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Causes of death in 184 patients with type 1 Gaucher disease from the United States who were never treated with enzyme replacement therapy

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ABSTRACT

Treatment for type 1 Gaucher disease (GD1) decreases morbidity from hematological cytopenias, hepatosplenomegaly and bone complications. Consequently, untreated symptomatic patients for study of late outcomes are hard to find. We identified 184 untreated GD1 patients (67.4% Ashkenazi; splenectomy 51.1%) who died between 1950 and 2010. Here, we report confirmed causes of death for these patients compared with the overall US population. Median age of death 66 years (2–97 years); causes of death (COD) with a high proportional mortality rate (PMR) included malignancies (PMR 1.57), suicide/drug overdose (PMR 3.86), liver disease (PMR 4.76) and septicemia (PMR 9.22). PMRs for CNS/gastrointestinal bleeding, pulmonary hypertension, post-splenectomy complications and Parkinsonism were also increased. PMR for heart disease (0.33) was significantly decreased. Average age at death was normal for heart disease, septicemia, suicide, and malignancies but younger for liver disease and Parkinsonism. COD more prevalent in splenectomy patients included liver disease, septicemia, pulmonary hypertension and GI bleeding. With timely diagnosis, improved risk assessment and obsolescence of splenectomy, GD1-associated malignancies, liver disease, septicemia, pulmonary hypertension, suicide and drug dependency may decrease with early institution of appropriate treatment. Our population of untreated patients is a valuable historical control for studies of the effect of GD1 treatment on premature mortality.

1. Introduction

Type 1 Gaucher disease (GD1) is caused by mutations in the gene encoding lysosomal glucocerebrosidase (GBA1) with resultant lifelong accumulation of the enzyme substrate glucosylceramide predominantly although not exclusively within hepatic, splenic, pulmonary and bone marrow macrophages [1]. Enzyme replacement therapy (ERT), intravenous infusion of recombinant glucocerebrosidase (imiglucerase, velaglucerase alfa, taliglucerase alfa) has proven to be generally safe and effective in decreasing morbidity attributable to the heterogeneous clinical manifestations of GD1: hematological cytopenias, symptomatic hepatosplenomegaly, bone pain, osteonecrosis, and osteopenia [2]. Oral substrate reduction therapy (SRT) by inhibition of glucosylceramide synthase (miglustat and eliglustat tartrate) is also now approved and prescribed for select GD1 patient populations [3]. Attention is now being focused on longer term complications whose responsiveness to conventional treatment is yet undetermined: atypical Parkinsonism often complicated by dementia and an increased risk for malignancies, particularly but not exclusively, myeloma and other plasma cell dyscrasias, other hematological and lymphoid malignancies and hepatocellular carcinoma [4–7].

Because of widespread use of ERT during the 25 years that it has been available in Western countries [8] and the attrition of older medical records, a control group of phenotypically representative, untreated symptomatic patients for study of these late outcome events is hard to come by. Fortuitously, between years 1961–1997, one of us (REL) collected basic clinical information on 395 US patients with GD1 [9]. We determined through public records that between years 1950–2010, 217 have died, of whom, to our best knowledge, 184 never received ERT or other definitive treatment for GD1. Here, we annotate and analyze confirmed causes of death (COD) for the untreated GD1 patients compared to COD reported for this time period in an age comparable general Caucasian US population. A sub-analysis of deaths caused by malignancies has been previously published [10].

2. Method

Following IRB approval, primary and secondary COD as recorded in official death certificates were accessed from the National Death Index (NDI) for available years 1979–2008. GD1 was included among the diagnoses on the death certificate in only 71/152 patients (46.7%). COD

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prior to 1979 was determined on the basis of autopsy or other direct information given to REL and, where possible, confirmed by death certificates obtained from State Bureaus of Vital Records. To our knowledge, no untreated patient has died subsequent to 2008. COD could not be determined for 9 patients all of whom died prior to 1979. Information on COD (1950–2008) for the general US white population is from US National Vital Statistics Reports available on-line [11]. Proportional mortality for each COD was determined at 5–8 years interval from 1950 to 2008 and mean values with 95% confidence intervals were calculated. The proportional mortality for each disease was compared to the mean value in the reference population.

In order to determine whether patients with GD1 died at a younger age than reference population patients with the same cause of death, proportional mortality ratios (PMR) were calculated for each disease by 10 year age intervals commencing at age 5 years.

The analysis included descriptive statistics, calculation of proportional mortality ratios [12], X^2 testing, and 2-tailed Fisher exact test calculations based on absolute death numbers in the GD1 and general population.

3. Results

Select demographics of the 184 patients who never received ERT or other definitive treatment for GD1 were calculated and are displayed in Table 1. The cohort includes 111/184 males (60.3%). Ethnicity in reference to Ashkenazi Jewish background was assessed at 124/184 (67.4%). The median age at death was 66 years (2–97 years) and the median year of death was 1984 (1923–2008). The median age at GD1 diagnosis (N = 102) was 39 years (1–83 years). Symptomatic bone disease was present in 74/184 (40.2%), absent in 7 (3.8%) and undocumented for 103 (60.0%) patients. Patients in whom a known splenectomy had been performed (94/184) represented 51.1% of the study population. The age at the time of the procedure was found for 88 of the 94 patients and the median age at splenectomy was 36 years (1.3 years–78 years). The remaining patients either had intact spleens, 56/184 (30.4%) or their status was unknown 34/184 (18.5%).

Further demographic analysis is shown in Table 2. Patients were sub-divided into 3 birth eras so as to reflect the substantial increase in general life expectancy in the US population between 1885 and 1975 (a range encompassing the birth years of all of the study patients). This time frame also encompasses the period of large scale emigration of Jews from eastern and central Europe to the US and the expansion of the US Ashkenazi Jewish population from miniscule to approximately 6 million. For the 79 GD1 patients in our study who were born prior to 1914, nearly 80% were Ashkenazi Jews, a percentage that progressively decreased in the two later birth eras. The median age at diagnosis was 60 (17–83) years and was substantially higher than that reported for study patients born between the two World Wars (28, 3–68 years) and those born after 1945 (4.5, 1–32 years). Fewer pre-1914 study subjects underwent splenectomy compared with those born later and where data is available, the median age at splenectomy was 59 years compared with 37 and 7.5 years for the later eras. Symptomatic bone disease also seemed somewhat less prevalent in subjects born prior to 1914 but data are not available for the majority of patients, regardless of birth year. 95% of the study subjects born prior to 1914 lived longer than the average 50 year US life expectancy for patients born between 1885 and 1914. The median age at death was 75 (42–97) years. On average, subjects born between 1914 and 1945 achieved the 60 year life expectancy for that time but 25% (N = 21) died younger than 50 years of age. Among subjects born between 1945 and 1975 (N = 23), the median age at death was 29 (2–55) years and only 2 patients lived to be older than 50 years. The average US life expectancy during this time frame was 69.6 years.

Causes of death could not be determined for 9 patients all of whom died prior to 1979. The different COD for the study population are compared with the control US general population in Table 3. COD for which the proportional mortality rate (PMR) was significantly increased ($p < 0.01$) in this untreated GD1 population included malignant neoplasms (PMR 1.57), suicide and drug overdose (PMR 3.86), chronic liver disease and cirrhosis (PMR 4.76) and septicemia (PMR 9.22). Other causes of death that were disproportionately represented in this GD1 patient population included CNS and gastrointestinal bleeding, post-splenectomy complications, pulmonary hypertension and/or fibrosis, and Parkinsonism. Heart disease/atherosclerosis was the only COD for which PMR was very significantly decreased (0.33).

COD was further categorized by spleen status. The median age of death for individuals who had undergone splenectomy (94/184) was 62.5 years. The median age of death for individuals with an intact spleen (56/184) was72.5 years and for those with an unknown spleen status (34/184) 68 years. Causes of death significantly more prevalent in surgically asplenic patients included chronic liver disease, pulmonary hypertension/fibrosis, post-splenectomy complications, GI bleeding and otherwise unspecified complications attributed to Gaucher disease (Fig. 1).

Table 1
Demographics of deceased, untreated GD1 study subjects with a date of death between 1950 and 2008.

Patients (N = 184)			Patients (N = 184)		
Age at death		Years	Symptomatic bone disease		N (%)
	Mean (SD)	62.8 (19.7)		Present	74 (40.2)
	Median	66		Absent	7 (3.8)
	Range	2–97		Unknown	103 (60.0)
	Mid-quartile range	51.8–77.0	Spleen status		
	5th–95th percentile	25.2–88.9			N (%)
				Splenectomy	94 (51.1)
Year of death	Mean (SD)	1983 (12.7)		Intact	56 (30.4)
	Median	1984		Unknown	34 (18.5)
	Mid-quartile range	1975–1992			
	5th–95th percentile	1959–2003	Age at splenectomy	N = 88	Years
				Mean (SD)	36.1 (21.6)
Year of birth		N (%)		Median	36
	1885–1914	80 (43.5)		Range	1.3–78
	1915–1944	81 (44.0)		Mid-quartile range	13.8–54
	1945–1975	23 (12.5)		5th–95th percentile	4–65.7
Gender		N (%)	Age at diagnosis	N = 102	Years
	Male	111 (60.3)		Mean (SD)	38.8 (23.4)
	Female	73 (39.7)		Median	39
Ethnicity				Range	1–83
		N (%)		Mid-quartile range	21–60
	Ashkenazi Jewish	124 (67.4)		5th–95th percentile	3–75
	Other/Unknown	60 (32.6)			

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Table 2
Demographics, age at death, age of diagnosis, splenectomy status and presence of symptomatic bone disease in study subjects sub-divided by year of birth.

Year of birth	1885–1914		1915–1944		1945–1975	
Average US life expectancy at birth	50.0 (1.3)		59.7 (3.6)		69.6 (1.4)	
Age at death (y)	N = 79		N = 82		N = 23	
Mean (SD)	74.0 (12.2)		62.0 (13.8)		27.2 (14.4)	
Median	75		64.5		29	
Range	42–97		30–89		2–55	
Mid-quartile range	65–82.5		51–72.8		18–36	
5th–95th percentile	53–93		38–81		4.3–51.2	
Gender						
Male N (%)	44 (55.7)		53 (64.6)		14 (60.9)	
Female N (%)	35 (44.3)		29 (35.4)		9 (39.1)	
Ethnicity						
Ashkenazi	63 (79.7)		51 (62.2)		10 (43.5)	
Other/unknown	16 (20.3)		31 (37.8)		13 (56.5)	
Age at diagnosis	N = 44		N = 42		N = 16	
Mean (SD)	56.1 (16.9)		31.4 (17.8)		10.3 (10.3)	
Median	60		28		4.5	
Range	17–83		3.5–68		1–32	
Mid-quartile range	44.5–70.3		18.5–43.8		3.0–15.8	
5th–95th percentile	28.2–76.0		5.0–62.8		1.8–28.3	
Spleen status	N (%)		N (%)		N (%)	
Splenectomy	27 (34.2)		50 (61.0)		17 (73.9)	
Intact	34 (43.0)		17 (20.7)		5 (21.7)	
Unknown	18 (22.8)		15 (18.3)		1 (4.4)	
Age at Splenectomy (y)	N = 25		N = 47		N = 16	
Mean (SD)	53.7 (14.5)		35.5 (18.6)		10.4 (8.9)	
Median	59		37		7.5	
Range	23–78		3–66		1.25–34	
Mid-quartile range	46–62		22.8–50.3		4.0–13.3	
5th–95th percentile	32–75		5.3–64.1		1.8–27.3	
Symptomatic bone disease	All	SpleneX	All	SpleneX	All	SpleneX
Present N (%)	28 (35.0)	9 (33.3)	35 (43.2)	24 (48.0)	11 (47.8)	9 (52.9)
Absent N (%)	3 (3.8)	1 (3.7)	3 (3.7)	1 (2.0)	1 (4.4)	0
Unknown N (%)	49 (61.2)	17 (63.0)	43 (53.1)	25 (50.0)	11 (47.8)	8 (47.1)

As previously reported [10], among the 57 patients who died of malignancies the proportional mortality rates were significantly increased ($p < 0.01$) for myeloma (9.66), kidney CA (4.63), liver CA (4.36), NHL (4.13), and all leukemia (3.19). To our surprise, the PMR for lung CA was 0.32 ($p = 0.002$). There was only 1 death from breast CA and single deaths from brain and CNS CA, larynx CA, oral cavity/pharynx CA and melanoma. No GD1 patients were found to have died from esophageal, cervical, ovarian, or stomach cancers. PMR for colorectal, pancreatic and prostate CA were not divergent from expected values. The median age of death from cancer for individuals who had undergone splenectomy (94/184) was 62.5 years compared to 72.5 years for individuals with an intact spleen (56/184). For those with an unknown spleen status (34/184) the median age was 69.5 years. Spleen status appeared irrelevant to prevalence of CA deaths including myeloma but was relevant for hepatocellular CA (splenectomy) and chronic lymphocytic leukemia (intact spleen) [10].

Compared to the control US population, the age distribution of deaths as a percentage of all deaths attributed to a specific cause of death appeared to be similar for heart disease and cancer diagnoses as a whole (Fig. 2A, B). Due to small numbers in our study population for each age point, statistical analysis was not attempted. Nevertheless, early deaths due to septicemia, chronic liver disease, suicide and possibly Parkinsonism appeared to be more common in the untreated GD1 subjects than in the control population (Fig. 2C–F).

4. Discussion and conclusions

Current ERTs and SRTs for patients with Gaucher disease were approved on the basis of small, usually short-term, randomized and non-randomized clinical trials whose endpoints were largely restricted to surrogate markers such as quantitative changes in hemoglobin concentration, platelet counts, biochemical markers, spleen and liver volumes, bone marrow burden scores and bone mineral density [2]. Longer term extension and post-marketing registry studies are also largely focused on these parameters [13–19]. With the exception of bone pain, studies focusing on patient reported outcomes are sparse and largely restricted to health-related quality of life measured with generic instruments, fatigue, and pregnancy associated events [20–25]. Although the clinical efficacy (if not necessarily the cost effectiveness) of GD-specific treatments is generally accepted and further supported by Markov modeling studies [26,27], evidence that such therapy reduces premature mortality caused by possibly preventable GD complications such as splenectomy-associated morbidity, clinical bone events, chronic liver disease, pulmonary hypertension, Parkinsonism and malignancies would be compelling. Unfortunately, despite enrollment of several thousand GD1 patients in national and international GD registries and many patient-years of follow up, there are yet no reported annotative studies of causes of death that compare untreated with treated patients.

With the advent and lengthy availability of effective GD-specific treatments in all developed countries, identifying parallel cohorts of phenotypically matched treated and untreated deceased patients for cause of death analyses seems nigh impossible. Although fraught with methodologic difficulties caused by changes over decades in societal health practices and disease prevalences as well as ascertainment bias, there seems to be no alternative to an historical control comprised of GD1 patients who died before ERT became available. Our study population of 184 untreated people with GD1 who died between 1950 and 2008 is the largest number (untreated or treated) in whom the causes of death have been annotated and analyzed. Based on ICD-10 codes and death certificates from 11 US states, Barczykowski et al. calculated an annual mortality rate for GD1 patients of 0.073 per million [28].

Table 3
All causes of death for untreated GD1 study subjects with a date of death between 1950 and 2008.

Cause of death	GD PTS	Mean % all deaths	95% limits	GD PTS (%)	PMR	P value	Fisher exact 2-tailed	O/E	CHI test
								1.00	
Heart disease and atherosclerosis	20	34.9	31.5–38.3	11.4	0.33	$p < 0.0001$	0.00000	0.33	0.0000
Malignant neoplasms	57	20.7	19.0–22.4	32.6	1.57	$p = 0.0002$	0.00017	1.57	0.0001
Cerebrovascular disease and stroke	7	8.3	7.0–9.6	4.0	0.48	$p = 0.0271$	0.02710	0.48	0.0397
Accidents	1	5.0	4.6–5.4	0.6	0.12	$p = 0.003$	0.00258	0.12	0.0074
COPD and related conditions	4	3.2	2.1–4.3	2.3	0.72	NS	0.82754	0.72	0.4920
Pneumonia and influenza	5	3.0	2.7–3.3	2.9	0.96	NS	0.65444	0.96	0.9291
Diabetes mellitus	2	2.2	1.9–2.5	1.1	0.51	NS	0.44736	0.51	0.3306
Suicide and drug overdose	9	1.3	1.2–1.4	5.1	3.86	$p = 0.00014$	0.00014	3.86	0.0000
Chronic liver disease and cirrhosis	11	1.3	1.1–1.5	6.3	4.76	$p < 0.0001$	0.00003	4.76	0.0000
Chronic kidney disease	4	1.1	0.8–1.4	2.3	2.16	NS	0.11560	2.16	0.0993
Septicemia	14	0.9	0.6–1.2	8.0	9.22	$p < 0.0001$	0.00000	9.22	0.0000
Alzheimers and dementia	3	1.8	0.2–2.0	1.7	0.93	NS	1.00000	0.93	0.9102
All other causes	38	17.4	16.0–18.8	21.7	1.25	NS	0.13449	1.25	0.1294

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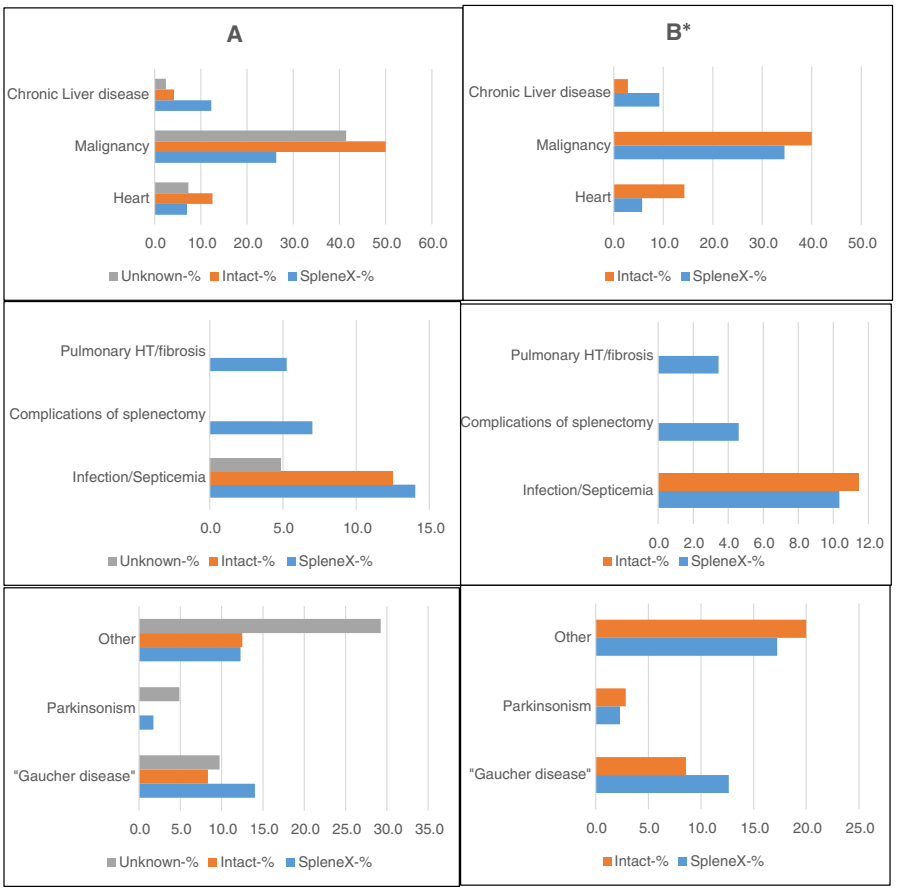

Fig. 1. Causes of death in the Pittsburgh Registry untreated patient population grouped by spleen status. A. Patients post-splenectomy, with intact spleens, and with splenectomy status unknown. B. Patients either post-splenectomy or with intact spleens. Patients in whom spleen status is unknown were assigned to one of the two groups as described in the footnote to the figure. *Imputed calculation. Among patients with known spleen status, the ratio of splenectomy patients to those with intact spleens is approximately 3:1. Patients with unknown splenectomy status were ranked by the age at death. Because the oldest patients at time of death were least likely to have had a splenectomy, the top quartile of the "unknown" patients (N = 11) were assigned to the intact spleen cohort and the others (N = 31) to the splenectomy cohort.

(This may be an underestimate in light of our finding that GD was included among the causes of death on <50% of the death certificates we reviewed.) Assuming an average US population of 225 million between 1950 and 2010, 952 individuals with GD1 should have died in that interval. Therefore, our study of 184 patients should theoretically represent 10–20% of all US deaths from GD1 from 1950 to 2010.

Our study confirms the common impression that, prior to 1991 (the pre-treatment era), GI and CNS bleeding, cirrhosis/portal hypertension, pulmonary hypertension, septicemia and surgical complications associated with splenectomy often led to premature death. These causes were predominant among our patients who died prior to age 55 years. Our finding of a nearly 4-fold greater than expected occurrence of deaths due to suicide or drug overdose in untreated GD1 patients (Table 2) is novel.

There is little other information about GD mortality due to these causes in the pre-ERT/SRT era. In a 1948 case study of 9 German and Dutch GD1 patients (one non-Jewish), Groen and Garber reported 7 deaths [29]: a 48 year old post-splenectomy patient with pulmonary hypertension and *cor pulmonale*; a 33 year old with immediate post-splenectomy bleeding; a 30 year old on a long term, markedly protein restricted vegan-type diet with wasting, edema and possible chronic liver disease. The other 4 patients died in German concentration camps, a cause of death that hopefully will never be replicated. One surviving patient had a successfully resected pancreatic islet cell tumor. The other survived a concentration camp but developed pulmonary tuberculosis. The authors also presciently commented about the frequency of cholelithiasis, the full spectrum of classical but variable GD bone complications, the marked phenotypic heterogeneity associated with GD1, the correlation between early age of onset and disease severity, and the need to avoid splenectomy when possible.

In 1954, Medoff and Bayrd described 29 GD1 Mayo Clinic patients of whom 8 were lost to follow up [30]. 12 of 21 patients appeared to have died but the COD was detailed only in two patients both of whom died shortly after splenectomy. Four other splenectomy patients died at age 4 years (1 year post-op), 40 years (14 years post-op), 42 years (6 years post-op) and 48 years (21 years post-op) for unspecified reasons. Six of 15 splenectomy patients were known to be alive 11–20 years post-operatively compared with 3 of 14 with intact spleens. Because patients had sustained hematologic improvement after splenectomy, the authors concluded that there are no contraindications to splenectomy other than technical considerations. Despite the report of Groen et al. [29], prior to 1991, there are only 3 Pub Med case reports of GD and pulmonary hypertension [31–33]. This is surprising considering the number of splenectomies that were performed in the pre-ERT era. However, among 48 GD patients who underwent total (75%) or partial (25%) splenectomy at Mount Sinai Hospital NY between 1963 and 1989, there was one intraoperative death due to massive bleeding, and, over a mean follow up period of 5–6 years, 8 subsequent deaths due to hematologic malignancies (3), sepsis (1), progressive Gaucher disease (1) and unrelated to GD (3). There were no deaths attributable either to pulmonary hypertension or chronic liver disease [34]. Autopsy findings on a GD1 patient with cirrhosis and ascites were reported in 1955 [35]. A fatal case of GD "masquerading" for several years as cirrhosis was published in 1964, and a death in what was described as the "seventh known case" of a pediatric GD patient with portal hypertension and hepatic fibrosis was reported in 1975 [36,37]. Among 21

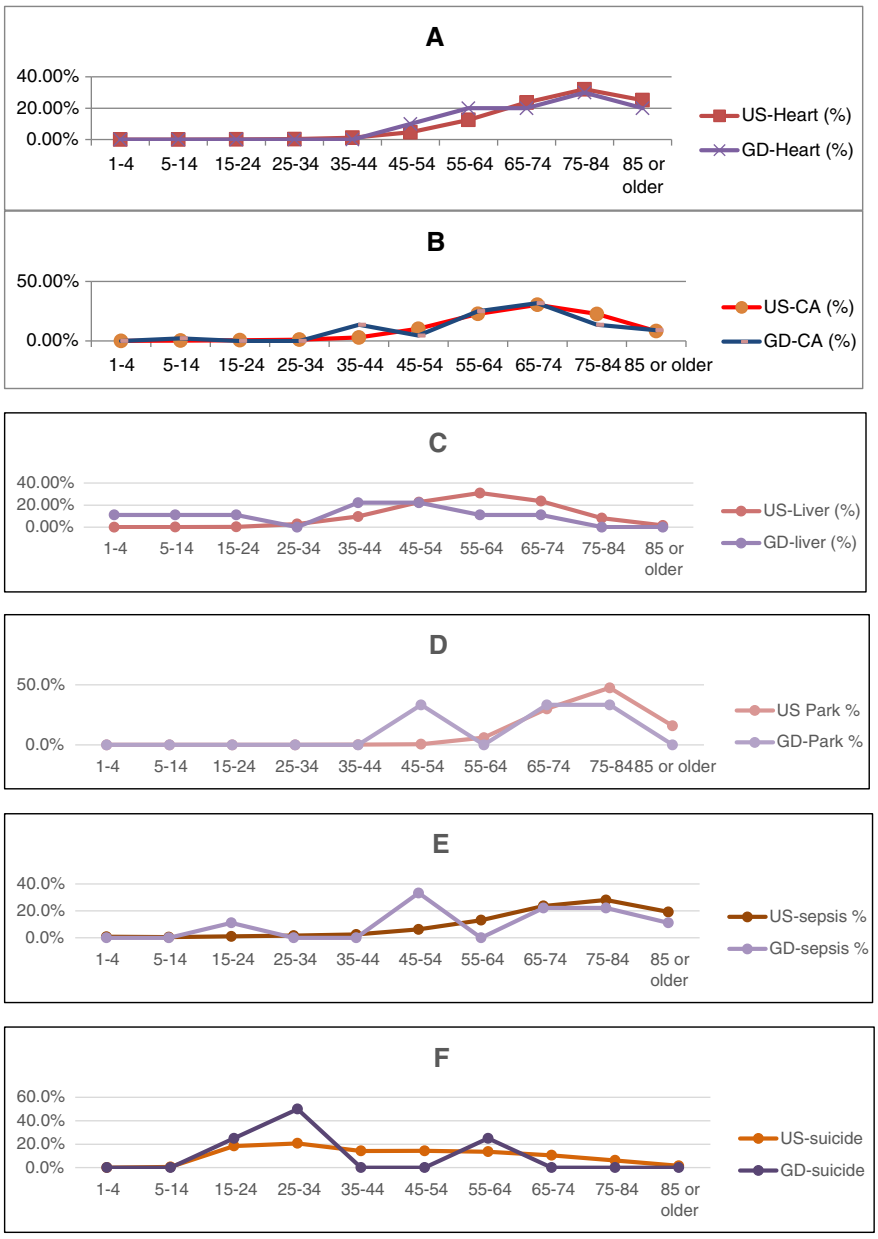

Fig. 2. Distribution of ages at death in the Pittsburgh Registry population compared with the US general population for six causes of death. A. Heart disease. B. Malignancies. C. Liver disease. D. Parkinsons disease. E. Septicemia and infection. F. Suicide and drug overdose.

patients with GD1 who were investigated for liver disease in 1981, only 3 were found to have cirrhosis and portal hypertension. One patient, who also had severe myelophthisic anemia died [38].

There are, as yet, few data about mortality and causes of death in patients in whom ERT or SRT was initiated after 1991. The French Gaucher Registry described 378 GD1 patients of whom 298 (78.8%) were on ERT/SRT and 27.5% were post-splenectomy [39]. 20 patients died at a median age of 64.5 years (38 years–83 years; N = 13). 15 patients were receiving ERT/SRT. The cause of death was unknown in 9 patients. Four patients died of malignancy (lymphoma-2; myeloma-1; osteosarcoma-1). Two patients suffered cardiac deaths (MI), 2 died with pulmonary hypertension and 3 with Parkinson disease. Among 370 GD1 patients enrolled in the Spanish Gaucher Registry, 62 patients (17.4%) were post-splenectomy and 84% were on GD treatment [40]. 28 patients were reported to have died at a mean age of 60.1 years (33 years–78 years). The most common causes of death were malignancy (myeloma-3; lymphoma-2; liver CA-1; melanoma-1; colon CA-1; gastric CA-1), pulmonary hypertension (5), liver failure, Parkinson disease, and septicemia. Despite the lower splenectomy rates, the prevalent causes of death in both studies are similar to those we found in untreated patients.

The International Collaborative Gaucher Group (ICGG) Registry reported causes of death for 63 of 102 deceased GD1 patients who were enrolled between 1991 and 2006 [41]. 90% were treated with imiglucerase for a median 5.4 years prior to their deaths. As shown in Table 4, the median age at death in the ICGG population was 61 years and 25% died before age 45 years. These results in treated patients are very similar to what we found in our untreated patients as was the percentage of post-splenectomy patients (48% and 51%). Therefore, it is not surprising that as with the French and Spanish studies, there was little difference between the ICGG study and our pre-treatment study in the proportions of patients whose deaths were attributed to heart disease, malignancies, liver disease, pulmonary hypertension and bleeding (Table 4). Deaths due to infection and septicemia may be proportionately greater in our population than in the ICCG cohort because of the advent of better antibiotics and infection control in more recent times. In the ICCG study,

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Table 4
Causes of death in patients with GD1 who were never treated with GD-specific therapy (Pittsburgh Registry) compared with COD in ICCG Registry patients of whom 90% were treated with ERT for a median 5.4 years.

Study population	Pittsburgh Registry N = 184	ICCG Registry N = 102
Median age at death (25,75 percentile)	66 years (52 years, 77) years	61 years (44 years, 75 years)
% with splenectomy	51	48
	N (% of known COD)*	N (% of known COD)**
Known COD	175 (95.1)	63 (61.8)
Heart disease	20 (11.4)	9 (14.3)
Malignancy	57 (32.6)	17 (27.0)
Cerebrovascular	7 (4.0)	6 (9.5)
Parkinson disease	6 (3.4)	0
Other neurological	3 (1.7)	5 (7.9)
COPD and unspecified lung disease	5 (2.9)	2 (3.2)
Accidents	1 (0.6)	1 (1.6)
Suicide and overdose	9 (5.1)	0
Diabetes	2 (1.1)	0
Pulmonary hypertension	4 (2.3)	2 (3.2)
Liver disease	11 (6.3)	4 (6.3)
Infections and septicemia	19 (10.9)	4 (6.3)
Renal disease	4 (2.3)	1 (1.6)
Bleeding	11 (6.3)	3 (4.8)
All other causes	16 (9.1)	9 (15.9)

* All other deaths from the following causes: post-splenectomy complications; Gaucher disease, unspecified; aplastic anemia, HIV, gangrene, pulmonary embolism.

** All other deaths from the following causes: multiple organ failure, pulmonary edema, pancytopenia, dehydration, and complications from bone marrow transplant or coronary artery bypass surgery.

with the large amount of missing COD data (38.2%), the absence of deaths due to Parkinsonism may reflect underreporting or inclusion of Parkinson death in the "other neurological" category. Although neither suicide nor drug overdose were reported as causes of death in the ICGG, French or Spanish studies, our current experience indicates that analgesic drug abuse and depression continue to afflict even adequately treated GD1 patients and should be recognized and addressed by treating physicians.

In reality, we did not anticipate that a significant change in causes of death would emerge from a comparison of our findings in historical untreated GD1 patients with early, preliminary and incomplete results in patients on ERT/SRT that commenced often many years after diagnosis and onset of symptoms and was administered for a relatively short period of time. Rather, we anticipate that with earlier diagnosis, improved risk assessment and phase-out of splenectomy [26,42], plausibly avoidable causes of premature death observed in our study population (chronic liver disease, GI bleeding, septicemia, PHT, suicide and drug dependency) should be increasingly rare with timely institution of appropriate treatment.

As a reference control, our patient cohort has some significant limitations. Although we estimate that our population of deceased, never treated patients includes 10–20% of all GD1 deaths experienced in the US between 1950 and 2008, it is likely skewed towards deaths in older individuals and fails to include causes of death for patients born in the late nineteenth and early twentieth centuries who died from GD complications at a young age (i.e. prior to 1950). It is also largely populated by Ashkenazi Jewish patients many of whom may have had somewhat less severe phenotypes and a different natural history than typically seen in non-Jewish GD populations. On the other hand, because the Pittsburgh Registry was a voluntary informational database, many of the enrolled patients may have been cherry picked by referring physicians, with selection bias favoring only the most severely affected or "interesting" patients and excluding patients with very mild phenotypes. It is also possible that not all causes of death were included on death certificates as highlighted by the fact that the diagnosis of Gaucher disease was omitted on half the death certificates we examined.

Nevertheless, our study results, including those published previously [10], confirm that as part of the natural history of type 1 Gaucher disease, adverse events including myeloma, B cell lymphoma, acute myeloid leukemia, liver and kidney cancers, Parkinsonism, chronic liver disease, infections and septicemia, suicide and drug abuse and overdose lead to premature mortality and are important targets for therapeutic intervention. The unexpectedly low occurrence we identified of lung, breast and gynecological cancers as causes of death in GD1 patients suggests that we should think about GD1 not only in terms of cancer induction, but also as it may relate to tumor-specific proclivities for metastatic disease. The relatively low occurrence of death due to atherosclerotic cardiovascular disease and diabetes mellitus in untreated patients is supportive of published investigations of carbohydrate and lipid metabolism in patients with GD1 that merit further observation of the effect of GD-specific therapies on these disease entities [43,44]. We conclude that our study population of untreated patients is a valid (possibly unique) control against which to evaluate the effect of GD1 treatment on mortality due to malignancy and other later course events.

Contributions of the authors

The original Pittsburgh Gaucher Registry was conceived and managed by REL. This study was conceived by NJW in collaboration with REL. NJW served as principal investigator, identified all deceased, untreated patients in the Pittsburgh Registry paper database, transferred the data to an electronic database and collected and reviewed the cause of death information on death certificates supplied on application to the National Death Index and state bureaus of vital statistics. Data analysis was performed by NJW and DB. The manuscript was drafted by NJW and DB, and reviewed and accepted by all the authors.

Disclosure of conflicts of interest

NJW serves on Medical or Scientific Advisory Boards for Genzyme-Sanofi, Shire HGT and Pfizer for which he has received honoraria. He has consulted for Genzyme-Sanofi and for Pfizer and has received research support from Genzyme-Sanofi and from Shire HGT.

DB and REL report no conflicts of interest.

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