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ORIGINAL ARTICLE

Economic Burden of Gaucher Disease at a Tertiary Care Public Hospital in Mumbai

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Abstract

Objectives To estimate the economic burden of patients diagnosed with Gaucher disease at a public hospital from a societal perspective.

Methods Data from 30 Gaucher patients visiting the Genetic Clinic of the Department of Pediatrics at the study site in Mumbai was analyzed between January 2019 and January 2021. A cost of illness analysis was undertaken to estimate direct, indirect and intangible costs. Costs in treated and treatment naive groups were compared.

Results The total cost (direct and indirect) for 30 patients was ₹25,45,74,743/- (3440199.2 USD). Majority of this cost (99.8%) was due to direct costs of which medications [Enzyme replacement therapy (ERT) and Substrate reduction therapy (SRT)] constituted 98.8%. The notional cost was ₹1,43,94,695. Total costs of 14 treated patients were ₹25,29,67,279 and 16 treatment naive patients were ₹16,15,064 with a ratio of 157:1. Direct costs and cost of school absenteeism were significantly higher in the treated subgroup. Overall, direct, total costs and costs of school absenteeism were significantly associated with age and disease duration.

Conclusions The economic burden of Gaucher disease is a staggering amount. This is an underestimate, as the expenses are highly subsidized in a public health facility. The highest contributor to cost component was direct costs, especially medication costs. Against the backdrop of the National Policy for Rare Diseases, resource allocation towards Gaucher disease should consider short term measures for judicious funding or reimbursement of disease-specific therapy and long-term cost-effective measures for promoting preventive strategies as the most practically feasible solution to reduce this economic burden.

Keywords Rare disease · Orphan disease · Lysosomal storage disorder · Cost of illness · Willingness to pay · Enzyme replacement therapy · Substrate reduction therapy

Introduction

Gaucher disease (GD), an orphan lysosomal storage disorder, results from deficiency of the lysosomal enzyme β-glucocerebrosidase (EC 3.2.1.45) [1]. GD has multisystem manifestations, namely anemia, bleeding, splenomegaly, hepatomegaly, bone marrow infiltration, osteopenia, bone pain, bone crisis, osteonecrosis/avascular necrosis, pathological fractures and neurological symptoms [2]. If left untreated, GD impairs quality of life and attenuates lifespan. The standard of care is enzyme replacement therapy (ERT) [3] and substrate reduction therapy (SRT) is also available [3].

The incremental cost effectiveness ratio of £200,000 per quality adjusted life years (QALY) for ERT in GD estimated elsewhere greatly exceeds thresholds to determine whether a treatment is economical [1]. This has prompted initiatives to evaluate cost-effectiveness and cost-utility of GD in USA, UK and Netherlands [4]. The National Policy for Rare Diseases (NPRD, 2021) has provision for funding rare diseases including GD [5], making a study of its economic burden pertinent.

Material and Methods

The study was approved by the Institution's Ethics Committee (EC/OA/203/2018). Written, informed consent was taken from participants (adult patients or parents).

The study was presented as a poster at the 22nd EMBICON 2021 (Annual Conference of Indian Academy of Pediatrics, Mumbai) and won second prize.

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This was a single center, prospective, cross-sectional, observational study in the Genetic Clinic of a tertiary care, university affiliated public teaching hospital in Mumbai conducted over a period of 25 mo [January 2019 - January 2021].

Treated and treatment naive adult GD patients or parents of children with childhood onset GD (including antenatal detection and deceased patients) diagnosed on the basis of β-glucocerebrosidase deficiency and/or detection of pathogenic variants in GBA gene [6] on follow- up for at least 12 mo were deemed eligible.

The standard treatment protocol at authors' center includes biannual or annual evaluation of growth, GD status and investigations recommended per guidelines [6, 7]. Carrier testing and parental segregation of GBA alleles by targeted molecular testing [6] is performed after diagnosis is confirmed in the index case. Prenatal diagnosis is achieved by molecular testing [6]. Untreated patients receive symptomatic, supportive care.

Demographic data, age at diagnosis, age at treatment initiation, duration of ERT/SRT and presence of co-morbidity/complications were recorded. Socioeconomic status was determined by modified Kuppuswamy scale [8] using average consumer price index for industrial workers in April 2020 (https://pib.gov.in/PressReleasePage.aspx?PRID=1627672).

The authors assessed cost of illness (COI) from a societal perspective by the prevalence-based approach [9, 10]. Periodicity of cost computation was biannual. Annual costs were computed by doubling semi-annual costs. Direct (one-time and recurrent costs), indirect and intangible costs [9] were calculated by interviewing parents and perusing invoices/ receipts (Fig. 1). Shared costs common to all patients [costs for establishment (staff salaries excluding increments/or bonuses), contingencies, medicines, instruments, special investigations, stores, repair and maintenance] were obtained from the Institution's budget section. Recurring costs were computed for the preceding one year or the last living year for deceased patients. Costs of concomitant medicines, special vaccines and consumables obtained from the hospital pharmacy were based on procurement price. Travel was reported as median cost paid by patients for a year for treatment related travel. Accommodation and meals were necessary for a few outstation patients and were also considered.

Indirect costs included work absenteeism computed by the human capital method for computing for loss of wages (number of days off for taking care of the patient multiplied by minimum wages per day) [11]. Annual loss of wages for a home maker was computed using minimum monthly wages for an unskilled worker of ₹10775/- per month (https://blog.sgcservices.com/revised-minimum-wages-maharashtra-special-allowance-2/) and extrapolated for 12 mo.

School absenteeism and intangible costs were computed by the contingent valuation method centered on elicitation of willingness to pay (WTP) by closed ended interative bidding [11, 12]. Participants were given their respective per capita income as initial bid [11].

Total costs (sum of direct and indirect costs) and notional costs (school absenteeism and intangible costs) in INR and USD were calculated for each patient along with measures of central tendency (mean, median, mode). Cost components were compared between the treated and untreated groups and expressed as median (range). Normality of quantitative data was assessed using the Shapiro Wilk test. Between group comparison for quantitative data was done using the Mann Whitney U test. Spearman's rank correlation was used to determine association of independent variables (age, gender, duration of the disease, socioeconomic class) with the dependent variables (direct, indirect, total, school absenteeism and intangible costs). All analyses were done using Microsoft Excel version v16.46 and SPSS version 27.0 at 5% significance.

Results

Thirty patients of the 38 screened [21 males, 8 females, (excluding one case diagnosed prenatally), M:F ratio 2.6:1] were enrolled. One was detected prenatally and four were deceased. Three received an alternate diagnosis, one was diagnosed in adulthood, parents of three declined consent and one patient had incomplete data. Table 1 gives age at diagnosis, type of GD, age at treatment and nature of therapy. Co-morbidities (hepatitis A, macular dystrophy, pulmonary tuberculosis, primary urinary incontinence) and complications (severe anemia/ heart failure, hypersplenism, pneumonia, gastroesophageal reflux, skeletal anomalies like osteopenia, lytic lesion, avascular necrosis, osteomyelitis; sensorimotor neuropathy, progressively increasing bilirubin, retroperitoneal Gaucheromas) were noted in 16.67% and 66.6% patients respectively.

Computation of direct, indirect and notional costs is presented in Table 2. Base year for cost calculation was 2020. Shared costs for patients receiving ERT on outpatient basis were ₹364.54 per patient and ₹25,294.25 for one patient hospitalized for receiving ERT (admission of five days in a one-year period). Cost for enzyme diagnosis and genotyping was ₹3000 and ₹15000 respectively. Unit cost of Imiglucerase obtained from the manufacturer was ₹1,82,040/vial, ₹1,44,670/vial for Velaglucerase alfa and ₹51,430/capsule of Eliglustat tartarate. Costs for preparing one blood and platelet bag respectively were ₹440 and ₹300 (though patients were not charged).

Median (range) of direct, indirect costs and notional costs is presented in Table 2, all of which were not normally

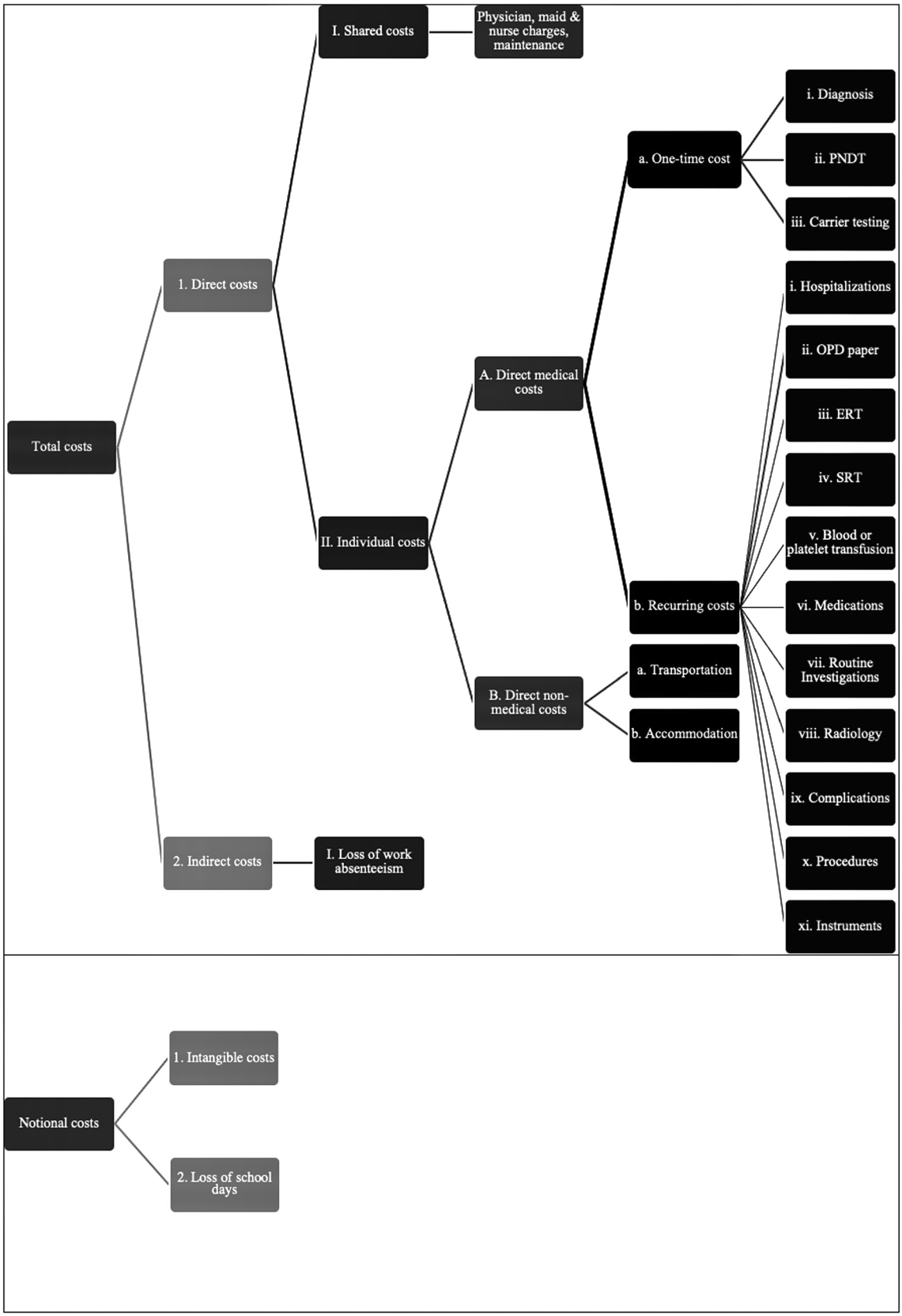

Fig. 1 Various components considered for computing treatment costs. *ERT* Enzyme replacement therapy, *OPD* Outpatient department, *PNDT* Prenatal diagnostic test, *SRT* Substrate reduction therapy

Table 1 Patient characteristics of the study population

Parameter	Number of cases (percentage)
Age at diagnosis (years) (n = 30)	
In-utero (prenatal diagnosis)	1 (3.3)
≤1	5 (16.7)
1 – 5	20 (66.7)
>5	4 (13.3)
Type of Gaucher disease (n = 30)	
Type I (non-neuronopathic)	17 (57)
Type II (acute neuronopathic)	3 (10)
Type III (chronic neuronopathic)	10 (33)
Age at commencing treatment (years) (n = 14)	
≤2	4 (28.6)
>2 – 5	6 (42.8)
>5	4 (28.6)
Nature of therapy (n = 14)	
Enzyme replacement therapy	12 (85.7)
Substrate reduction therapy (Eliglustat tartrate)	2 (14.3)

distributed. The total annual cost of treating 30 patients of GD in Mumbai was ₹25,45,74,743 or USD 34,40,199.2 (exchange rate of 1USD= ₹74, November 2020) [13] with cost per patient per year being ₹84,85,824.8 (USD 1,14,673.31). Direct and indirect costs constituted 99.8% and 0.2% each of the total costs. Disease-specific treatment contributed to 98.8% [ERT (76.7%), SRT (22.1%)] of total costs and 99% of direct costs. Total costs for 14 treated patients [12 = ERT and 2 = SRT] were ₹25,29,67,279 (USD 34,18,476.74) or ₹1,80,69,091.36 (USD 2,44,176.91) per patient and 16 treatment naive patients were ₹16,15,063.9 (USD 21,825.19) or ₹1,00,941.5 (USD 1,364.07) per patient (Ratio= 157:1) (Fig. 2) and a ratio of 206:1 for direct individual costs, 1:11 for hospitalization charges (four untreated deceased patients incurred 65% of total hospitalization charges in their last living year whereas hospitalization cost was subsidized at study site in the treated group), 336:1 for intangible cost and 293:1 for costs of school absenteeism.

In the treated subgroup, direct costs and cost of school absenteeism were significantly higher (p <0.01 and 0.013 respectively). Overall, direct, total costs and costs of school absenteeism were significantly associated with age and disease duration while association of socioeconomic class was significant with direct, total, intangible and notional costs (Table 3). Age and duration of disease correlated with direct and total costs in the treated subgroup and with costs of school absenteeism in treatment naïve subgroup and socioeconomic class with intangible and notional costs in treatment naïve subgroup.

Table 2 Components of cost analysis of Gaucher disease

Total costs (n = 30)*	Parameters	Costs (₹)	No. of cases	% (total costs)
Direct cost: ₹254060348/-	Shared costs	62477.33	7	0.025%
	Diagnosis	704034	30	0.277%
	Prenatal diagnosis	74500	5	0.029%
	Carrier detection	34500	4	0.014%
	Hospitalizations	731220	12	0.287%
	OPD	11805	20	0.005%
	ERT	195274452	12	76.706%
	SRT	56315850	2	22.122%
	Blood/platelet transfusion	13200	3	0.005%
	Medications	53363.4	21	0.021%
	Routine investigations	167630	24	0.066%
	Radiology	176680	27	0.069%
	Complications	9200	1	0.004%
	Instruments	53739.24	16	0.021%
	Transportation	363857	29	0.143%
	Accommodation	13840	5	0.005%
Indirect cost: ₹514395/-	Work absenteeism	514395	30	0.202%
Total cost: ₹254574743/-				
Notional costs (Willingness to pay) ₹14394695/-	Intangible costs	14351000	29	99.7%
	Costs of school absenteeism	43695	11	0.3%

ERT Enzyme replacement therapy, *OPD* Outpatient department, *SRT* Substrate reduction therapy

*base year for costs calculation was 2020.

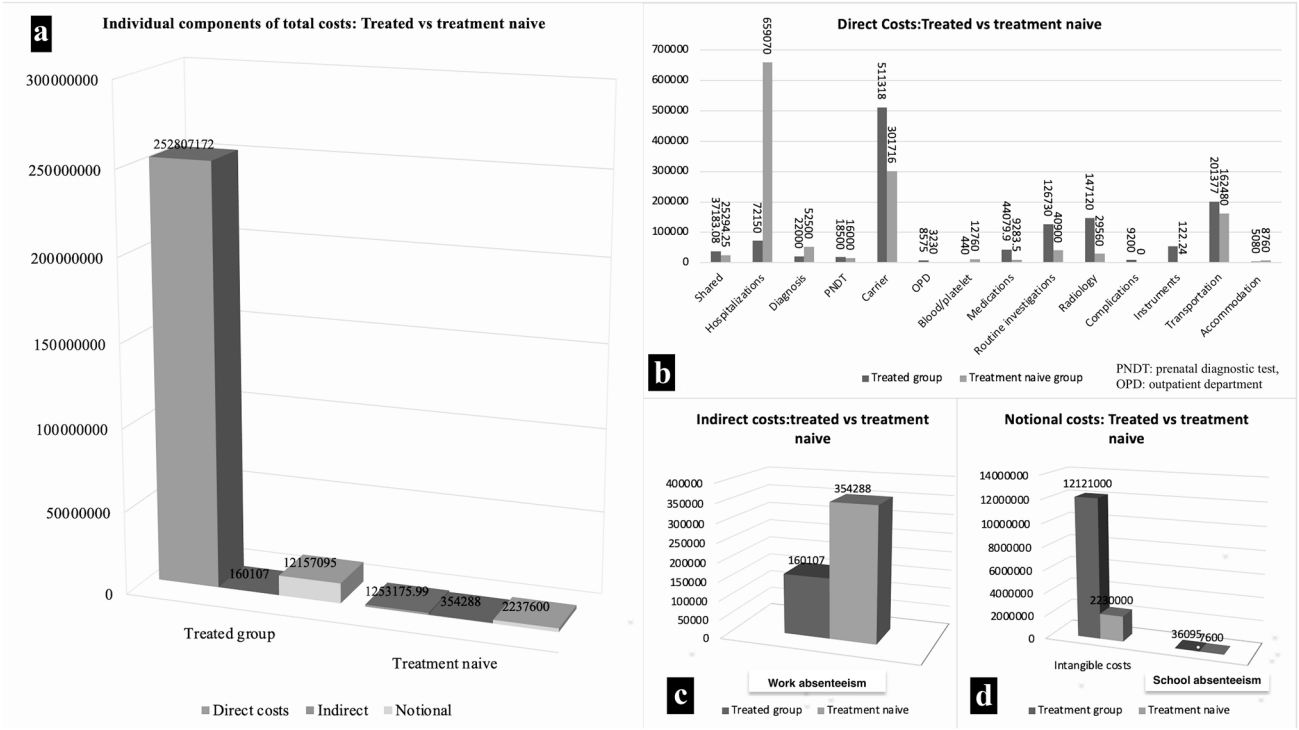

Fig. 2 Comparison of costs (in INR) between treated and treatment naive group. (**a**) Within the treated group, proportion of direct costs far exceeds indirect and notional costs while within the untreated group, proportion of notional costs was highest. (**b**) Comparison of various components of direct costs between the treated and untreated group shows that all cost components (shared costs, costs for prenatal diagnosis and carrier testing, OPD paper charges, medications, investigations, radiology, instruments and transportation) incurred by the treated group were higher than the untreated group except costs of hospitalization, diagnosis, blood/platelet transfusion and accommodation that were higher in untreated patients. Indirect costs due to work absenteeism were higher in the untreated group (**c**) and intangible costs were higher in the treated group (**d**)

Discussion

The present COI study was planned to enable identification of various cost components, their relative contribution to healthcare utilization for GD, providing information for clinical management of GD at the national level to aid modification of clinical guidelines and pin point cost drivers underlying variability of costs across different costs components [9–11].

Health policy makers worldwide are under pressure to curtail health expenditure and maintain equity in allocation of limited health resource in the context of competing healthcare priorities [14] but stakeholders like the patient community and patient advocacy groups demand

Table 3 Regression analysis showing association between various costs (dependent variables) and the independent variables (age, gender, duration of disease and socioeconomic class)

Components	Independent Variables			
Dependent variable: Costs	Age	Gender	Duration of disease	Socioeconomic class
Direct	**<0.01***	0.68	**<0.01***	**0.02***
Indirect	0.26	0.62	0.51	0.21
Total (sum of direct and indirect costs)	**<0.01***	0.65	**<0.01***	**0.017***
Intangible	0.26	0.29	0.21	**0.02***
School absenteeism	**<0.01***	0.21	**<0.01***	0.26
Notional (sum of intangible costs and costs of school absenteeism)	0.11	0.43	0.08	**0.004***

*p <0.05

reimbursement of therapy for orphan diseases [14]. It is therefore critical to determine economic burden of orphan drugs against the backdrop of India's NPRD [5]. At a decisive juncture of implementation of the NPRD 2021, policy makers in India will be faced with a dilemma of financing expensive therapies for GD. The present study provides a context for policy makers in India for resource allocation for GD to adopt cost-effective strategies and eliminate wastage of resources consumed by ineffective or inefficient practices.

The authors estimated a total cost of ₹84,85,824.77 (USD 1,14,673.3) per patient per year (60.4 times the per capita GDP of India of USD 1900 in the year 2020) for treating GD in a public health care institution in Mumbai. The study also documents a substantial cost of ₹1,00,941.5 (USD 1,364.07) per patient per year even without disease-specific treatment. At 99.8%, the most significant contributor to the total costs was direct cost. The study also draws attention to the specific cost drivers across the various categories of cost components which constitute target areas for cost containment measures. ERT and SRT accounted for majority of direct costs in treated patients, whereas cost of work absenteeism was higher in the untreated group. There was disparity in individual components of direct costs between treated and untreated groups with costs for hospitalization, diagnosis, blood transfusion and accommodation being higher in the untreated group.

Reduction of cost of ERT or SRT would yield the most dramatic and most meaningful reduction of direct costs. The annual cost for treating 20,000 patients of GD in India with ERT (prevalence of 1.33 to 1.75 per 1,00,000 population [15] in a population of 1.3 billion, assuming all patients are correctly diagnosed) would vary from ₹5800 crores (weight of 10 kg @ 60 units/kg, approximate current unit cost of 1 vial of 400 units each = ₹73,000) to ₹30,000 crores (weight of 50 kg @ 60 units/kg). Reimbursement of such a staggering amount by the government for just one rare disease would be challenging in a resource constrained budget of a low-middle income country like India with competing health priorities.

Some countries have adopted unique methods to curtail cost of ERT. Cost of ERT contributed to 95.2% of total direct medical cost of care for GD in Iran during the years 2016 to 2017 in a study by Davari et al. [16]. A 49% reduction in ERT cost was possible in Iran when market exclusivity of Imiglucerase was challenged by introduction of competitor Abcertin [16]. Dussen et al. documented improvement in incremental costs per QALY ratio in Netherlands after reduction in price of ERT and suggested making pricing of ERT negotiable through public-private partnership [1]. Other measures identified by Davari et al. to reduce costs were minimizing wastage of ERT by accurate diagnostic methods and correct assignment of disease subtypes to prevent inadvertent administration of ERT for type 2 GD and non-Gaucher diseases [2, 7, 16]. Another study from Brazil documented 38% reduction in requirement for ERT resulting in saving of USD 3 million over a period of three years by optimizing dosing without compromising clinical efficacy through specialized centers and standardized treatment protocols [17]. Ontario province in Canada adopted a strategy of limiting reimbursement of ERT to those patients objectively judged to have severe disease [14].

Based on the experiences in other countries, some immediate and practical strategies can be implemented in India to curtail expenditure for ERT by prioritizing patients for treatment with optimum doses. Treatment could be financed for patients with severe disease on recommendations of experts at National Centers of Excellence in India. The NPRD has already nominated eight centers of excellence in India [5]. Among these eight National Centers of Excellence, those with expertise in management of GD could be selected on a priority to identify patients with severe or complicated GD requiring treatment and recommending optimum dosing and funding of ERT. These centers of excellence would provide guidance to local health care facilities and could be linked via telemedicine. Additionally, Indian guidelines for GD recommending nature of diagnostic tests, tests for ascertaining disease burden, periodic monitoring and indications and dose of ERT are already published [7]. Though the present study did not examine cost components with respect to deviations from these published guidelines, it would be worthwhile to undertake studies to determine notional savings from following guidelines, examining efficacy of low dose ERT in Indian patients [18] and the need for revising Indian guidelines.

The present study showcases scope for reducing other cost components. Though components such as diagnosis, prenatal diagnosis, carrier detection, investigations, radiology, travel and accommodation, accounted for a very small proportions of direct costs, these assume significance from a user perspective as they are out of pocket expenses. Such costs impose a substantial financial burden on an individual as 46.67% of our study population belonged to the lower middle socioeconomic class. Untreated patients also contribute to societal burden of GD. Though disease-specific treatment costs were 157 times the costs of treatment-naïve patients, treatment-naïve patients incurred higher hospitalizations costs due to complications arising from GD and costs in terms of work absenteeism. Measures like early diagnosis saves healthcare provider costs of hospitalization and minimizes costs due to work and school absenteeism by prevention or early treatment of complications. Accurate diagnosis by adopting β-glucocerebrosidase enzyme activity estimation [2, 7] at the outset, particularly from dried blood spot (DBS) specimens as recommended by the Indian consensus

guidelines, eliminates some direct medical costs and wastage of ERT through misdiagnosis. Increasing uptake of DBS would substantially reduce direct out-of-pocket expenditure as testing is offered free of cost [7].

Policy makers in India also need to plan long term measures to reduce economic burden of GD. Extending benefits of schemes like Ayushman Bharat Pradhan Mantri Jan Arogya Yojana (PM-JAY) to cover GD would substantially reduce several components of direct medical out of pocket user expenditure for diagnosis, hospitalization, transfusions and radiology. Bringing carrier detection and prenatal diagnosis under the umbrella of PM-JAY will lessen the burden to individual families. User behaviour such as compliance with diagnostic tests, investigations for monitoring disease progress and timely follow-up with physician and reducing work absenteeism may improve if these aspects of healthcare were affordable and locally available and accessible.

The present study is limited by its small sample. Underestimation of the economic burden of GD was due to several factors- highly subsidized costs in a public health facility, reliance on parents' recall and preservation of expenditure records, hours of leisure time devoted to informal care and costs involved in achieving therapeutic goals with ERT (achieving and maintaining therapeutic goals at optimum individualized dose of ERT could escalate the economic burden) were not assessed, and inability to capture lifetime costs of GD, that vary according to the disease stage, by a cross-sectional, prevalence-based approach. Attribution of loss of wages for a full year for homemakers could have inflated computation of indirect costs as it was based on the assumption that homemakers would have otherwise been employed.

In conclusion, India urgently requires a policy for reducing GD's economic burden. Scarce financial resources and government funding utilized for preventive strategies would curtail the huge economic burden of treating patients with GD. Adhering to the Indian consensus guidelines for GD would also help.

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Authors' Contributions MM conceptualized the study, designed the study protocol, supervised collection and analysis of data and wrote the manuscript; NJG contributed intellectually for framing the study protocol and supervised statistical analysis, critically revised the manuscript for important intellectual content and edited and approved the final draft of the manuscript; SPM drafted the study protocol, collected and analyzed data and approved the final manuscript. MM will act as guarantor for the paper.

Declarations

Conflict of Interest None.

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