equally to this study.

patients with GD in France. We described patients' characteristics, and estimated the incidence, prevalence, and standardized mortality ratios of GD. We compared the evolution of diagnostic methods, diagnosis delays, and treatment over time, and assessed the incidence of bone events, malignancies, and Parkinson's disease. Between 1980 and 2024, 706 confirmed GD were included. In 2024, 447 patients were alive (413 type 1, 34 type 3). GD incidence was 0.21/1 000 000 PY, and GD prevalence was 0.61 and 0.05/100 000 inhabitants for type 1 and 3, respectively. The standardized mortality ratio was 0.70 for type 1 GD and 16.23 for type 3 GD. Over time, we observed a decrease in the delay between first symptoms and diagnosis (5.4 years before 2000; 0.8 after 2020; $p = 0.001$), with enzyme assays becoming the primary diagnostic method, a reduction in splenectomies, and a gradual increase in the use of substrate reduction therapy in type 1 GD. The incidences of bone events, malignancies, and Parkinson's disease were 23, 2.7, and 1.07 per 1000 person-years, respectively. This study provides updated epidemiological data on GD in France, showing improvements in disease knowledge, faster and less invasive diagnoses, and reassuring outcomes for type 1 GD, with lower mortality and a relatively low incidence of malignancies and Parkinson's disease.

1 | Introduction

Gaucher disease (GD) is a lysosomal autosomal recessive disorder due to a deficiency of glucocerebrosidase, a lysosomal enzyme, or more rarely, its activator (saposin C) [1]. This deficiency leads to an accumulation of its substrate, glucosylceramide, in macrophages.

GD is a rare disease, with an incidence varying between 0.4 and 5.8 per 100 000 inhabitants [2]. Its average prevalence is around 1/60 000 in the general population, but varies widely depending on the population, ranging from 1/136 000 in France to 1/1000 in the Ashkenazi Jewish population [2, 3]. GD with Fabry disease is the most common lysosomal disorder.

GD manifests across a range of phenotypes, varying from severe forms apparent at birth to milder phenotypes [4, 5]. The main manifestations of GD include splenomegaly, hepatomegaly, bone involvement such as bone infarcts, avascular osteonecrosis, or pathological fractures, anemia, and/or thrombocytopenia. Traditionally, the disease has been classified into three primary forms, although there is a continuum that exists between them [6]. Type 1 GD is the most common phenotype and is characterized by liver and spleen enlargement and dysfunction, and bone damage resulting in fractures and infarctions. Although Type 1 is generally considered non-neuronopathic, increasing evidence suggests that these patients may also experience neurological issues such as Parkinson's syndrome and Lewy body dementia [7]. Type 2 GD is rare and associated with an acute neurodegenerative course in addition to visceromegaly that leads to death often at a very young age or before birth due to non-immune hydrops fetalis. Type 3 GD, on the other hand, comprises a heterogeneous group of patients who present with either attenuated or severe systemic disease and neurological involvement that typically begins in childhood to early adulthood [8].

GD prognosis has been considerably improved since the development of enzyme-replacement therapy (ERT), including alglucerase (Ceredase, Genzyme Corporation, available since 1991) [9], followed by imiglucerase [10–13] (Cerezyme, Genzyme Corporation, available since 1996), velaglucerase alpha [14] (Vpriv, Shire, available since 2010), and taliglucerase (Uplyso, Pfizer, only authorized for temporary use in 2010–2011 in France). These treatments are efficient to reduce symptoms, especially organomegaly and cytopenia. Subsequently, substrate reduction therapy, taken orally, has been available for type 1 GD: Miglustat (Zavesca, Actelion, available since 2002, when ERT is unsuitable), and Eliglustat [15–18] (Cerdelga, Sanofi-Genzyme Corporation, available since 2015).

Several countries established exhaustive national registries, and international registries have been developed by Genzyme/Sanofi [19] and Shire/Takeda [20]. Since 2004, France has created referral centers to improve the clinical management of rare diseases, including patient care, professional practices, and clinical research with the collection of epidemiological data. In this context, a national GD-patient registry was created in 2009 to help improve the understanding and management of the disease. The first description of the French cohort has been published in 2012 [3].

In this study, we aimed to describe the current GD epidemiology in France in terms of prevalence, incidence, mortality, complications, and the evolution of diagnosis and treatments over the years.

2 | Patients and Methods

2.1 | The French Gaucher Disease Registry

The French GD Registry (FGDR) was created in 2009 by the Referral Center for Lysosomal Diseases and the French Evaluation of GD Treatment Committee (EGDTC), a national scientific committee aiming to monitor and optimize GD management in France [3]. The FGDR aims to improve GD patient clinical care and professional practices, and to collect epidemiological data for academic studies.

The registry includes all consenting patients with GD followed in France since 1980. All patients were diagnosed by the demonstration of deficient glucocerebrosidase activity in blood. To ensure the exhaustive identification of cases, patients were enrolled in the registry through three different sources: (1) accredited diagnosis laboratories (included in the EGDTC) including patients with enzyme deficiency; (2) data of the French national health insurance informing by Rare Disease Committee members to validate GD diagnosis to ensure health coverage; (3) during requests for GD treatment through a multidisciplinary consultation meeting with the EGDTC members. Every time, the treating physicians

are solicited to collect patients' consent to be included in the FGDR. Patients who did not give consent for the registry were not included ($N = 3$).

In the FGDR, clinical information, biological and radiological findings at GD diagnosis and during follow-up are recorded, with the identification of intercurrent events, particularly bone complications or malignancies. Data were retrospectively collected before 2010, and as of 2011, all data have been recorded prospectively.

In June 2024, the vital status (alive or deceased) of patients was checked using public data on deceased people in France to ensure the exhaustivity of vital statuses.

2.2 | Study Population

We conducted a retrospective multicentric study of data in the FGDR. We defined three populations: (1) the entire cohort of patients included in the FGDR since 1980 to describe incidence, prevalence, and mortality; (2) patients registered in the FGDR and alive in 2024, to describe the evolution of GD management including splenectomies and ERT or SRT since their availability, and the current prescribed treatment; (3) alive patients with complete follow-up data to describe the occurrence of GD complications and associated disease.

2.3 | Baseline Characteristics

Patients' characteristics were extracted from FGDR on June 30, 2024. They included: age (at first symptoms, and at GD diagnosis), vital status (as of the date of extraction), the modality which led to the diagnosis, GD phenotype, genotype, affected family members, and clinical symptoms at diagnosis including hepatomegaly, splenomegaly, fatigue, neurological involvement, acute bone crisis, chronic bone pain, or bleeding. Since symptoms can emerge over time and the definition of type 3 GD can be challenging [21], patients being reclassified as type 3 Gaucher during their follow-up were considered as type 3 in the present study.

2.4 | Treatment Evolution

Treatments included all available ERT (alglucerase, imiglucerase, taliglucerase, velaglucerase alpha) and SRT (miglustat, eliglustat) in France. For each prescription of ERT or SRT, the date of treatment initiation was recorded, and, if applicable, the date and the cause of treatment discontinuation. Modalities of treatment administration of ERT (hospital or home infusion) were also collected. As splenectomy was considered a treatment before the ERT era, we also collected the number of splenectomies in the entire cohort and their date, and whether splenectomies were performed before or after the diagnosis of GD.

2.5 | Complications and Associated Diseases

In the third cohort of patients with complete follow-up data, the occurrence of bone events (bone infarcts, avascular osteonecrosis, pathological fracture, vertebral fracture), malignancies (solid cancers, hematological malignancies including lymphoma and multiple myeloma), and Parkinson's disease (PD) were collected, as their date of diagnosis compared to the date of GD diagnosis.

2.6 | Statistical Analysis

Baseline characteristics were described with median (interquartile range [IQR]) for continuous variables and count (%) for categorical variables. Descriptive analysis was performed for each of the three populations. GD incidence was calculated by dividing the number of newly diagnosed cases of GD diagnosed per year by the overall French population per year during the 1990–2023 period, as estimated by the French National Institute of Statistics and Economic Studies (INSEE) [22]. This incidence rate differs from the birth incidence rate (defined as the total number of cases divided by the total number of live births during the same period).

Prevalence was calculated by dividing the number of living patients in 2024 by the population living in France in 2024, as estimated by INSEE.

Standardized mortality ratios (SMR) were estimated with public data from the national institute for demographic studies (INED) with yearly publication of mortality rates by age, sex, and calendar year since 1946 [23]. We calculated in our population mortality rates by age, sex, and calendar year starting at 1980 for patients with a diagnosis of GD after 1980. This cut-off was imposed to minimize selection bias of patients diagnosed before 1980 who survived to present days and would therefore present with milder phenotypes and, therefore, lower mortality. We used a Poisson regression model with observed death rates as dependent variables and expected deaths as offsets in each age, sex, and calendar year category to estimate standardized mortality ratios and their 95% confidence intervals.

Regarding treatment evolution, we represented the number of patients treated by each ERT or SRT according to 5-year time periods, among patients with at least one recorded treatment (second cohort) and described treatments and their modalities of patients who were currently treated by ERT or SRT at the time of data extraction.

Finally, we described the rate of complications and their occurrence compared with the date of GD diagnosis among the third cohort of patients with complete follow-up data. The incidences of complications were calculated from the date of diagnosis of GD to the onset of the event and were presented as the number of events per 1000 person-years.

All analyses were performed with R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

2.7 | Ethics

The FGDR was approved by the French Data-Protection Commission and certified by the French Institute for Public

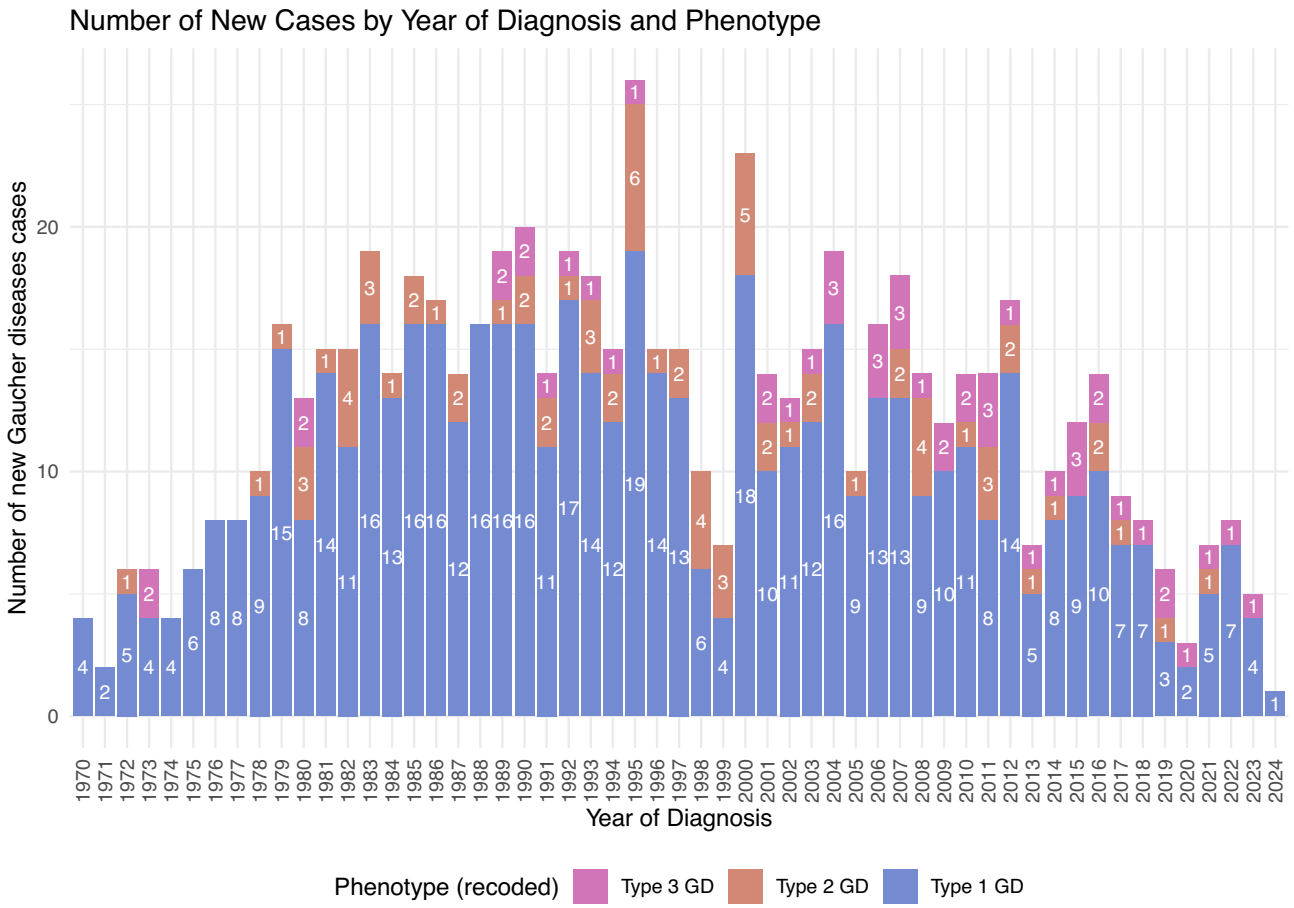

FIGURE 1 | Evolution of new diagnoses of Gaucher disease according to phenotype.

Health Surveillance and the National Institute of Health and Medical Research (INSERM). All patients gave written informed consent for the use of their data. This study was performed in accordance with the ethical standards of the Helsinki Declaration and was approved by the local Institutional Review Board.

3 | Results

3.1 | Incidence, Prevalence and Mortality

In June 2024, the FGDR contained data of 706 patients with confirmed GD in France between 1980 and 2024, including 662 with known phenotype (cohort 1): 533 GD type 1, 78 GD type 2, 51 GD type 3, and 44 patients whose phenotype was unknown (Table S1).

The number of newly diagnosed GD cases by year since 1990 is shown in Figure 1. Since 2010, 135 new cases of GD have been diagnosed. Between 1990 and 2023, the average (IQR) incidence rate in the overall French population was 0.21 cases/1 000 000 person-years (0.14–0.25) for GD (0.16 [0.11–0.21] for type 1 GD; 0.035 [0.016–0.043] for type 2 GD; 0.017 [0.015–0.032] for type 3 GD).

In June 2024, 447 patients with known phenotype were alive, including 413 patients with type 1 GD and 34 patients with type 3 GD. No patient with type 2 GD was alive in 2024. The prevalence of GD was 0.66 cases per 100 000 inhabitants (0.61 for type 1 GD [1/162000] and 0.05 for type 3 GD [1/2 000 000]).

In June 2024, 208 patients included in the FGDR had died, including 100/533 (18.8%) patients with type 1 GD, 78/78 (100%) type 2 GD, 17/51 (33.3%) type 3 GD, and 13/44 (9.1%) with unknown phenotype. Median (IQR) age at death was 68 (54–78) years for type 1 GD, 1 (1) for type 2 GD, and 7 (3–16) for type 3 GD. The standardized mortality ratio (95% CI) was 0.70 (0.53–0.93) for type I GD, and 16.23 (95% CI 9.17–28.74) for type 3 GD. Causes of death were known for 70 patients, including eight malignancies, six infections, and two PD.

3.2 | Characteristics at Diagnosis

The baseline characteristics of the 662 patients with known phenotype included in the registry (alive or deceased), and of the 447 patients alive in 2024 with known phenotype (cohort 2) are presented in Tables S1 and 1. Among the 447 living patients, 228 (51%) were women, 413 (92.4%) had type 1 GD, and 34 (7.6%) had type 3 GD.

The median (IQR) age at diagnosis was 21 (7–34) years, with a difference between type 1 (23 years old; 9–35) and type 3 GD (2 years old; 1–3) years at diagnosis. In 2024, the median age of patients was 55 (41–66) years for type 1 GD and 16 (10–31) years

TABLE 1 | Characteristics of patients enrolled in the French Gaucher Disease Registry cohort alive in 2024 ($N = 447$) according to the phenotype.

Characteristic	*N* available data	Overall ($N = 447$)	GD type I ($N = 413$)	GD type 3 ($N = 34$)
Sex = female	447	228/447 (51%)	211/413 (51%)	17/34 (50%)
Age at GD diagnosis, years	447	21 (7, 34)	23 (9, 35)	2 (1, 3)
< 15 years old at diagnosis	447	176/447 (39%)	147/413 (36%)	29/34 (85%)
Age in 2024, years	447	52 (37, 65)	55 (41, 66)	16 (10, 31)
< 15 years old in 2024	447	24/447 (5.4%)	9/413 (2.2%)	15/34 (44%)
Age at first symptoms, years	290	13 (4, 26)	16 (5, 29)	1 (1, 2)
Symptom-to-diagnosis interval, years	290	0.6 (0.0, 2.7)	0.6 (0.0, 3.3)	0.2 (0.0, 1.2)
Year of diagnosis	447			
< 1990		170/447 (38%)	168/413 (41%)	2/34 (5.9%)
1990–2000		99/447 (22%)	96/413 (23%)	3/34 (8.8%)
2000–2010		96/447 (21%)	82/413 (20%)	14/34 (41%)
2010–2020		70/447 (16%)	58/413 (14%)	12/34 (35%)
2020–2024		12/447 (2.7%)	9/413 (2.2%)	3/34 (8.8%)
Genotype	251			
p.Asn409Ser/p.Asn409Ser		53/251 (21%)	53/232 (23%)	0/19 (0%)
p.Leu483Pro/p.Leu483Pro		16/251 (6.4%)	0/232 (0%)	16/19 (84%)
p.Leu483Pro/other		9/251 (3.6%)	6/232 (2.6%)	3/19 (16%)
p.Asn409Ser/p.Leu483Pro		60/251 (24%)	60/232 (26%)	0/19 (0%)
p.Asn409Ser/other		113/251 (45%)	113/232 (49%)	0/19 (0%)
Test diagnosing GD[a]	323			
Enzymatic assay		93/323 (29%)	77/294 (26%)	16/29 (55%)
GBA-gene sequencing		5/323 (1.5%)	2/294 (0.7%)	3/29 (10%)
Bone-marrow aspiration		157/323 (49%)	148/294 (50%)	9/29 (31%)
Bone-marrow biopsy		24/323 (7.4%)	24/294 (8.2%)	0/29 (0%)
Bone biopsy		5/323 (1.5%)	5/294 (1.7%)	0/29 (0%)
Hepatic biopsy		9/323 (2.8%)	8/294 (2.7%)	1/29 (3.4%)
Spleen pathology		22/323 (6.8%)	22/294 (7.5%)	0/29 (0%)
Other		8/323 (2.5%)	8/294 (2.7%)	0/29 (0%)
Familial form	237	151/237 (64%)	141/217 (65%)	10/20 (50%)
Manifestations at diagnosis				
Splenomegaly	261	244/261 (93%)	230/245 (94%)	14/16 (88%)
Hepatomegaly	233	171/233 (73%)	159/217 (73%)	12/16 (75%)
Neurological involvement	416	6/416 (1.4%)	3/384 (0.8%)	3/32 (9.4%)
Chronic bone pain	426	84/426 (20%)	81/393 (21%)	3/33 (9.1%)
Bone crisis	417	27/417 (6.5%)	27/385 (7.0%)	0/32 (0%)
Bleeding	424	75/424 (18%)	73/391 (19%)	2/33 (6.1%)
Pulmonary involvement	418	1/418 (0.2%)	1/386 (0.3%)	0/32 (0%)

(Continues)

TABLE 1 | (Continued)

Characteristic	*N* available data	Overall (*N* = 447)	GD type I (*N* = 413)	GD type 3 (*N* = 34)
Thrombocytopenia < 50 g/L	251	30/251 (12%)	28/236 (12%)	2/15 (13%)
Fatigue	427	99/427 (23%)	98/394 (25%)	1/33 (3.0%)
Biological parameters at diagnosis				
Hemoglobin (g/dL)	46	11.1 (10.3–12.9)	11.2 (11.0–13.0)	9.6 (7.3–10.3)
Platelet count (Giga/L)	251	94 (68–125)	93 (68–125)	100 (73–134)
Ferritin	71	457 (175–767)	500 (185–804)	117 (98–210)
Chitotriosidase	104	7622 (1888–15 698)	7240 (1863– 15 793)	10 374 (4518–14 276)

Note: Data are presented as *n*/*N* (%) for categorical variables and median (IQR) for continuous variables.
Abbreviation: GD = Gaucher disease.
[a]All patients had their definitive diagnoses confirmed by enzymatic assay.

for type 3 GD. Among 151 patients with an affected family member, all but 3 (1 mother, 1 uncle, 1 cousin) were siblings.

Regarding their manifestations at diagnosis, 244/261 (93%) of patients had splenomegaly, and 171/233 (73%) clinical hepatomegaly; 84/426 (20%) had chronic bone pain. The median platelet count was 94 g/L (63–125).

The genotype was known for 251 (56%) of the patients, with a majority of patients having at least one p.Asn409Ser allele (90%), of whom 53 (21%) were homozygous, and 16 (6.4%) patients had the p.Leu483Pro/p.Leu483Pro genotype, exclusively type 3 GD.

The median time (IQR) from onset of symptoms to diagnosis of GD was 0.6 years (0.0–2.7) with a maximum delay of 56.6 years. Several diagnoses were made in the absence of symptoms, notably through family screening. This interval significantly decreased over time, with a median (min-max) of 5.4 (0.0–56.6) years before 2000, 3.0 (0.0–30.7) between 2000 and 2010, 2.7 (0.0–25.5) between 2010 and 2020, and 0.8 (0.0–3.5) after 2020 ($p = 0.001$).

Although all patients had their definitive diagnosis confirmed by enzymatic assay, the test initially leading to the diagnosis was bone-marrow aspiration for 157/323 (49%) patients, enzymatic assay for 93/323 (29%) patients, bone-marrow biopsy for 24/323 (7.4%) patients, or spleen (6.8%), liver (2.8%) or bone (1.5%) pathology (Table 1 and Figure 2). A few patients (1.5%) have been diagnosed directly by the search for genetic mutations in the GBA genes before having an enzymatic test.

Similarly, diagnostic methods have changed over time, with enzyme assays playing an increasingly important role in making the diagnosis of GD, and bone marrow aspiration and biopsies playing a lesser role in making the diagnosis (Figure 2). Thus, after 2020, almost 63% of new GD diagnoses were made directly by an enzymatic assay in blood, while bone marrow aspiration led to the diagnosis in 31.6% of cases (Figure 2). Similarly, in the whole cohort, the number of splenectomies performed prior to the diagnosis of GD, and therefore leading to the diagnosis, has fallen considerably over time, with only one since 2005 (Figure 4).

3.3 | Treatment

The number of treated patients according to the different available ERT or SRT since 1990 is shown in Figure 3. Since 2010, there has been a decrease in the use of ERT, with a gradual increase in the use of eliglustat from 19 patients between 2010 and 2015 to 89 patients between 2020 and 2024, according to the registry.

In June 2024, among the 447 alive patients, data on ERT/SRT were known for 316/447 (70%) patients (Table 2). For the other patients, data on ERT/SRT was unknown or patients were not treated. Among them, 178/316 (56%) patients were treated with imiglucerase, 82 (26%) with eliglustat, and 56 (18%) with velaglucerase alpha. The characteristics of treated patients are presented in Table 2.

Among the 82 patients treated with eliglustat, 12/82 (14.6%) were ERT/SRT–naive and therefore received eliglustat as first-line treatment.

3.4 | Splenectomy

Overall, in the whole cohort (cohort 1), 116/706 (16%) had splenectomy at a median (IQR) age of 24 (16–36) years: 62/116 (53%) before GD diagnosis, leading to the diagnosis of GD in 40/62 (64%) cases, and 54/116 (44%) after GD diagnosis (after a median [IQR] of 5.7 [0.7–8.9] years).

The evolution of the number of splenectomies realized before and after GD diagnosis across the years is shown in Figure 4. Since the availability of ERT (1991), the number of splenectomies, especially those realized after GD diagnosis (thus considered as treatment), considerably decreased (Figure 4). The reasons for splenectomies after GD diagnosis during the era of ERT are presented in Table S2. All splenectomies but one (alglucerase) were performed in the absence of ERT or SRT.

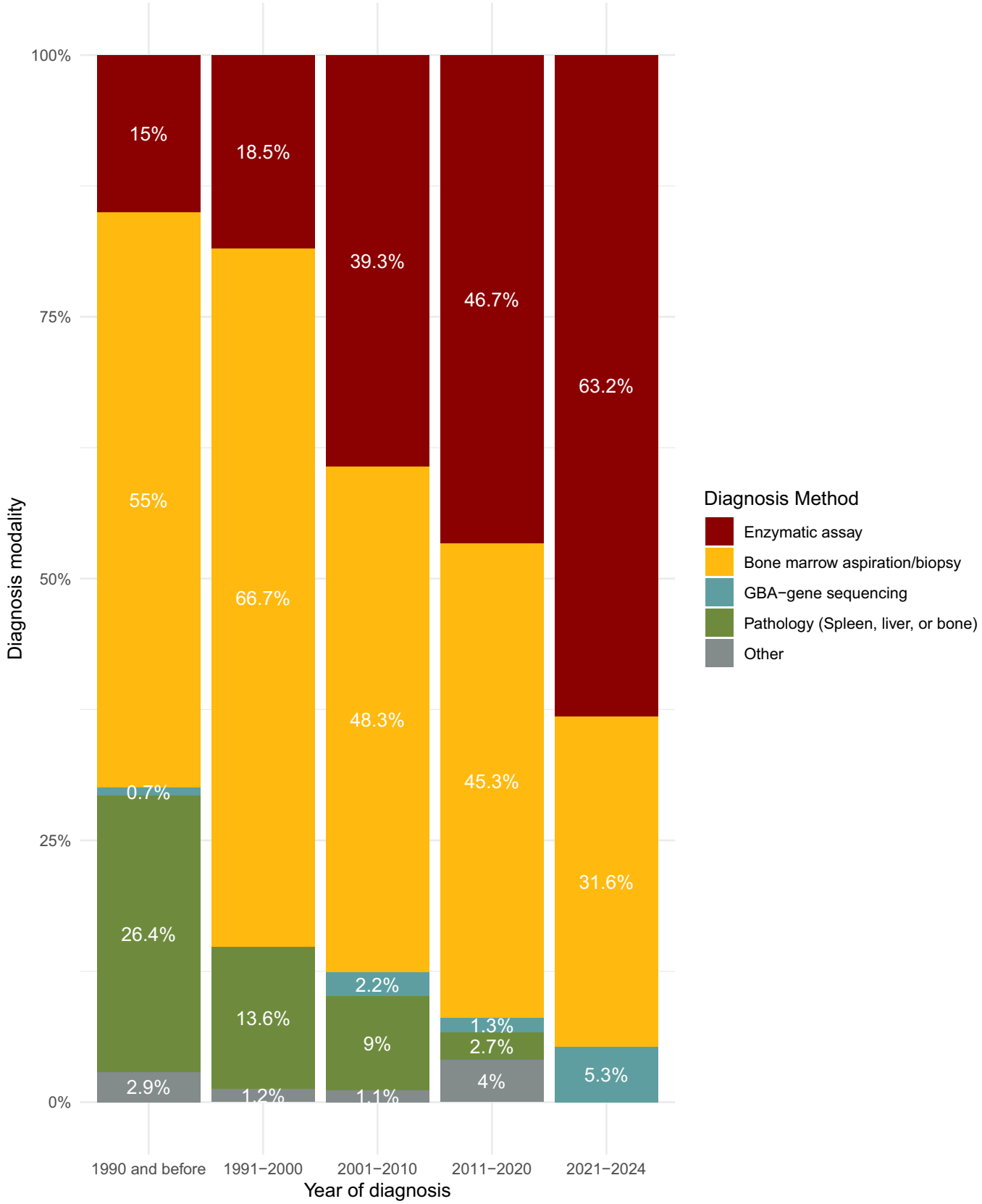

FIGURE 2 | Evolution of the test initially leading to Gaucher disease diagnosis. All patients had their definitive diagnosis confirmed by enzymatic assay.

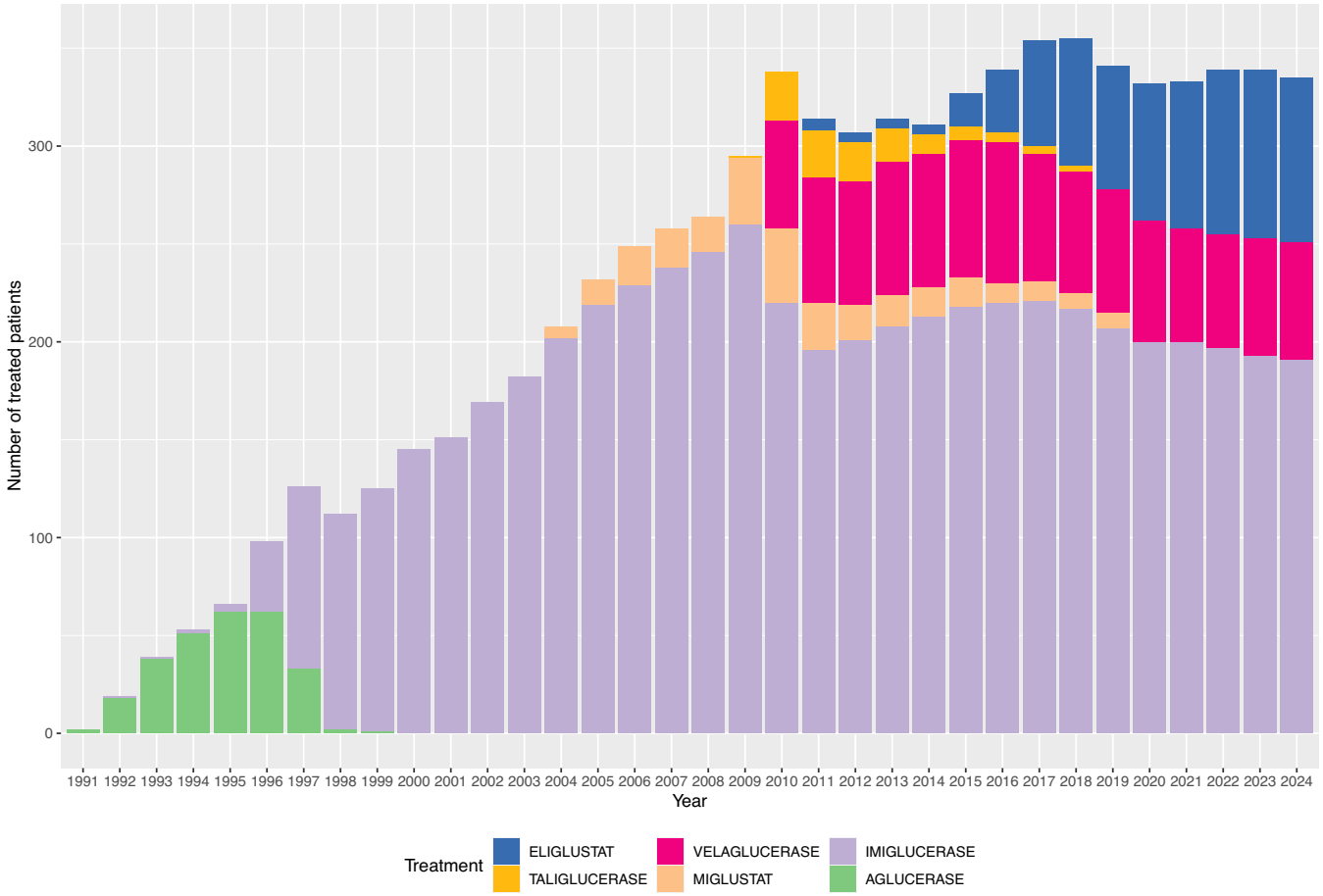

FIGURE 3 | Treatment evolution of patients included in the French Gaucher Disease Registry.

3.5 | GD Complications and Associated Diseases on Patients With Complete Follow-Up Cohort

A total of 210 patients, type 1 (90%) or type 3 (10%) patients, had complete follow-up data (cohort 3). The median follow-up duration was 26.7 (15.1–38.5) years. The characteristics at diagnosis were similar to those of the entire cohort. Among them, 181/210 (86.2%) were treated by ERT or SRT, and 204/210 (97.1%) were still alive in 2024.

During follow-up, 88/210 (41.9%) patients experienced bone events, with a median (min–max) of 2 (1–10) bone events per patient for a total of 184 bone events, including 38 avascular necroses, 56 bone infarcts, 71 pathological fractures, and 19 vertebral collapses. The cumulative incidence of bone events since the date of GD diagnosis was 23 events/1000 person-year (Figure 5A). Among the 181 treated patients with ERT/SRT, 61/181 (33.7%) had bone events after the initiation of treatment (bone infarct [$N=21$], avascular necrosis [$N=8$], fracture [$N=32$]), with a median [IQR] of 7.1 [2.8–12.8] years after ERT/SRT start (Figure 5B).

Regarding malignancies, 15/210 patients (9%) developed 19 cancers or hematological malignancies during follow-up, including breast cancer ($N=5$), bladder cancer ($N=2$), multiple myeloma ($N=3$), MALT lymphoma ($n=2$), myeloproliferative syndrome ($N=2$), or other types of solid cancers ($n=5$). The cumulative incidence of cancer or hematological malignancies was 2.7 per 1000 person-year and is shown in Figure 5C.

Finally, 6/210 (3%) developed PD during follow-up, representing 1.07 per 1000 person-year (Figure 5D). All of them were type 1 GD with a median (IQR) age at GD diagnosis of 32.6 [28.1–36.0] and a median (IQR) age at PD diagnosis of 61.3 [56.1–66.3] years, with a median delay between GD and PD diagnoses of 27.0 [21.5–32.7] years. None of these patients had neurological involvement at the time of diagnosis of GD. All cases of PD occurred while patients were being treated with ERT ($n=5$) or SRT ($N=1$).

4 | Discussion

Based on a national registry of 706 patients, this study allowed an updated description of the evolution of GD epidemiology in France in terms of incidence, prevalence, complications, diagnostic modalities, and management strategies.

With a prevalence of 0.66 cases per 100 000 inhabitants, GD remains a very rare condition. This prevalence is consistent with the global prevalence estimated at 0.9 cases per 100 000 inhabitants according to a recent meta-analysis, and 0.7 cases per 100 000 in Europe, estimated from four studies [24]. This prevalence varies considerably depending on the country and ethnic

TABLE 2 | Treatment characteristics of patients currently treated with enzyme reduction therapy or substrate reduction therapy ($N = 316$).

		Current Gaucher disease treatment		
Characteristic	**N**	**Eliglustat $N = 82$**	**Imiglucerase $N = 178$**	**Velaglucerase alpha $N = 56$**
Gender	316			
Female		36 (44%)	91 (51%)	30 (54%)
Male		46 (56%)	87 (49%)	26 (46%)
Age at GD diagnosis	311	19 (9–32)	17 (5–27)	24 (9–33)
Current age	311	50 (40–61)	49 (29–63)	56 (43–69)
GD phenotype	316			
Type 1		82 (100%)	154 (86%)	54 (96%)
Type 3		0 (0%)	24 (14%)	2 (3.6%)
Treatment modality	243			
Intravenous treatment				
At hospital		NA	66 (57%)	34 (67%)
Home intravenous hospital		NA	50 (43%)	17 (33%)
Oral treatment		77 (100%)	NA	NA
Unknown		0	61	4
Start of ongoing treatment	316			
1995–2000		—	13 (7%)	—
2000–2005		—	12 (7%)	—
2005–2010		—	24 (13%)	—
2010–2015		1 (1%)	52 (29%)	24 (43%)
2015–2020		52 (63%)	48 (27%)	18 (32%)
2020–2024		29 (35%)	29 (16%)	14 (25%)
Previous treatments (several possible)				
Imiglucerase	316	61 (74%)	—	40 (71%)
Velaglucerase alpha	316	27 (33%)	8 (4.5%)	—
Taliglucerase	316	8 (9.8%)	15 (8.4%)	0 (0%)
Miglustat	316	18 (22%)	22 (12%)	7 (13%)
Eliglustat	316	—	13 (7.3%)	10 (18%)

Note: Data are expressed as median (interquartile range) and count (percent).
Abbreviations: GD = Gaucher disease; NA = non applicable.

origin, with a much higher prevalence in the Ashkenazi Jewish population, with a prevalence of 20.2 per 100 000 inhabitants in Israel and 139 in the Ashkenazi Jewish population of the United States of America [25].

We also reported an incidence of new diagnoses of 0.21 cases/1 000 000 person-years based on our registry, close to the 0.26/1 000 000 person-years reported in the previous study [3]. To our knowledge, there are very few data on the incidence of newly diagnosed cases, but available data focused on the birth incidence, defined by the number of new diagnoses of the disease divided by the total births in the same periods, or the data from newborn screening programs [25]. This differs, as our estimate relies on diagnoses based on clinical symptoms leading to a diagnosis of GD (outside of family-based screening); thus, it does not account for undiagnosed cases. However, our data are similar to the population of Spain, where 8–10 new cases were diagnosed/year in 2019 [25].

In the last decade, we have observed a decrease in the number of diagnosed cases per year and thus in the incidence. This can have several explanations, including a "saturation effect," with an initial improvement in the knowledge of the clinical signs of the disease, which allowed the initial detection of all cases that were previously undiagnosed but monitored for hepatosplenomegaly, and thereafter, the diagnosis of fewer new cases.

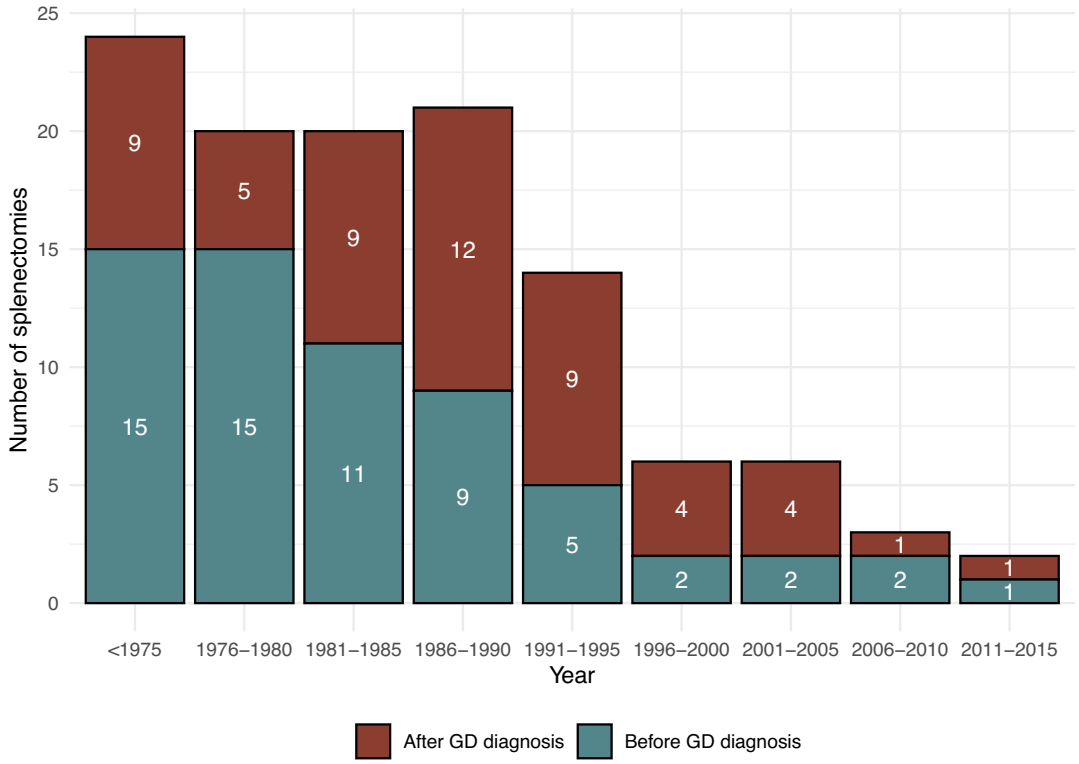

FIGURE 4 | Evolution of the number of splenectomies occurring before and after Gaucher disease diagnosis performed over time ($N = 115$).

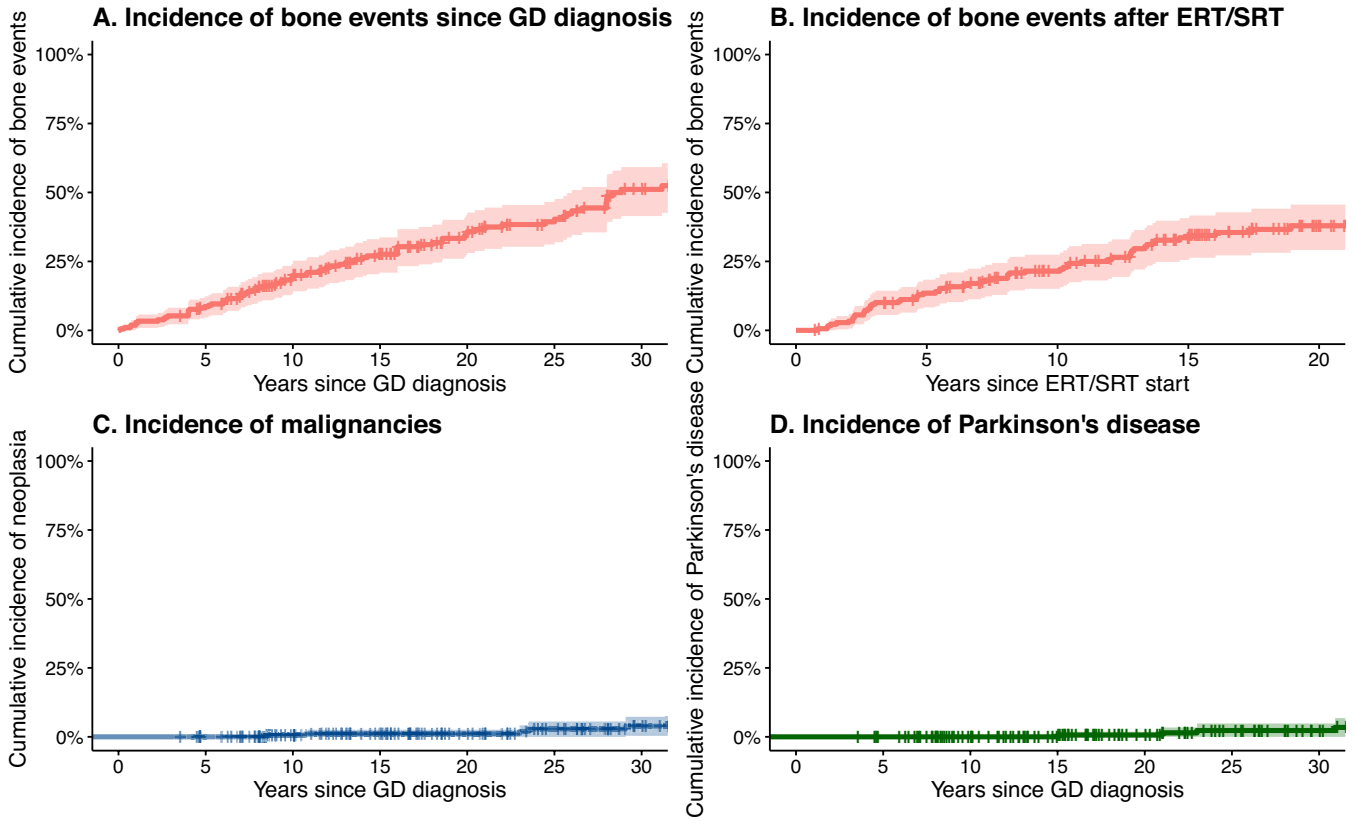

FIGURE 5 | Cumulative incidences of bone events (A) Since GD diagnosis and (B) after ERT/SRT start, (C) malignancies and (D) Parkinson's disease since the date of Gaucher disease diagnosis ($N = 210$). ERT = enzyme replacement therapy; GD = Gaucher disease; SRT = substrate reduction therapy.

In addition, despite our effort to maintain exhaustivity, it is still possible that not all cases are being captured in the registry, especially if the diagnosis is not made through enzyme assay, and if the patient does not require treatment.

One inherent challenge of rare diseases is the diagnostic delay related to a lack of awareness of the disease. Nevertheless, over time, we observed an improvement in the recognition of this disease by healthcare professionals, reflected by the reduction in the diagnostic delay, an increased use of enzymatic tests (on leukocytes, or more recently on dried blood spots) compared to invasive tests like bone marrow aspiration, and a decrease in the time between the onset of symptoms and diagnosis.

Furthermore, we were able to estimate the SMR, which was significantly higher for type 3 GD compared to the general population but lower for type 1 GD. This decrease in SMR in type 1 GD may be the result of significant improvements in care since the introduction of SRT/ERT and better screening for comorbidities. In 2008, Weinreb et al. estimated the life expectancy in type 1 GD and stated that the estimated life expectancy at birth for GD1 patients was approximately 9 years less than the reference population [26]. However, those data do not reflect actual management of GD diseases, as 27% had total or partial splenectomy, and most patients died before 2000 (IQR 1993–2006) and thus have lived most of their lives without ERT/SRT. In our analyses, we focused on patients diagnosed after 1980, which may better reflect actual management of patients with GD. Thus, these findings provide a reassuring message for patients with type 1 GD, without an excess of mortality. However, mortality in type 3 GD is still increased.

Additionally, we were able to illustrate the evolution of SRT/ERT prescriptions over the years, which also corresponds to successive approvals of treatments in France. We can observe that, although still relatively infrequent, SRT prescriptions are playing an increasingly important role, both as follow-up and as first-line treatments. According to our data, only 40% of patients treated with ERT are treated at home. This can be related to the organization of the French healthcare system, where patients can easily choose between outpatient hospital structures or home treatments. However, it is possible that our rate is underestimated, notably if there have been recent changes.

Finally, in a sub-cohort with extended follow-up, we were able to estimate the incidence of various complications, including bone events, neoplasia (including multiple myeloma), and PD. As previously described in our previous report [3], despite the effectiveness of ERT/SRT on bone pain reduction, bone crises, and improvement in bone mineral density [27, 28], these therapies do not entirely prevent BE, as indicated by the number of bone events under treatment. Patients on ERT/SRT likely experience fewer complications compared to if they had not received treatment. In our previous study, we found that the occurrence of bone events prior to treatment increased the risk of bone events during therapy, as splenectomy and delays in initiating GD treatment. Thus, bone events remain a challenge that is not completely resolved by current therapies [3]. However, as bone events include both bone infarcts and pathological fractures, some events might be the consequence of previous bone fragility before treatment.

In addition, while multiple myeloma and PD are classically associated with type 1 GD, with an incidence of 2.7 and 1.07 per 1000 person-year, respectively, in our registry, these complications remain rare. Further studies are needed to identify which patients are at risk for these complications among those with type 1 GD.

There are limitations to our study. The FGDR is a comprehensive national cohort (all patients diagnosed with GD in France are identified); however, as with any registry, some data, such as genetic information, follow-up, complications, and treatments, are missing, particularly for older cases. Thus, we analyzed complications in a sub-cohort of patients with regular follow-up, which could introduce a bias, particularly related to screening among healthcare providers more experienced in disease management. Nevertheless, we made efforts to ensure data completeness regarding new diagnoses through multiple sources and mortality by manually verifying the data of all patients included in the registry against the national death registry. However, undiagnosed cases are not accounted for, and even though the recognition of GD has significantly improved over time, some cases, particularly those with minimal symptoms, may remain undiagnosed, leading to an underestimation of disease prevalence. Furthermore, treatment data were available for 70% of living patients, while the treatment status of other patients is either unknown or untreated. A study dedicated to untreated patients based on registry data has been published [29, 30].

Nevertheless, our study has undeniable strengths, particularly in terms of the number of patients, the richness of the longitudinal data, and of the follow-up. We were able to estimate a standardized mortality ratio based on the exhaustivity of the diagnosed cases and the vital status of the patients, and to estimate the incidence of complications using a sub-cohort with complete longitudinal follow-up.

In conclusion, our study enabled us to update the epidemiology of GD in France, while noting an improvement in knowledge of the disease, resulting in less invasive and more rapid diagnoses. We were able to show that the standardized mortality of patients with type 1 GD was not increased, and on the contrary decreased compared with the general population, while that of type 3 GD remained increased. Finally, the complications classically associated with the risk of type 1 GD, such as neoplasia and PD, remained rare.

Author Contributions

Study conception and design: Y.N., N.B., J.S. Acquisition of data: All authors. Statistical analysis: Y.N. and M.B. Analysis and interpretation of data: All authors. Drafting the manuscript: Y.N. Revising the manuscript: All authors.

Acknowledgments

The authors are indebted to all patients included in the French Gaucher Disease Registry. They acknowledge all author members of the Evaluation of Gaucher Disease Treatment Committee.

Ethics Statement

The FGDR was approved by the French Data-Protection Commission and certified by the French Institute for Public Health Surveillance

and the National Institute of Health and Medical Research (INSERM). This study was performed in accordance with the ethical standards of the Helsinki Declaration and was approved by the local Institutional Review Board.

Consent

All patients gave written informed consent for use of their data.

Conflicts of Interest

Bénédicte Héron received travel fees from Sanofi. Anaïs Brassier received travel fees from Sanofi and Takeda, and consulting fees or other remuneration including fees as speaker from Sanofi and Takeda. Florence Dalbies received consulting fees or other remuneration, including a fee as a speaker from Sanofi. Bérengère Cador received travel fees from Sanofi and Takeda. Francis Gaches received travel fees from Sanofi. Agathe Masseau received a fee as a speaker from Sanofi and Takeda. Magali Pettazzoni received travel fees from Sanofi, and consulting fees or other remuneration including fees as speaker from Sanofi and Takeda. Wladimir Mauhin received fees for consultancy, speaking, travel grants, and meetings from Sanofi, Takeda, and Amicus therapeutics. Yann Nadjar received research grants from Takeda and received consulting fees or other remuneration, including fees as speaker, from Sanofi; assisting in the design of and/or participating in clinical studies using products manufactured by Sanofi. Christine Serratrice received consulting fees or other remuneration, including fees as a speaker from Takeda and Sanofi. Fabrice Camou received fees for consultancy, speaking, travel grants, and meetings from Sanofi and Takeda. Nadia Belmatoug received fees for consultancy, speaking, travel grants, and meetings from Sanofi and Takeda. The other authors declare no conflicts of interest.

Data Availability Statement

Data are available upon reasonable request after approval of the scientific committee.

References

1. R. O. Brady, J. N. Kanfer, and D. Shapiro, "Metabolism of Glucocerebrosides. II. Evidence of an Enzymatic Deficiency in Gaucher's Disease," *Biochemistry and Biophysics Research Communications* 18 (1965): 221–225.

2. L. Nalysnyk, P. Rotella, J. C. Simeone, A. Hamed, and N. Weinreb, "Gaucher Disease Epidemiology and Natural History: A Comprehensive Review of the Literature," *Hematology Amsterdam* 22, no. 2 (2017): 65–73.

3. J. Stirnemann, M. Vigan, D. Hamroun, et al., "The French Gaucher's Disease Registry: Clinical Characteristics, Complications and Treatment of 562 Patients," *Orphanet Journal of Rare Diseases* 7 (2012): 77.

4. J. Stirnemann, N. Belmatoug, F. Camou, et al., "A Review of Gaucher Disease Pathophysiology, Clinical Presentation and Treatments," *International Journal of Molecular Sciences* 18, no. 2 (2017): 441.

5. Y. Nguyen, J. Stirnemann, and N. Belmatoug, "La maladie de Gaucher: quand y penser?," *Rev Médecine Interne* 40 (2019): 313–322.

6. E. Sidransky, "Gaucher Disease: Complexity in a "Simple" Disorder," *Molecular Genetics and Metabolism* 83, no. 1 (2004): 6–15.

7. B. Rosenbloom, M. Balwani, J. M. Bronstein, et al., "The Incidence of Parkinsonism in Patients With Type 1 Gaucher Disease: Data From the ICGG Gaucher Registry," *Blood Cells, Molecules & Diseases* 46, no. 1 (2011): 95–102.

8. A. Tylki-Szymańska, A. Vellodi, A. El-Beshlawy, J. A. Cole, and E. Kolodny, "Neuronopathic Gaucher Disease: Demographic and Clinical Features of 131 Patients Enrolled in the International Collaborative Gaucher Group Neurological Outcomes Subregistry," *Journal of Inherited Metabolic Disease* 33, no. 4 (2010): 339–346.

9. N. W. Barton, R. O. Brady, J. M. Dambrosia, et al., "Replacement Therapy for Inherited Enzyme Deficiency-Macrophage-Targeted Glucocerebrosidase for Gaucher's Disease," *New England Journal of Medicine* 324, no. 21 (1991): 1464–1470.

10. R. J. Wenstrup, K. A. Kacena, P. Kaplan, et al., "Effect of Enzyme Replacement Therapy With Imiglucerase on BMD in Type 1 Gaucher Disease," *Journal of Bone and Mineral Research* 22, no. 1 (2007): 119–126, https://doi.org/10.1359/jbmr.061004.

11. G. A. Grabowski, N. W. Barton, G. Pastores, et al., "Enzyme Therapy in Type 1 Gaucher Disease: Comparative Efficacy of Mannose-Terminated Glucocerebrosidase From Natural and Recombinant Sources," *Annals of Internal Medicine* 122, no. 1 (1995): 33–39.

12. N. J. Weinreb, J. Charrow, H. C. Andersson, et al., "Effectiveness of Enzyme Replacement Therapy in 1028 Patients With Type 1 Gaucher Disease After 2 to 5 Years of Treatment: A Report From the Gaucher Registry," *American Journal of Medicine* 113, no. 2 (2002): 112–119.

13. N. J. Weinreb, J. Goldblatt, J. Villalobos, et al., "Long-Term Clinical Outcomes in Type 1 Gaucher Disease Following 10 Years of Imiglucerase Treatment," *Journal of Inherited Metabolic Disease* 36, no. 3 (2013): 543–553.

14. D. E. Gonzalez, H. B. Turkia, E. A. Lukina, et al., "Enzyme Replacement Therapy With Velaglucerase Alfa in Gaucher Disease: Results From a Randomized, Double-Blind, Multinational, Phase 3 Study," *American Journal of Hematology* 88, no. 3 (2013): 166–171.

15. E. Lukina, N. Watman, M. Dragosky, et al., "Eliglustat, an Investigational Oral Therapy for Gaucher Disease Type 1: Phase 2 Trial Results After 4years of Treatment," *Blood Cells, Molecules & Diseases* 53, no. 4 (2014): 274–276.

16. T. M. Cox, G. Drelichman, R. Cravo, et al., "Eliglustat Compared With Imiglucerase in Patients With Gaucher's Disease Type 1 Stabilised on Enzyme Replacement Therapy: A Phase 3, Randomised, Open-Label, Non-Inferiority Trial," *Lancet* 385, no. 9985 (2015): 2355–2362, https://doi.org/10.1016/S0140-6736(14)61841-9.

17. P. K. Mistry, E. Lukina, H. B. Turkia, et al., "Effect of Oral Eliglustat on Splenomegaly in Patients With Gaucher Disease Type 1: The ENGAGE Randomized Clinical Trial," *JAMA* 313, no. 7 (2015): 695–706, https://doi.org/10.1001/jama.2015.459.

18. N. Belmatoug, M. Di Rocco, C. Fraga, et al., "Management and Monitoring Recommendations for the Use of Eliglustat in Adults With Type 1 Gaucher Disease in Europe," *European Journal of Internal Medicine* 37 (2017): 25–32.

19. N. J. Weinreb, "The International Cooperative Gaucher Group (ICCG) Gaucher Registry," *Best Practice & Research. Clinical Haematology* 36, no. 4 (2023): 101522.

20. A. Zimran, N. Belmatoug, B. Bembi, et al., "Demographics and Patient Characteristics of 1209 Patients With Gaucher Disease: Descriptive Analysis From the Gaucher Outcome Survey (GOS)," *American Journal of Hematology* 93 (2018): 205–212.

21. A. Tajima, T. Yokoi, M. Ariga, et al., "Clinical and Genetic Study of Japanese Patients With Type 3 Gaucher Disease," *Molecular Genetics and Metabolism* 97, no. 4 (2009): 272–277.

22. "Statistiques et études | Insee."

23. "Taux de mortalité par sexe et âge - Mortalité, cause de décès - France—Les chiffres," Ined—Institut national d'études démographiques.

24. M. Wang, F. Li, J. Zhang, C. Lu, and W. Kong, "Global Epidemiology of Gaucher Disease: An Updated Systematic Review and Meta-Analysis," *Journal of Pediatric Hematology/Oncology* 45 (2023): 181–188.

25. G. Castillon, S. C. Chang, and Y. Moride, "Global Incidence and Prevalence of Gaucher Disease: A Targeted Literature Review," *Journal of Clinical Medicine* 12, no. 1 (2022): 85.

26. N. J. Weinreb, P. Deegan, K. A. Kacena, et al., "Life Expectancy in Gaucher Disease Type 1," *American Journal of Hematology* 83, no. 12 (2008): 896–900.

27. K. Sims, G. Pastores, N. Weinreb, et al., "Improvement of Bone Disease by Imiglucerase (Cerezyme) Therapy in Patients With Skeletal Manifestations of Type 1 Gaucher Disease: Results of a 48-Month Longitudinal Cohort Study," *Clinical Genetics* 73, no. 5 (2008): 430–440.

28. E. Lukina, N. Watman, M. Dragosky, et al., "Outcomes After 8 Years of Eliglustat Therapy for Gaucher Disease Type 1: Final Results From the Phase 2 Trial," *American Journal of Hematology* 94, no. 1 (2019): 29–38.

29. C. Serratrice, J. Stirnemann, A. Berrahal, et al., "A Cross-Sectional Retrospective Study of Non-Splenectomized and Never-Treated Patients With Type 1 Gaucher Disease," *Journal of Clinical Medicine* 9, no. 8 (2020): 2343.

30. A. Nasce, Y. Nguyen, N. Belmatoug, et al., "Never-Treated, Non Splenectomised Patients With Gaucher Disease (The French GANT Study): The Prospective Follow-Up," *Journal of Inherited Metabolic Disease* 48, no. 2 (2025): e70026.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.