Original Article

Economic and Humanistic Burden of Gaucher Disease in Greece

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Abstract
Background: Gaucher disease (GD) is a rare, autosomal recessive genetic disorder. It is caused by a deficiency of the lysosomal enzyme, glucocerebrosidase, which leads to an accumulation of its substrate, glucosylceramide, in macrophages. The disease burden on Greek patients and caregivers is unknown. **Objective:** To determine the societal economic and humanistic (HRQoL) burden of GD in Greece. **Methods:** A cross-sectional study was conducted in which an online questionnaire was completed by GD patients and their caregivers. A cost of illness (COI) model was developed in which costs per GD patient were calculated from a societal perspective and extrapolated to the total affected population in Greece. Last, the 36-item PedsQL™ Family Impact Module was used to measure the HRQoL of families with GD members. **Results:** The economic burden of GD was estimated at €137,074 per patient in 2023. When extrapolating this outcome across all affected persons, the average annual cost was €23,850,789. Out-of-pocket expenses accounted for 1.8% of the total. Results of the analysis on HRQoL indicated a significant burden of GD on patients and family members with the majority of scores falling below 50 and a mean total score of 34.5. **Conclusions:** The results highlight the considerable burden of GD not only in terms of the high costs but also in terms of reduced HRQoL for patients' families.

Keywords: Gaucher disease, cost of illness, quality of life, disease costs, disease burden, rare disease

Introduction

Gaucher disease (GD) is a rare, autosomal recessive genetic disorder. It is caused by a deficiency of the lysosomal enzyme, glucocerebrosidase, which leads to an accumulation of its substrate, glucosylceramide, in macrophages (Stirnemann et al., 2017). The main cause of the cytopenia, splenomegaly, hepatomegaly, and bone lesions associated with the disease is considered to be

the infiltration of the bone marrow, spleen, and liver by Gaucher cells. Type-1 GD, which affects the majority of patients is characterized by effects on the viscera, whereas types 2 and 3 are also associated with neurological impairment, either severe in type 2 or variable in type 3 (Stirnemann et al., 2017).

In the general population, its incidence is approximately 1/40,000 to 1/60,000 births, rising to 1/800 in Ashkenazi Jews (Stirnemann et al., 2017). Disease-specific treatment consists of intravenous enzyme replacement therapy (ERT) using one of the currently available molecules (imiglucerase, velaglucerase, or taliglucerase). Orally administered inhibitors of glucosylceramide biosynthesis can also be used (miglustat or eliglustat) (Stirnemann et al., 2017).

The economic and societal burden of GD has not been explored in Greece. The objective of this study was to estimate the economic burden of GD to society and quantify how the disease affects patients' and family's health-related quality of life (HRQoL) and the functioning of the family. Our aim was to generate evidence to help policymakers devise appropriate intervention programs for patients with GD and their families.

Methods

A cross-sectional study was conducted between December 2022 and March 2023. An online questionnaire with 21 queries about patients' health care resource use (HCRU) was developed to capture patients' socio-demographic parameters and HCRU such as public healthcare, non-healthcare resource use, costs of professional private care, informal care, issues regarding equipment and services necessary for patients' daily activities during the last year, issues regarding equipment and services necessary for patients' daily activities, as well as socio-demographic parameters. To capture all possible HCRU as accurately as possible the questionnaire was reviewed and validated by GD patients and carers, members of the Panhellenic Association of Patients and Friends suffering from Lysosomal Diseases 'The Solidarity and the "95" Rare Alliance Greece, which are Greek non-profit organizations advocating for those living with a rare disease.

The main caregiver was responsible for the completion of the self-administered questionnaire in case of adolescent patients. The participants were informed about the study objectives as well as the confidentiality and anonymity of the data and gave their written consent to participate in the study, with the option of data withdrawal. The participants gave their informed consent. Final questionnaires were provided by Health Care Professionals in hard copy or completed online via the Computer Assisted Web Interviewing (CAWI) method. The present study was conducted in accordance with the Declaration of Helsinki and the Greek legislation (Law 2328/1995, Presidential Decree 310/1996, Law 3603/2007, Law 2472/1997, Law 3471/2006), stating that there is no need for ethics approval in telephone and internet surveys such the one presented here.

The questionnaire was divided into two sections, one devoted to HCRU and one to HRQoL. Overall, 8 patients with GD returned a completed HCRU questionnaire. The HCRU as reported by respondents with GD was leveraged as input in the cost of illness (COI) model. Cost inputs were retrieved by official sources and inserted into the model to be combined with HCRU and produce the results.

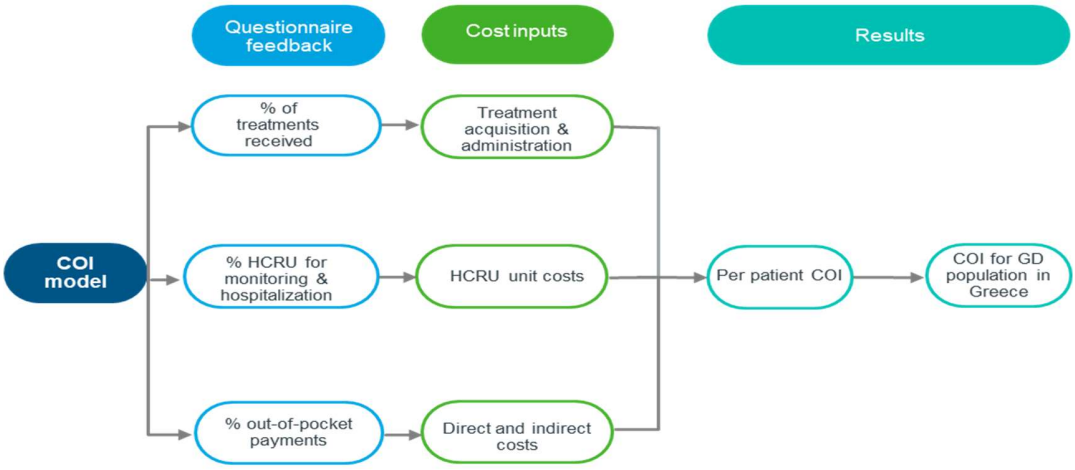
Following the queries focused on assessing the economic burden, the 36-item PedsQL™ Family Impact Module (FIM) was used to assess the impact on the family's HRQoL (Varni et al., 2004). This section of the questionnaire was completed by 19 patients/ caregivers. The 36-item PedsQL™ FIM Scales encompasses 6 scales measuring parent self-reported functioning: 1) physical functioning (6 items), 2) emotional functioning (5 items), 3) social functioning (4 items), 4) cognitive functioning (5 items), 5) communication (3 items), 6) worry (5 items), and 2 scales measuring parent reported family functioning; 7) daily activities (3 items) and 8) family relationships (5 items) (Varni et al., 2004). Each item is scored on a five-point response scale, then converted to a 0 to 100 scale. A 5-point response scale is utilized (0 = never a problem;

4 = always a problem). Items are reverse-scored and linearly transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), so that higher scores indicate better functioning (less negative impact). Scale scores are computed as the sum of the items divided by the number of items answered (this accounts for missing data) (Varni et al., 2004).

Cost of illness analysis: A COI model was developed to estimate the average annual economic burden of GD in the Greek population from a societal perspective. The model adopted a prevalence approach and as such all prevalent cases of GD in Greece were considered.

To estimate the number of GD patients, the prevalence value reported by Orphanet (i.e., 1/60,000) (Orphanet, 2012) was used. Applying this to the total Greek population (10,432,481), (ELSTA, 2021a) it was estimated that there are currently 174 patients with GD in Greece. The resources used, as reported in the questionnaires, were multiplied by the unit costs (Government Gazette, 2012) to calculate the annual cost per patient and per total GD population using 2023 as the reference year. An overview of the model structure is illustrated in Figure 1.

Figure 1 Model structure



HCRU, Healthcare resource use; GD, Gaucher disease; COI, cost of illness

Healthcare resource use inputs

HCRU of patients with GD as reported by respondents is presented in **Table 1**. Overall, the healthcare resources with the highest usage from patients were visits to a healthcare practitioner, complete blood count testing and hospitalisations. One sixth of the patients reported requiring approximately 2.5 hospitalizations during the previous year (including hospitalizations for the administration of treatment) with each hospitalization lasting approximately for 20 days.

Table 1. Yearly healthcare resource use of patients with GD

	Average annual HCRU	Proportion of patients
Medical visit	6.88	100%
Complete blood count	3.63	100%
Hospitalisation	2.50	13%
Endocrine test	1.60	63%
Cardiac check-up	1.43	88%
DXA scan	1.29	75%
Orthopedic examination	1.20	50%
MRI scan	1.14	88%
X-ray	1.13	88%
CT scan	0.83	63%
Gastroenterological examination	0.80	38%
Pulmonological examination	0.50	25%
Physiotherapy	0.75	37.5%
Psychotherapy	0.75	25%

HCRU, Healthcare resource use; CT, computerized tomography

Further, based on the questionnaire feedback, the costs for physiotherapy and psychotherapy were covered at a rate of 93.5% from the public payer in Greece, with the remaining amount being an out-of-pocket expense for the patients.

Moreover, 25% of GD patients required additional resources to manage the disease on a daily basis, which were only required purchasing once. It is also common for patients to visit hospitals and clinics at regular intervals for the treatment administration, which contributes to the already high out-of-pocket costs due to the transportation costs that burden the patients and their caregivers. Last, approximately, 50% of the respondents stated that they are unable to work due to the burden of GD. Furthermore, those who could work, they had to take approximately 23 days off from work annually due to disease complications.

Cost inputs: Cost inputs comprise of treatment costs (acquisition and administration), monitoring and hospitalization as well as out-of-pocket expenses and indirect costs (e.g., loss of productivity).

Treatment acquisition unit costs were based on the recommended dosing schemes as sourced from each treatment's Summary of Product Characteristics (SPC) issued by European Medicines Agency (EMA) (EMA, 2024a; EMA, 2024b; EMA, 2024c), and the published unit prices as sourced from the latest Drug price bulletin issued by the Greek Ministry of Health (Greek Ministry of Health, 2022). In treatments administered via intravenous infusion, an administration cost of €80 (Government Gazette, 2011) was applied. The drug acquisition costs are presented in Table 2. Unit costs of the resources accounted for the monitoring and hospitalization were based on official National Organization for Healthcare

Provision (EOPYY) reimbursed prices and Diagnosis Related Groups (DRGs) (Government Gazette, 2012) and are presented in the Table 3.

In addition to reimbursed costs, patients and their families are required to make significant out-of-pocket payments including physiotherapy, psychotherapy, genetic tests and OTC medicines. Regarding the out-of-pocket expenses, the average cost of the home adjustments was estimated at €313, and it was assumed that takes place once in lifetime. Out-of-pocket transportation costs contributed on average an additional €494 per year per patient. An overview of out-of-pocket unit cost inputs is illustrated in Table 4.

Last, indirect costs were calculated based on working patients' reported absence days from work (23 days annually) and the average daily wage (€56.7) as sourced from Hellenic Statistical Authority (ELSTAT, 2021b). The annual productivity loss cost was estimated at €1304.

Cost of illness

Cost of illness comprise of the summary of treatment acquisition and administration costs, monitoring and hospitalization as well as out-of-pocket expenditure. Overall, the average annual cost of GD was estimated at €137,074 per patient in 2023. Subsequently, the average annual out-of-pocket expenditure per patient were €2,420 which represents the 1.8% of the average annual cost. Extrapolating the results to the whole affected population with GD indicates that average annual economic burden was estimated at €23,850,789, with drug costs representing the majority of the costs (88%) followed by direct HCRU (9%). The COI results are illustrated in Table 6.

Health-related quality of life

Results of the analysis indicate that the impact of GD on the family's HRQoL was high with the scores in the majority of the scales falling below 50 (Table 7). The scales of "Worry" and "Daily activities" are the ones with the lowest scores while the scale of "Cognitive functioning" the one with the highest. The mean HRQoL score was estimated at 34.5, which is considered low when compared with a score of 100 representing perfect health. It is evident from these results that GD constitutes a considerable burden on the HRQoL of the families.

Table 2. Treatment cost inputs

Treatment	Unit per vial/tab	Vials/tablets per pack	Cost per pack	Cost per vial/tab	Units (vials/tabs) per year	Annual cost
Imiglucerase	400mg	1	€1,048.81	€1,048.81	259.2	€271,851.42
Velaglucerase alfa	400mg	1	€1,099.73	€1,099.73	259.2	€285,049.89
Eliglustat	84mg	56	€15,877.51	€283.53	730	€206,974.62

Table 3. Unit costs of HCRU.

Resource	Unit cost	Source
Medical visit	€ 10	EOPYY reimbursed price based on physicians reimbursed fee
Complete blood count	€ 2	EOPYY reimbursed price of complete blood count based on Greek list of laboratory and imaging tests' prices (Greek reference: 157/18, 157/24)
CT scan	€ 45	EOPYY reimbursed price of CT scan based on Greek list of laboratory and imaging tests' prices (Greek reference: 81/23, 49976/05-12-2012)

X-ray	€ 4	EOPYY reimbursed price of spirometry based on Greek list of laboratory and imaging tests' prices (Greek reference 157/39)
MRI scan	€ 131	EOPYY reimbursed price based on average of 3 MRI types
DXA scan	€ 26	EOPYY reimbursed price of spirometry based on Greek list of laboratory and imaging tests' prices (Greek reference 138/28)
Hospitalization	€80	One-day clinic
Orthopedic examination	€10	EOPYY reimbursed price based on physicians reimbursed fee
Endocrine test	€10	EOPYY reimbursed price based on physicians reimbursed fee
Gastroenterological examination	€10	EOPYY reimbursed price based on physicians reimbursed fee
Pulmonological examination	€11	EOPYY reimbursed price of spirometry based on Greek list of laboratory and imaging tests' prices (Greek reference 157/15)
Cardiac check-up	18.3 €	EOPYY reimbursed price of spirometry based on Greek list of laboratory and imaging tests' prices (Greek reference: 04/326/24-08-95)
Physiotherapy	€15	EOPYY reimbursed price based on physicians reimbursed fee
Occupational therapy	€15	EOPYY reimbursed price of occupational therapy based on Greek list of laboratory and imaging tests' prices (Greek reference: 1233/11-04-2012)
Psychotherapy	€15	EOPYY reimbursed price of psychotherapy based on Greek list of laboratory and imaging tests' prices (Greek reference: 138/43, 127/1)
One-off costs		
Splenectomy	€1,399	Government Gazette 946/2012 - DRGs List - 1/3/2012
Thyroidectomy	€1,880.5	Government Gazette 946/2012 - DRGs List - 1/3/2012 Average of Ξ06M & Ξ06X
Bone marrow transplant	€9,525	Government Gazette 946/2012 - DRGs List - 1/3/2012 Average of ΞE07A, E08M & E08X
Joint replacement surgery	€4,335	Government Gazette 946/2012 - DRGs List - 1/3/2012 Average of M03M, M03X, M04M, M04X, M05M & M05X

CT, computed tomography; MRI, magnetic resonance imaging

Table 4. Yearly out of pocket costs.

Resource	**Cost per visit***
Physiotherapy	€5.9
Psychotherapy	€7.0
Non reimbursed medications	€825
Transportation	€494
Genetic tests	€837
One-off costs	
Adjustments in the home	€313

* Cost per visit was calculated combining the resource use as derived from questionnaires' feedback with respective unit costs sourced from local official sources

Results

Sample demographic characteristics

The main characteristics of the participants are shown in Table 5. The average age of the participants was 50.41 years and 74% were males. All the patients reported to have a disability rate equal or greater than 67%, a percentage which represents the cut-off point of severe disability according to the Disability Committee classifications. Time to diagnosis from the appearance of the first symptoms ranged from 12 weeks to 2 years with a median time to diagnosis of 56.6 weeks.

Table 5. Demographic characteristics of the study participants (n=19).

Characteristics	**N (%)**
Age	
Mean (SD)	50.41 (18.57)
Minimum-maximum	31.84-68.98
Gender	
Female	5 (26%)
Male	14 (74%)
% Disability	
<67%	0 (0%)
>67%	19 (100%)
Treatment	
Imiglucerase	5 (26%)
Velaglucerase alfa	3 (16%)
Eliglustat	3 (16%)

GD, Gaucher disease; SD, standard deviation

Table 6. COI results breakdown.

Cost category	**Average annual cost**	
	Per patient	**For total GD population (N=174)**
Drug costs*	€120,533	€20,972,742
Direct HCRU	€12,817	€2,230,158
Out of pocket	€2,420	€420,993
Indirect	€1,304	€226,896
Total	**€137,074**	**€23,850,789**

HCRU, healthcare resource use *Drug costs comprise of acquisition and administration costs

Table 7. PedsQL FIM scores in different functioning categories.

Scale	Mean	Median
Total scores	34.51	29.78
Physical functioning	41.67	39.58
Emotional functioning	39.47	35.47
Social functioning	39.33	34.02
Cognitive functioning	24.74	23.49
Communication	33.33	35.41
Worry	37.11	32.11
Daily activities	35.97	34.31
Family relationships	31.58	31.83

FIM: family impact module; HRQoL: health-related quality of life; PedsQL: paediatric quality of life

Discussion

Our study showed that the economic and humanistic burden on patients with GD is considerable. According to our findings the average annual economic burden per GD patient was estimated at €137,074. Drug costs accounted for approximately 88% of the total costs, followed by healthcare resource utilization (HCRU) costs (9%), out-of-pocket costs (2%), and indirect costs (1%). The mean health-related quality of life (HRQoL) score for the family was estimated at 34.5, which is considered low compared to a score of 100, representing perfect health.

To the best of our knowledge, this is the first attempt to measure the total economic burden of GD in Greece -and in Europe in general- from a societal perspective, as well as the HRQoL of families with GD member.

Other similar studies in the literature conducted mainly in Asia (Koto et al., 2023; Mhatre et al., 2024; Hu et al., 2021; Qi et al., 2021; Davari et al., 2019) and in the United States (Damiano et al., 1998). There is also a study conducted in Spain, though it attempts to measure only the HRQoL of GD patients and caregivers (Remor and Baldellou, 2018).

Regarding economic burden results, an Indian study estimated that it would cost 114,672 $ per patient over a year for treating GD in a public healthcare institution in Mumbai in 2022. This amount is equal to 60 times the country's GDP per capita. Our estimate is quite close to the above, representing though a number 6.6 times the Greek GDP per capita (ELSTAT, 2021b).

Hu et al. (2021) and Qi et al. (2021) estimated that the average economic burden of patients caused by GD in China in 2021 was approximately $22,691 and $49,92, respectively. Although there is a deviation between these two estimates, both studies attribute the largest share of the burden to the high treatment costs (Hu et al., 2021; Qi et al., 2021). Qi et al. (2021) also took into account out-of-pocket expenses, which likely accounts for the discrepancy, imposing a significant financial burden on patients and their families, consistent with our observations.

Another important element yielded from the study by Qi et al. (2021) is the estimation of the indirect cost derived from productivity loss per caregiver, which was $1,980, representing 15% of the Chinese GDP per capita (Qi et al., 2021), while our estimate of €1,304 represents 6% of the Greek GDP per capita.

In Iran, Davari et al. (2019) estimated the annual direct healthcare costs to be $20,758 per patient in 2014, with 95.2% of the direct healthcare costs being a percentage that confirms our findings, with drug costs representing the majority of the costs (88%). These statistics clearly indicate that

the majority of resources utilized by patients with GD are taken up by pharmaceutical expenses.

Regarding the past HRQoL findings, a recent study conducted in Japan (Koto et al., 2023) evaluated the level of burden in caregivers of patients in GD using the Caregiver Impact Questionnaire (CIQ) and Zarit Caregiver Burden Interview (ZIB) as tools. The ZBI score was below the cut-off score, indicating a severe burden. These results are not entirely in line with our findings, even though they were measured with different tools than PedsQL™, which indicates that Greek families perceive the disease as imposing a severe QoL diminishment. According to the authors, their results may reflect the characteristics of the Japanese people, who tend to endure and persevere through difficult situations, and who may have rated their level of burden lower than non-Japanese caregivers, despite having a high burden of care for their patients (Koto et al., 2023).

Hu et al. (2021) reported that the mean EuroQol Visual Analogue Scale (EQ-VAS) score of GD patients was 76.4 ± 15.5, which represents a notable burden for the patients; however, there was no measurement regarding caregivers or family members.

Lastly, an evaluation of HRQoL in children and adolescents living with GD as reported by their parents via PedsQL™ was conducted in 2018 in Spain (Remor and Baldellou, 2018). The HRQoL values of the examined GD patients, as well as their parents, were higher than ours, with mean values exceeding 80 on a 0–100 scale. Since all patients in the Spanish study were receiving ERT, the authors hypothesize that these results could be attributable to the efficacy of ERT in controlling symptoms in pediatric patients (Remor and Baldellou, 2018).

Moreover, two other studies conducted in Greece sought to underpin the HRQoL of families with a member affected by a rare disease using PedsQL™ (Kontogiannis et al., 2023; Sotiropoulou et al., 2023). The mean PedsQL™ score of the sample was considerably lower than those reported by Sotiropoulou et al. (2023) and Kontogiannis et al. (2023) for Neurofibromatosis and Spinal Muscular Atrophy, respectively, in Greece.

A limitation of our study relates to the sample size, which is often the case for studies on rare diseases where data collection is challenging. Secondly, patients and caregivers were recruited through a patient association group in Greece and may represent a more compliant and motivated patient cohort in general. Therefore, the findings may not be generalizable to all. Thirdly, this study relied on respondents' recall of health service utilization, which may introduce recall and preference biases. Fourth, our study underestimates the indirect costs of GD. More specifically, the indirect costs were calculated based only on the reported absence days from work of working patients. The attribution of loss of wages for a full year for those completely unable to work was not included in the indirect costs. Lastly, some researchers claim that HRQoL of patients with lysosomal storage disorders (LSDs) cannot be explicitly elucidated through a cross-sectional study alone; it may require in-depth investigation using a randomized controlled trial or longitudinal data (Hu et al., 2021).

This is the first study in Greece to highlight the considerable economic burden among patients with GD as well as the impact in the HRQoL of families.

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