Gaucher disease epidemiology and natural history: a comprehensive review of the literature

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ABSTRACT

Objectives: The objectives of this research were: (1) to heighten awareness of Gaucher disease (GD), a rare lysosomal storage disorder with highly heterogeneous patterns of organ involvement and disease severity, to clinicians most likely to encounter these patients, and; (2) to summarize the published evidence on GD epidemiology which is essential to accurately depict the total societal burden of this rare worldwide disorder.

Methods: A comprehensive literature review was undertaken to summarize the published evidence on the epidemiology of GD. MEDLINE, EMBASE, CENTRAL, and ‘grey’ literature sources published in English between January 1990 and March 2015 were searched to identify relevant publications.

Results: In total, 188 full-text articles were reviewed and findings from 49 studies are summarized herein. The standardized birth incidence of GD in the general population varied from 0.39 to 5.80 per 100,000, and prevalence ranged from 0.70 to 1.75 per 100,000, respectively. Time from onset of GD symptoms to clinical diagnosis was highly variable, with median delays of up to 7 years reported.

Discussion: The incidence and prevalence of GD is substantially higher among the Ashkenazi Jewish population than the general population. Limited epidemiologic information was available from Latin America, Africa, Asia, and developed nations such as the United States, Germany, and the United Kingdom.

Conclusions: Signs and symptoms of GD frequently mimic more common hematologic conditions resulting in missed or delayed diagnosis. Early diagnosis and prompt initiation of treatment when indicated is crucial to prevent or minimize life-altering or life-threatening liver and skeletal complications.

KEYWORDS

Gaucher disease; epidemiology; incidence; prevalence; natural history; mortality; review; lysosomal storage disorder

Introduction

Gaucher disease (GD) is a rare inherited lysosomal storage disorder (LSD) caused by autosomal recessive inheritance of mutations in the GBA gene encoding the lysosomal enzyme acid β-glucosidase [1]. Inadequate enzymatic activity causes progressive accumulation of the sphingolipid glucosylceramide in lysosomes of macrophages (referred to as Gaucher cells), mainly in the liver, spleen, bone, and bone marrow [1]. Accumulation of potentially pathogenic secondary substrates such as glucosylsphingosine also occurs in multiple cell types [2].

Three major subtypes of GD have been described based on the presence or absence of early-onset neurologic involvement. Type 1 (GD1), formerly called non-neuronopathic, is the most common subtype in the Western world, accounting for 94% of all GD cases in this population [3]. The prevalence of GD1 in the Ashkenazi Jewish (AJ) population is much higher than in non-Jewish populations. The carrier frequency among AJ individuals is estimated to be 6%, compared to 0.8% in non-Jewish populations [4,5], and the GD prevalence in the AJ population is estimated at 1 in 850 (118 per 100,000) compared to 1–2 per 100,000 in non-Jewish populations [6].

GD1 is characterized by highly variable clinical symptomatology with a spectrum ranging from minimally affected individuals to those with hematologic manifestations, visceral manifestations, and skeletal manifestations [7]. Clinically unaffected or minimally affected individuals may account for at least half of all genetically affected people in the AJ population. The incidence of such mildly affected individuals in the non-Jewish population is unknown.

Type 2 (GD2) and type 3 (GD3) are less common than GD1 and are estimated to occur in one in 100,000–300,000 births. Neurologic pathology dominates the clinical presentation of GD2 and GD3, although severe systemic (non-central nervous system) manifestations may also occur [8]. Hallmark neurologic manifestations of GD2 and GD3 include abnormal eye movements (saccades) and myoclonic or generalized seizures [1]. GD2 represents the acute neuronopathic disease subtype, with an onset during infancy [1]. Even when it is not associated with neonatal mortality, GD2 progresses.
rapidly and affected infants have a very short life expectancy, at most, 2–3 years despite the best supportive care [1,8]. Because of longer survival, GD3 (the subacute or chronic neuroopathic phenotype) is more prevalent than GD2 and is associated with later onset in childhood than GD2 [9]. Like GD1, GD3 is clinically heterogeneous. Patients often suffer from systemic features (e.g., hepatosplenomegaly, hematologic complications, and skeletal manifestations) similar to patients with GD1, with overt neurologic symptoms resembling those of GD2 later in the disease course. This presentation can lead to diagnostic challenges and difficulty in distinguishing between GD2 and GD3, and occasionally even between GD3 and GD1 [8]. Although some mutations or genotypes are associated with either type 1, 2, or 3, unique phenotypes (e.g. type 3c), or severity of GD, the correlation between genotype and phenotype is imprecise and insufficient for classification purposes.

In symptomatic patients, GD1 is generally a progressive ailment that, if left untreated, can result in hematologic disease, irreversible organ damage, severe morbidity, reduced health-related quality of life (HRQoL), and even premature death. Effective palliative treatment for GD is available in the form of intravenous enzyme-replacement therapy (ERT) and oral substrate reduction therapy (SRT) which have been shown to reverse or prevent many of the manifestations of GD1 [10–17] and to control the non-neurologic consequences of GD3 [18–20].

Despite the availability of accurate, minimally invasive diagnostic tests (such as peripheral white blood cell enzyme assays), patients are frequently misdiagnosed [6] and experience significant diagnostic delays [21,22]. This is likely a consequence of the relative rarity of the disease and a lack of awareness among clinicians, who often do not consider a GD diagnosis because the signs and symptoms frequently mimic other more common conditions, including hematologic malignancies. It is therefore very important to heighten awareness of GD, especially among specialists most likely to encounter these patients (e.g., hematologists). Increased awareness of GD should lower the threshold for testing and reduce the rate of inaccurate or delayed diagnoses for patients with GD and promote earlier initiation of treatment, when clinically indicated. When GD is recognized, assessed, and treated appropriately, most patients can aspire to a favorable prognosis. With this goal in mind, a comprehensive literature review was undertaken to scrutinize and summarize the published evidence on GD epidemiology, information that is essential to accurately depict the total societal burden of this rare worldwide disorder.

Methods

A literature search was conducted to identify published studies examining the epidemiology of GD including incidence, prevalence, age and timeliness of diagnosis, and mortality. This study is preliminary to a larger project that will focus on the individual, family, and societal burdens of GD in terms of physical, emotional, psychosocial, and economic costs of GD especially as modulated by therapies that are already in clinical use. MEDLINE (via PubMed), EMBASE, and CENTRAL were searched for relevant abstracts. The general search included relevant studies published in English from January 1990 to March 2015. Reference lists of review articles were reviewed manually to supplement the above electronic searches and ensure that the most relevant studies were identified. Articles that investigated only in vitro, animal, fetal, molecular, genetic, pharmacokinetic/pharmacodynamic, or biomarkers were excluded, as were studies involving fewer than five patients and editorials and expert opinion pieces. Abstracts and full articles were reviewed by two investigators. Relevant data on study design, patient characteristics, and outcomes of interest were extracted from identified publications.

Epidemiologic data were reported differently across studies. Generally however, one or more of the following were reported: (1) birth incidence: number of postnatal diagnoses during the study period divided by the total births in the same period; (2) other incidence: rates of newly diagnosed cases among hospital visits, and incidence of GD carrier couples identified by genetic screening; (3) birth prevalence: post-natal and live-born prenatal diagnoses divided by the total number of births in a given period; (4) birth frequency: number of newborns at risk of GD due to the identification of homozygous genotypes during genetic screening; (5) standard prevalence: total number of GD cases divided by the total population. Incidence and prevalence values were extracted as reported in the identified studies. Standardized estimates were calculated by converting the denominator to 100 000 using cross multiplication.

Results

Two thousand fifty-nine citations were identified by the literature searches (2037 citations from database searches and 22 citations from conference abstracts; Supplementary Figure 1). After initial filtration, 188 full-text publications were reviewed for inclusion with a total of 49 relevant studies summarized in this manuscript. Studies describing the epidemiology of GD were reported from multiple geographic regions (Figure 1). Epidemiologic outcomes were reported in 23 studies including disease incidence (Figure 1(a)), prevalence (Figure 1(b)), and prevalence of genetic mutations associated with GD.

Incidence

The majority of 11 studies reporting on the incidence of GD were conducted in general populations of mixed
ancestry [5,23–31], with one study specifically focused on the AJ population (Figure 1(a)) [32]. Birth incidence among the general population varied considerably in studies with clearly identified methods, ranging from 0.39 per 100 000 in a Canadian study [24] to 5.80 per 100 000 in a study conducted in Austria [28]. A Japanese study reported the lowest incidence for GD at 0.30 per 100 000 but cases were identified from hospital records, and the study did not describe how incidence was calculated [29]. Two studies, identified by the supplemental search, reported birth incidence rates similar to and as discrepant as those identified in the initial search: 0.40 per 100 000 in a Moroccan study [31] and 2.30 per 100 000 in a population pilot study to determine the performance of newborn blood spot screening in Missouri, United States (US) [26].

Population genetic testing confirms long-established knowledge that AJ individuals have a much higher risk for GD than other ethnicities [33]. In an Israeli study, 28 893 individuals were screened for GD; 83 carrier couples (i.e., both parents carry a single known GD mutation) were identified [32]. Genotypes indicated that 82 carrier couples were at risk of offspring with non-neuronopathic GD1 (i.e. an N370S mutation was present in at least one partner); one couple was at risk of offspring with neuronopathic type 2/3 GD. Sixty-eight carrier couples consented to prenatal screening. As anticipated by Mendelian rules for autosomal recessive inheritance, 16 pregnancies (23.5%) were confirmed as resulting in affected homozygous or compound heterozygous offspring. Based on genotype, 13 fetuses were predicted to have post-natal asymptomatic/mild disease and three to have moderately severe disease.

In a retrospective analysis of data from the two units in Sweden that diagnose LSDs, the reported incidence of GD was 2.11 per 100 000 [27]; the relatively high incidence was accounted for by a specific Swedish ancestry...
(Norbottanian) variant of GD3. GD was shown to be the most common LSD in a retrospective analysis of patients in India, with a reported relative frequency (total number of patients diagnosed with GD divided by the total number of patients diagnosed with an LSD) of 0.127 [34].

**Prevalence**

The global frequency of GD1 is often estimated at 1:50 000–1:100 000 [6]. Prevalence estimates were reported in nine studies, including seven in mixed populations [5,23,35–39] and two in AJ populations (Figure 1(b)) [40,44]. In a retrospective registry study conducted in France [23], the standard prevalence of GD was 0.74 per 100 000. In 2000, a Spanish study reported a standard prevalence of 0.33 per 100 000 [36], but in 2012, a larger study of Iberian GD patients reported a standard prevalence of 0.67 per 100 000, a figure much closer to that of the French registry study [35]. The difference between the two Spanish reports is not clear, but may be due to the larger sample size from a wider geographical area in the 2012 study (436 patients compared with 155 patients in the earlier study), or due to methodological differences including criteria for diagnosis and methods for genotyping [35,36]. Birth prevalence ranged from 1.13 per 100 000 live births in the Czech Republic [39] to 1.75 per 100 000 live births in an Australian retrospective case study analysis [5]. Studies restricted to the AJ population demonstrated a much higher prevalence of GD compared with the general population (Figure 1(b)) [4,40].

Four studies (all conducted in patients of AJ descent) assessed the prevalence of known GD genetic mutations [4,40–42]. In the largest (n = 8069), 0.11% of the population were homozygous for any mutation, the majority of which were N370S/N370S genotypes (0.10%); 6.5% were identified as a carrier of a GD genotype, most of which had an N370S mutation (6%) [41]. In a fifth study that retrieved the records of 93 South Florida patients with GD1 from the International Collaborative Gaucher Group (ICGG) Gaucher Registry, 61.9% were shown to be homozygous for the N370S mutation [43]. These findings are most likely a consequence of the large AJ population of South Florida.

Few studies reported on the epidemiology of neuropathic GD. In three studies, prevalence of GD2 and GD3 subtypes were lower than that of GD1. Standardized prevalence rates (per 100 000) for combined GD2 and GD3 were 0.34 in the Czech Republic, 0.26 in the Netherlands, and 0.55 in Portugal, compared with rates of 0.79, 0.90, and 0.80 for GD1, respectively [37–39]. These studies also reported that late-onset GD1 (diagnosed at ≥15 years) was more prevalent than early-onset disease (diagnosed at <15 years). In an 11-year retrospective Moroccan study published in 2015, nine patients (81%) had GD1 and two (19%) had GD2 [44]. All these studies, none of which emanated from the Far or non-Israeli Middle East where GD2 and GD3 phenotypes are more prevalent than in Western countries, suggest that a greater proportion of patients worldwide have neuropathic GD than the 6% reported from the ICGG Gaucher Registry.

**Age and timeliness of diagnosis of GD**

A number of studies reported data on the age of patients at diagnosis or symptom onset [3,21,23,29,43–66]. In an Israeli retrospective pediatric cohort study predominantly including patients of AJ descent, the mean age at GD diagnosis was 5.1 ± 2.2 years [57] whereas in an adult US population participating in a cross-sectional survey, the mean age at diagnosis was 28.9 ± 21.2 years [21]. Initial diagnosis of GD1 has been reported prenatally and as late as the ninth decade [3,65]. In one study, age at GD1 diagnosis was reported by genotype: mean age at diagnosis was older than 10 years for patients with genotypes N370S/?, N370S/N370S, N370S/L444P, and N370S/rare allele; age at diagnosis of younger than 10 years was reported in patients with N370S/84GG, L444P/L444P, L444P/?, and N370S/IVS2+1 genotypes all of which are often associated with severe GD symptomatology [3]. Three additional studies reported a mean age at diagnosis ranging from 6 years in the Moroccan study of 11 patients to 50 years in 93 patients from South Florida included in the ICGG Gaucher Registry [43,44]; the Moroccan study also identified two cases of GD2 diagnosed at 3 months and 18 months, respectively; age at diagnosis of seven GD3 cases ranged from 10 months to 2 years and 7 months in a study of Taiwanese patients [58]. In a multinational observational study (24-month study duration) enrolling all non-Ashkenazi patients (who had been seen for a hematological evaluation), the mean age at diagnosis was 32.6 years [60].

Substantial delays in time-to-diagnosis were reported in several studies [21,23,55]. Delays between clinical onset and diagnosis of 5.7 years (mean) and 7 years (median) were reported in a Romanian [55] and a French study [23], respectively. In a multinational cross-sectional survey, mean time from first symptoms to diagnosis was estimated to be 4 ± 11 years in the US and 3 ± 7 years in Australia and New Zealand [21].

**Mortality**

Nine publications reported numbers of deaths and/or causes of deaths in country-specific, often small patient cohorts [23,35,45,46,48,49,51,52,56]. Of these,
four described mortality in patients primarily with GD2 and GD3 [45,48,51,56]. From 378 French GD patients identified between 1980 and 2010, Stimermann et al. [23] reported 15 deaths in patients with GD2 and 3 in patients with GD3. Of 350 GD1 patients, 11 died of causes related to GD (lymphoma, myeloma, osteosarcoma, Parkinson’s disease, and complications of anemia or thrombocytopenia). Nine died of concurrent illness deemed unrelated to GD. From 370 Iberian patients with GD1, Giraldo et al. [35] reported 28 deaths at a mean age of 60 years (range 33–78 years). The major causes of death were liver failure, Parkinson’s disease, malignancies, and sepsis. Two reports discussed the causes of death among 184 patients with GD1 who never received ERT or other specific GD treatment [46,49]. Fifty-seven died of malignancies among which myeloma, other hematologic malignancies, hepatocellular, and kidney cancers occurred more frequently than expected. Among the 118 patients who died from non-cancer causes, death was most likely directly or indirectly related to complications of GD including septicemia, chronic liver disease and cirrhosis, hemorrhage, pulmonary hypertension and/or fibrosis and suicide, or accidental drug overdoses. Splenectomy and its complications were a major contributor to early mortality.

Two studies reported mortality data from an epidemiologic or actuarial perspective [29,64]. Based on ICD-10 E75.2 codes and death certificates from 11 US states with open record access (including California, Connecticut, Massachusetts, Michigan, and Ohio where many AJ individuals reside in select urban and suburban areas), Barczykowski et al. calculated US annual mortality rates for various leukodystrophies and lysosomal storage diseases. For 1999–2004, six GD deaths were found in patients younger than 5 years and 20 deaths in patients 5 years of age or older (range 7 months to 93 years). The mortality rate for the very young cohort (probably with GD2 or GD3 variants) was calculated at 0.221 per million in the population. For the older patients, most presumably with GD1, the annual mortality rate was 0.073 per million.

Using worldwide ICGG Gaucher Registry data, life expectancy from birth was estimated to be 9 years lower than that of the US general population 68 years vs. 77 years [64]. The difference in life expectancy between GD1 and the US reference population was largest among newborns and decreased steadily with age until rising again in patients aged 85 years or older. Compared with the reference population, life expectancy was lower in splenectomized patients than in non-splenectomized patients (decrease of 13.2 years vs. 5.1 years).

The life expectancies reported in this study are likely impacted by a positive effect of ERT on survival (80% of the patients were treated for some portion of their lives) and by possible under-reporting of deaths by site investigators. The accuracy of the reported life expectancies may also be compromised by selection bias. Patients with clinically mild phenotypes may have never been enrolled in the Registry and contemporaneous untreated patients with clinically aggressive GD phenotypes who died before founding of the Registry in 1991 were of necessity left out. It is also possible that some of the younger patients who died early in life had GD3 rather than GD1 and should have been excluded.

**Discussion**

GD is a rare genetic disorder with significant and burdensome morbidity. Although severity score systems appear to accurately measure the physical burden of disease in individual patients and average physical burden of disease in patient cohorts [67], to better understand the societal burden of this disease and the cost-effectiveness of treatments, accurate information is needed on the incidence and prevalence of GD globally and, in light of marked worldwide genotypic and phenotypic heterogeneity, in eco-populations defined by geography and ethnicity. Therefore, the current review was conducted using a robust search strategy to assess and summarize the best up to date evidence on GD epidemiology. Despite the number of studies reporting epidemiologic data, we found it difficult to compare and draw meaningful conclusions because of differences in study populations and designs.

Birth incidence and prevalence data in the general population were available from a number of countries and range from 0.39 to 5.80 per 100 000 and 1.33 to 1.75 per 100 000, respectively. As long known, incidence and prevalence is substantially higher among the AJ population [4,32,40]. The number of all individuals with GD1 genotypes in the US is uncertain primarily because of low clinical penetrance in the AJ population. However, it can be estimated at approximately 6600 based on an assumed prevalence of 118 per 100 000 among the AJ [6] (about 3.5 million individuals with four AJ grandparents taking into account that currently about 31% of US Jews have intermarried) [68], and an assumed prevalence of 0.7 per 100 000 in the rest of the population (316.5 million) [23,35]. There are approximately 1800 treated and untreated US GD patients enrolled in the ICGG Gaucher Registry. If a similar number have been diagnosed and have not been enrolled, 3000 individuals with GD1 genotypes would remain as undiagnosed and unidentified.

Assuming the annual birth incidence (0.023 per 100 000 births) reported from Missouri and New York based neonatal screening [26] is representative for the entire US, we estimate that, based on the birth incidence and the annual mortality rate of 0.0073 per 100 000 [29], excluding immigration/emigration, the total number of individuals with genotypic GD1 in the US will increase by about 30–50 annually.
The findings of studies that reported prevalence of known genetic mutations should be viewed with some caution since few actually included full GBA1 sequencing. The growing library of uncommon GD alleles suggests that clinical incidence and prevalence predictions based on older literature could represent an underestimate. It is therefore interesting that reported GD1 prevalence in France and Iberia is considerably less than anticipated based on reported mutation frequencies in Western populations [23,35].

In the AJ population, it is commonly accepted that 50–60% of genetically affected individuals lack a clinically recognizable phenotype, a phenomenon usually attributed to the frequent low penetrance of the N370S/N370S genotype [34]. It is therefore not surprising that substantial numbers of genetically affected AJ individuals have not been diagnosed. In current Western European populations, N370S homozygous GD1 is relatively uncommon despite N370S being the most common allele variant [44]. It is unknown to what extent lower than expected GD1 prevalence is indicative of substantial penetrance variation even in common European genotypes such as N370S/L444P that are traditionally associated with more clinically severe disease. Alternatively, the lower than expected prevalence could be a function of under-diagnosis as observed in the US [8,21]. Neonatal screening, if broadly accepted and applied, should provide future information [41].

Studies reviewed herein demonstrate that the time from onset of GD symptoms to clinical diagnosis was highly variable, with median delays of up to 7 years [23]. This finding likely reflects the rarity of the disease, minimal exposure to GD in the process of medical education, the non-specific and heterogeneous manifestations, and the frequency with which individual patients initially present with only a partial set of GD1 pathologies [7]. Thus, GD is often not included in differential diagnosis by physicians with limited familiarity of the disease and its spectrum of signs and symptoms. Manifestations of GD often mimic a different disease; in a global survey of 406 hematologists/oncologists, only 20% of respondents considered GD in the differential diagnosis of all its classic symptoms and were more likely to give a diagnosis of leukemia, lymphoma, or multiple myeloma [21].

Diagnostic delays and odysseys may have far-reaching physical and psychosocial consequences for patients. Some patients suffer severe, irreversible, or life-threatening complications such as osteonecrosis, gastrointestinal or central nervous system bleeding, chronic bone pain, sepsis, pathologic fractures, and liver disease [7]. Unnecessary medical procedures or drug treatments may be prescribed in some patients. The stress, inconvenience, and cost of consulting multiple different physicians in order to achieve a diagnosis is compounded by the potential for labeling as a malingerer. It has been reported that patients with GD consulted a mean of three different doctors before receiving a correct diagnosis [21]. There is evidence for a shift towards diagnosis of GD at a younger age [35] that may be due to an increase in the awareness of GD following the introduction of ERT, which effectively and safely reverses and/or prevents many GD pathologies including hepatomegaly, splenomegaly, bone pain, bone crisis, osteopenia, anemia, and thrombocytopenia, and improves previously impaired HRQoL [7,10,15,63,65,69–73]. Timely diagnosis, prompt initiation of treatment, and continued monitoring are important to minimize the impact of severe, often irreversible GD complications.

Limitations
Despite the robust search strategy employed in this literature review, the findings should be interpreted within the limitations of the methodology. While extensive, the review was not exhaustive and more data are available on the burden of illness of GD than are reported herein. The intent was not, however, to include all available data, but rather to summarize the most representative studies. Several data gaps were identified as a result of the current literature search. For example, limited epidemiologic information was available from Latin America, Africa, Asia, and even from developed nations such as the US, Germany, and the United Kingdom. In addition, few studies reported standardized mortality rates making comparison across different populations difficult. This was a targeted and narrative review and no assessment of the evidentiary quality of the publications was attempted. The reported data are also subject to a number of limitations such as limited or small patient samples, which negatively affects the generalizability of the findings.

Conclusion
GD is a rare hereditary disease that is associated with major patient, caregiver, societal, and economic consequences. Despite this, evidence that clarifies the integrated burden and impact of this illness is limited. More data derived from newly available screening technologies in which stable specimens are easily obtained and transportable to central reference laboratories are necessary to accurately determine the incidence of GD globally and in specific populations. Early diagnosis and prompt initiation of treatment when medically indicated are crucial to limit disease progression and the development of severe or life-threatening complications. Effective, albeit expensive, treatments are available that reverse or prevent complications and improve HRQoL. However, misdiagnosis and diagnostic delays are still common among patients with GD. Despite its relative rarity, raising awareness
about GD in the medical community and especially among hematologists whose consultative input is so often the key to a correct diagnosis and proper treatment, is a goal that affirms societal ethical principles including beneficence, non-maleficence, Oxford, and just allocation of healthcare resources in the context of protection of minorities.

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Disclosure statement

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