JIMD Reports
DOI 10.1007/8904_2012_136

RESEARCH REPORT

Quality of Life of Brazilian Patients with Gaucher Disease and Fabry Disease

Fabiane Lopes Oliveira • Taciane Alegra • Alicia Dornelles • Bárbara Corrêa Krug • Cristina B. O. Netto • Neusa Sica da Rocha • Paulo D. Picon • Ida Vanessa D. Schwartz

Received: 16 June 2011 / Revised: 16 February 2012 / Accepted: 17 February 2012 / Published online: 18 April 2012

Summary *Objective*: To evaluate QoL in a sample of Brazilian patients with Gaucher (GD) and Fabry (FD) disease using the SF-36 survey.

Method: Observational cross-sectional study. The SF-36 survey was administered to cognitively able patients 12 years or older, who were seen in the Medical Genetics Service of Hospital de Clínicas de Porto Alegre, Brazil.

Results: Thirty-five patients were included in the study (GD = 21, FD = 14), mean age was 29.8 ± 14.2 years and 29 (82.9%) were receiving ERT. Patients with GD receiving ERT had better scores in the general health ($p = 0.046$) domain of the SF-36 than patients with FD receiving ERT. Comparison of patients with GD naive to ERT and those receiving ERT revealed differences only in the bodily pain domain ($p = 0.036$). The Zimran score showed a moderate negative correlation with the following domains of the SF-36: physical functioning ($p = 0.035$), role-physical ($p = 0.036$), general health ($p = 0.023$) and role emotional ($p = 0.021$).

Discussion and Conclusion: Although limited because of the small number of patients included, findings suggest that patients with GD receiving ERT have a better QoL than patients with FD or with GD not receiving ERT. Imiglucerase has a beneficial effect against pain for patients with GD. Further studies should be conducted to confirm our findings.

Communicated by: Ed Wraith

Competing interests: None declared

F.L. Oliveira · B.C. Krug · I.V.D. Schwartz
Post-Graduate Program in Medical Sciences, School of Medicine, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil

T. Alegra
Post-Graduate Program in Genetics and Molecular Biology, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil

A. Dornelles · C.B.O. Netto · I.V.D. Schwartz (✉)
Medical Genetics Service, Hospital de Clínicas de Porto Alegre (HCPA), Rua Ramiro Barcellos, 2350,
Porto Alegre, RS 90035-003, Brazil
e-mail: ischwartz@hcpa.ufrgs.br

I.V.D. Schwartz
Department of Genetics, UFRGS, Porto Alegre, Brazil

N.S. da Rocha
Department of Psychiatry and Legal Medicine, UFRGS, Porto Alegre, Brazil

P.D. Picon
Department of Internal Medicine, HCPA, State Health Department of Rio Grande do Sul, Porto Alegre, Brazil

Introduction

The concept of quality of life (QoL) as a health outcome measure was introduced in the 1970s and has evolved since then (Panzini and Bandeira 2005). According to the World Health Organization (WHO) (1994), quality of life is an individual's perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards, and concerns. According to this definition, disease may affect an individual's health as well as other general aspects of their life.

Lysosomal storage diseases (LSD) are rare inherited disorders caused by specific enzyme deficiencies that lead to an abnormal storage of normal substrates or their catabolic products in the lysosomes (Meikle et al. 1999a). LSDs form a group of about 50 diseases (Wraith 2002) with an estimated incidence of 1:7,000 live births (Meikle et al.

1999b; Poorthuis et al. 1999). LSDs are classified according to the substrate stored: sphingolipidoses, such as Gaucher disease (GD) or Fabry disease (FD); mucopolysaccharidoses (MPS); glycoproteinoses; and others (Gieselmann 1995; Raas-Rothschild et al. 2004). Enzyme administration of the recombinant form of the enzyme that is deficient in LSD patients is known as enzyme replacement therapy (ERT). ERT is currently available for the following LSDs: GD, FD, MPS I, MPS II, MPS VI, and Pompe disease. The effects of ERT on the QoL of patients with GD have already been described (Damiano et al. 1998; Masek et al. 1999; Giraldo et al. 2000; Pastores et al. 2003; Giraldo et al. 2005; Weinreb et al. 2007), but are still unknown for patients with FD.

No studies in the literature have evaluated the QoL of Brazilian patients with LSDs, and no disease-specific instrument to evaluate their QoL has been evaluated, translated, or validated.

This study used the SF-36 survey to evaluate the QoL of patients with GD or FD seen in the Medical Genetics Service of Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil (SGM-HCPA), a national reference center for the diagnosis and treatment of LSD located in southern Brazil.

Methods

All patients with GD or FD seen at the SGM-HCPA were invited to participate in this observational cross-sectional study during their routine follow-up visits from September to October 2008. Patients should meet all of the following inclusion criteria: (a) age 12 years or older; (b) cognitive ability to fill out the survey; (c) signature of an informed consent form (ICF) agreeing to participate in the study. In the case of patients younger than 18 years, the consent form should also be signed by a parent or guardian.

Patients were evaluated using the SF-36 survey, which was administered after an interview to collect general data, such as type of LSD, current age, age at diagnosis, and time on ERT. Clinical severity of GD was defined using the Zimran (Zimran et al. 1992) severity score index recorded in the patient's chart for each patient on the date closest to the time the SF-36 was administered. The Zimran score is calculated according to the following disease characteristics: presence of cytopenia; hepatosplenomegaly; splenectomy; involvement of the central nervous system; skeletal findings defined by radiological, scintigraphic and clinical findings such as the occurrence of pain; involvement of other organs such as the lungs; as well as liver disease. Higher Zimran scores indicate greater clinical severity (mild = 0–10; moderate = 11–19; severe = $\geq$20). In the case of FD, the medical team at SGM-HCPA at the time of this study did not use severity scores when evaluating patients.

Medical Outcomes Study: 36-Item Short Form Health Survey (SF-36)

SF-36 is a generic instrument (Ware and Sherbourne 1992) that has 36 items organized in eight domains. Four of these domains provide a physical component score: physical functioning, which assesses the presence and severity of limitations associated with physical capacities; role limitations due to physical health, which assesses limitations according to type and amount of work, as well as how much these limitations affect work and activities of daily living; bodily pain, which assesses the presence of pain, its intensity, and how it affects activities of daily living; and general health, which assesses how patients feel about their personal health in general. The other four provide a mental component score: role limitations due to emotional problems, which assesses the impact of psychological aspects on the patient's well-being; vitality, which takes into consideration the level of energy and fatigue; social functioning, which analyzes the integration of the individual in social activities; and mental health, which includes questions about anxiety, depression, changes in behavior or emotional unbalance, and psychological well-being (Ware et al. 1993; McHorney et al. 1993; Hsiung et al. 2005). The survey has dichotomous or ordinal response items and should be answered considering a 4-week period before its administration (Ware et al. 1993; Weinreb et al. 2007). Higher scores indicate better QoL.

Statistical Analysis

Means and standard deviations were used to describe the quantitative variables, which were analyzed for the whole group of patients in the study, as well as for sample subgroups. The Kolmogorov-Smirnov test was used to check whether data distribution was significantly different from normal. Because most SF-36 items showed normal distribution, and all studies published so far on SF-36 in GD have used means to describe them, we chose to use means in all cases.

No studies in the literature reviewed evaluated QoL using the SF-36 in patients with FD receiving ERT. For patients with GD receiving ERT, six studies were retrieved (Damiano et al. 1998; Masek et al. 1999; Giraldo et al. 2000, 2005; Pastores et al. 2003; Weinreb et al. 2007). The study conducted by Masek et al. (1999) with North American patients with GD was used for comparisons with our study. The Student t test was used to compare QoL of Brazilian and American patients with GD receiving ERT. For the comparison with a normal population, the reference was the group of elderly patients studied by Lima et al. (2009) because similar studies with Brazilian adults defined as healthy were not found in the literature.

Table 1 Characteristics of the sample included in the present study ($n = 35$)

Characteristic	Gaucher disease $n = 21$ (type I = 20; III = 1)	Fabry disease $n = 14$
Age (mean ± SD) years	24.9 ± 13.4	37.3 ± 12.9
Gender (female/male)	11/10	4/10
Time on ERT (mean ± SD) years	8.5 ± 4.5	3.5 ± 2.1
n	15 (imiglucerase)	10 (agalsidase alpha = 7; agalsidase beta = 3)

SD Standard deviation

The level of statistical significance was set at 5% for all analyses. Statistical calculations were made using the software SPSS® for Windows® 18.0.

Definition of Clinically Significant Change

Changes in domain scores were classified as clinically significant according to the study conducted by Kosinski et al. (2000), who evaluated patients with rheumatoid arthritis in the USA. The minimally significant changes defined by those authors were as follows: physical functioning – 8.4; role-physical – 21.0; bodily pain – 14.7; general health – 4.2; vitality – 11.1; social functioning – 11.7; role-emotional – 17.9; and mental health domain – 7.3. The same criteria were used by Weinreb et al. (2007) in their study about the evaluation of QoL in patients with GD.

Results

Thirty-five patients were included in the study. Only one patient with GD type I did not agree to participate in the study due to personal reasons. Patient characteristics are summarized in Table 1. Of the patients included, only six, all with GD, were younger than 18 years (4/6 were 12–14 years).

Gaucher Disease ($n = 21$)

Mean Zimran score was 6.02 (range = 1–29); the disease was mild in 19 patients, moderate in 1, and severe in 1. There was a statistically significant correlation between the Zimran score and the following SF-36 domains: physical functioning ($r = -0.462$; $p = 0.035$); role-physical ($r = -0.460$; $p = 0.036$), general health ($r = -0.494$; $p = 0.023$), and role-emotional ($r = -0.501$; $p = 0.021$).

In the group of patients receiving ERT ($n = 15$), the mean SF-36 domain scores ranged from 67.6 (vitality) to 77.3 (mental health); for the patients not receiving ERT ($n = 6$), from 38.8 (role-emotional) to 72.0 (mental health) (Tables 2 and 3). The comparison of patients on ERT and patients naïve to ERT revealed that bodily pain was the only domain whose score had a statistically significant difference between groups ($p = 0.036$), and the higher scores were found to be for the ERT group. According to the criteria established by Kosinski et al. (2000), this change may also be classified as clinically significant. The physical functioning, role-physical, general health, social functioning, and role-emotional domains also showed clinically significant changes that favored the ERT subgroup (Table 3).

Fabry Disease ($n = 14$)

In the group of patients with FD, eight were receiving ERT with agalsidase alpha and four with agalsidase beta (Table 1). In the analysis of male patients only ($n = 10$, all receiving ERT), mean domain scores ranged from 45.0 (role-physical) to 66.6 (role-emotional) (Table 3). A summary of clinical manifestations and domain scores for heterozygous women included in the study is given in Table 4.

Comparisons Between GD and FD Patients Receiving ERT and Other Populations

The comparison of patients with GD and FD receiving ERT showed a statistically significant difference in the general health domain ($p = 0.046$), which was higher in patients with GD. The comparison with other GD patients and with a Brazilian normal population is shown in Tables 2 and 3.

Discussion

This is the first study to evaluate QoL of Brazilian patients with LSD using the SF-36 survey. Our findings suggest that the QoL of patients with GD and FD is significantly affected and that ERT has a beneficial effect on the QoL of patients with GD.

The SF-36 survey is, in fact, a general instrument to evaluate health-related quality of life that has not been validated for use in patients with LSD. However, it was used in our study for two main reasons: first, most studies in the literature published about this issue until 2008 used the SF-36 survey; second, this questionnaire has been validated for the Brazilian population (Ciconelli et al. 1997). These reasons

Table 2 Comparison of quality of life of Brazilian and North American patients with GD receiving enzyme replacement therapy, according to SF-36 survey responses*

	Brazilian patients with Gaucher disease ($n = 15$)	American patients with Gaucher disease (Masek et al. 2009) ($n = 25$)	p
Mean age (years)	22.3	41.7	
Mean treatment time (years)	8.5	2	
SF-36			
Physical component			
Physical functioning	76.3 ± 26.0	76.7 ± 29.5	0.965
Role-physical	70.0 ± 42.4	80.4 ± 32.8	0.318
Bodily pain	76.5 ± 27.3	66.3 ± 25.6	0.241
General health	71.1 ± 21.6**	59.3 ± 24.0**	0.126
Mental component			
Vitality	67.6 ± 20.6**	56.3 ± 23.3**	0.129
Social functioning	70.0 ± 20.9**	87.0 ± 18.6**	0.011[a]
Role-emotional	68.8 ± 42.6	75.3 ± 36.6	0.612
Mental health	77.3 ± 9.7	73.9 ± 14.5	0.426

* Data described as means and standard deviations for the SF-36 domains.

** Clinically significant changes for the SF-36 scores defined according to the criteria for patients with rheumatoid arthritis in the USA (see Methods)

[a] $p < 0.05$

Table 3 Comparison of quality of life of Brazilian patients with Gaucher and Fabry diseases and a group of Brazilian elderly according to the SF-36[a]

	Gaucher disease receiving ERT ($n = 15$)	Gaucher disease not receiving ERT ($n = 6$)	Fabry disease receiving ERT ($n = 10$)	Elderly(Lima et al. 2005) ($n = 1.958$)[b]
Mean age (years)	22.3 ±13.0	31.5 ±13.1	33.5 ± 12.9	60 ± 69.6
SF-36				
Physical component				
Physical functioning	76.3 ± 26.0[b]	59.1 ± 38.3[a,b]	66.0 ± 26.5	71.4
Role-physical	70.0 ± 42.4[b]	41.6 ± 46.5[a,b]	45.0 ± 44.7[a]	81.2
Bodily pain	76.5 ± 27.3[b,c]	47.8 ± 22.7[a,b,c]	59.7 ± 28.5	74.2
General health	71.1 ± 21.6[b,d]	62.5 ± 19.1[a,b]	50.3 ± 26.8[a,d]	70.1
Mental component				
Vitality	67.6 ± 20.6[b]	56.6 ± 16.3[b]	63.5 ± 21.6	64.4
Social functioning	70.0 ± 20.9[a,b]	55.2 ± 31.2[a,b]	65.0 ± 25.4[a]	86.1
Role-emotional	68.8 ± 42.6[b]	38.8 ± 49.0[a,b]	66.6 ± 41.3[a]	85.9
Mental health	77.3 ± 9.7[a]	72.0 ± 11.8	64.4 ± 25.3	69.9

* Data described as means and standard deviations for SF-36 components and domains

** Standard deviations of SF-36 scores not reported in original study

[a] Clinically significant differences in comparison with group of elderly patients

[b] Clinically significant differences between the groups of patients with GD receiving or not receiving ERT

[c] $p < 0.05$ (GD receiving ERT x GD not receiving ERT)

[d] $p < 0.05$ (GD receiving ERT × FD receiving ERT)

should be taken into consideration when discussing our findings because general instruments, such as the SF-36 survey, may not be sensitive enough to detect specific patterns of QoL impairments. In addition, although the SF-36 survey has been validated for individuals older than 18 years, the Gaucher Registry suggests its administration for individuals as young as 14 years, and there is at least one study about this survey used for patients with GD 14 years and older (Damiano et al. 1998). Our study included individuals at least 12 years old, but most were 14 years or

Table 4 Fabry disease – summary of clinical characteristics and mean SF-36 scores of heterozygous women included in the study

Patient	Age (years)	Clinical manifestations	ERT	PF	RP	BP	GH	VT	SF	RE	MH
A	33	Acroparesthesia, angiokeratoma, verticillate cornea, proteinuria	No	100	100	72	100	75	100	66	84
B	41	Acroparesthesia, angiokeratoma, depression, migraine, proteinuria, hematuria	No*	75	100	74	72	70	87.5	100	80
C	52	Acroparesthesia, depression, joint pain	Yes	20	0	31	25	35	84.3	0	40
D	61	Hypertension, transient ischemic attack, tinnitus, dizziness, intolerance to heat and cold	Yes	90	100	100	52	85	87.5	100	92

ERT enzyme replacement therapy, *PF* physical functioning, *RP* role-physical, *GH* general health, *VT* vitality, *SF* social functioning, *RE* role-emotional, *MH* mental health

*Patient started ERT immediately after responding to SF-36

older. The lower limit of age adopted as an inclusion criteria was justified by the need to have a larger study sample and because individuals 12 years and older are usually capable of responding questionnaires such as the SF-36 (Streiner et al. 1995).

Our sample size made it impossible to analyze the effects of ERT on FD or the analysis of a possible differential effect between the two forms of agalsidase.

The lack of similar studies for comparisons has also limited our analysis. The comparison with a sample of Brazilian elderly individuals (Lima et al. 2009) revealed that patients with GD receiving ERT had clinically significant differences in social functioning, with a higher score for the elderly, and mental health, with a higher score for the patients with GD. The patients with GD not receiving ERT had clinically significant differences in all the domains, (with higher scores for the elderly), except in the vitality and mental health domains. In the group of patients with FD receiving ERT, clinically significant differences were found in the role-physical, general health, social functioning, and role-emotional domains, all with higher scores for the elderly.

Gaucher Disease

According to our results, ERT has a significant and positive effect on the QoL of GD patients. These findings suggest that the generic approach to evaluate QoL was sensitive to detect changes in the health of patients with GD on ERT or ERT-naïve, and corroborate findings by Masek et al. (1999), who compared the QoL of the general population in the USA with that of patients with GD receiving ERT. Their results demonstrated a significant improvement in vitality, role-physical, and social functioning. Giraldo et al. (2005) evaluated the QoL of patients after 2 years of treatment and the importance of bone pain. They showed that role-physical and bodily pain are negatively associated with QoL, but failed to demonstrate that ERT improved QoL for their patients. Weinreb et al. (2007) evaluated ERT efficacy before and after 4 years of treatment. They reported that treatment had a positive effect on the QoL of patients with GD.

Patients with GD not receiving ERT had lower scores in the role-emotional domain of the mental component score; in the physical component score, the lowest score was in the role-physical domain. These domains are associated with depression, anxiety, and poor physical performance reported by patients when not able to complete or keep the pace of their daily activities, such as their work activities (McHorney et al. 1993). The domain with the highest score was mental health, also in the group receiving ERT. This finding may be explained by the fact that all patients included in this study, except one, had GD type I (the non-neuropathic form).

The comparison between Brazilian and North American patients with GD receiving ERT (Masek et al. 1999) revealed clinically significant changes in general health and vitality (higher scores in the Brazilian group) and social functioning (higher score in the American group). The better findings in the Brazilian patients may be partially explained by the differences in age and treatment duration between the two populations, as the Brazilians had a lower mean age and a longer time on ERT. The scores found in social functioning might be explained by cultural (or socioeconomic) differences between the two samples. Socioeconomic data or mean imiglucerase dose received by the patients could not be compared because Masek et al. (1999) did not report those findings.

The analysis of Zimran scores revealed a significant negative, as expected, but moderate correlation, particularly with the physical domain. The only physical domain that had no significant correlation was bodily pain, exactly the one that, in our study, showed a significant positive difference in the group receiving ERT. According to the definition of relevant clinical change adopted in this study, patients with GD receiving or not receiving ERT also had a difference, although not statistically significant, in the three domains of the physical component that had a significant correlation with the Zimran score (physical functioning, role-physical, general health) and in two domains of the mental component of the SF-36

(social functioning and role-emotional), but only the role-emotional domain had a significant correlation with the Zimran score. These findings suggest that the Zimran score, originally developed to evaluate the severity of disease in patients with GD in studies about the association between genotype and phenotype, is an adequate instrument to detect mainly physical changes associated with GD, but not to detect the effect of the treatment.

Fabry Disease

Unlike GD, FD is an X-linked disorder, and heterozygous women may be either asymptomatic, oligosymptomatic, or have a disease similar to that found in hemizygotes (Pinto et al. 2010). As expected, the heterozygous women in this study usually had higher SF-36 scores than men.

Male patients receiving ERT had the lowest scores in the role-physical domain of the physical component score. This domain is associated with the number of times that the patient had to reduce daily activities due to physical problems. Patient activities may be impaired due to associated clinical comorbidities, such as depression, paresthesias, or heart disease. In the mental component score, the lowest result was in the vitality domain, which is associated with the levels of energy and fatigue (McHorney et al. 1993); this finding might also be associated with the psychiatric abnormalities seen in the patients.

Conclusion

Data in this study suggest that patients with GD receiving ERT have a better QoL than patients with FD and GD not receiving ERT and that ERT with imiglucerase has a beneficial effect against the pain felt by patients. In the group of patients with FD, scores were higher in the group of heterozygous women, which may be explained by the fact that FD is an X-linked disorder. Further studies should be conducted to confirm our findings.

Acknowledgments The authors thank the staff of the Medical Genetics Service of HCPA and the staff of the Reference Center for Gaucher Disease for their support and collaboration in the conduction of this study. We also thank the Research and Graduate Program of HCPA, Porto Alegre, Brazil, for their support and preparation of statistical analysis, especially the statistician Marilyn Agranonik.

Synopsis of the Article

This study evaluated the quality of life of patients with Gaucher and Fabry diseases using a nonspecific instrument, the SF-36 questionnaire. Results suggested that ERT has a positive effect against the pain domain for patients with Gaucher disease.

Authors Contributions

Fabiane Lopes Oliveira Conception and design, analysis and interpretation of data, drafting of the article.

Taciane Alegra Analysis and interpretation of data, drafting of the article.

Alicia Dornelles Analysis and interpretation of data, drafting of the article.

Bárbara Corrêa Krug Analysis and interpretation of data, drafting of the article.

Cristina B. O. Netto Analysis and interpretation of data, drafting of the article.

Neusa Sica da Rocha Analysis and interpretation of data, drafting of the article.

Paulo D. Picon Analysis and interpretation of data, drafting of the article.

Ida Vanessa D. Schwartz Conception and design, analysis and interpretation of data, drafting of the article.

Guarantor for the Article

Ida Vanessa D. Schwartz.

Competing Interest

All authors declare that the answer to all questions on the JIMD competing interest form is No, and therefore they have nothing to declare.

Funding

This study was partially funded by FIPE/HCPA, Porto Alegre, Brazil (project # 08-209), and by grants from the Brazilian Agency of Research-CNPq (MCT/CNPq/MS-SCTIE-DECIT 33/2007; MCT/CNPq/MS-SCTIE-DECIT 37/2008; and MCT/CNPq/MS-SCTIE-DECIT 67/2009).

Ethics Approval

This study was approved by the Ethics in Research Committee of the Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil.

Patient Consent

All patients or their guardians signed an informed consent form.

References

Ciconelli RM, Ferraz MB, Santos W, Meinão I, Quaresma MR (1997) Brazilian-Portuguese version of the SF-36. A reliable and valid quality of life outcome measure. Rev Bras Reumatol 39:50

Damiano AM, Pastores GM, Ware JE (1998) The health-related quality of life of adults with Gaucher's disease receiving enzyme replacement therapy: results from a retrospective study. Qual Life Res 7:373–386

Gieselmann V (1995) Lysosomal storage diseases. Biochim Biophys Acta 1270:103–136

Giraldo P, Pocoví M, Pérez-Calvo J, Rubio-Félix D, Giralt M (2000) Report of the Spanish Gaucher's Disease Registry: clinical and genetic characteristics. Haematologica 85:792–799

Giraldo P, Solano V, Pérez-Calvo JI, Giralt M, Rubio-Félix D, Spanish Group on Gaucher Disease (2005) Quality of life related to type 1 Gaucher disease: Spanish experience. Qual Life Res 14:453–462

Hsiung PC, Fang CT, Chang YY, Chen MY, Wang JD (2005) Comparison of WHOQOL-bREF and SF-36 in patients with HIV infection. Qual Life Res 14:141–150

Kosinski M, Zhao SZ, Dedhiya S, Osterhaus JT, Ware JE Jr (2000) Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. Arthritis Rheum 43:1478–1487

Lima MG, Barros MB, Cesar CL, Goldbaum M, Carandina L, Ciconelli RM (2009) Health related quality of life among the elderly: a population-based study using SF-36 survey. Cad Saude Publica 25:2159–2167

Masek BJ, Sims KB, Bove CM, Korson MS, Short P, Norman DK (1999) Quality of life assessment in adults with type 1 Gaucher disease. Qual Life Res 8:263–268

McHorney CA, Ware JE Jr, Raczek AE (1993) The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 31:247–263

Meikle PJ, Hopwood JJ, Clague AE, Carey WF (1999a) Prevalence of lysosomal storage disorders. JAMA 281:249–254

Meikle PJ, Ranieri E, Ravenscroft EM, Hua CT, Brooks DA, Hopwood JJ (1999b) Newborn screening for lysosomal storage disorders. Southeast Asian J Trop Med Public Health 30(Suppl 2):104–110

Panzini RG, Bandeira DR (2005) Quality of life and spiritual-religious coping relations. Qual Life Res 14:2106–2107

Pastores GM, Barnett NL, Bathan P, Kolodny EH (2003) A neurological symptom survey of patients with type I Gaucher disease. J Inherit Metab Dis 26:641–645

Pinto LL, Vieira TA, Giugliani R, Schwartz IV (2010) Expression of the disease on female carriers of X-linked lysosomal disorders: a brief review. Orphanet J Rare Dis 5:14

Poorthuis BJ, Wevers RA, Kleijer WJ et al (1999) The frequency of lysosomal storage diseases in *The Netherlands*. Hum Genet 105:151–156

Raas-Rothschild A, Pankova-Kholmyansky I, Kacher Y, Futerman AH (2004) Glycosphingolipidoses: beyond the enzymatic defect. Glycoconj J 21:295–304

Streiner DL, Norman GR (1995) Health measurement scales: a practical guide to their development and use. Oxford University Press, Oxford

The WHOQOL Group (1994) Development of the WHOQOL: rationale and current status. Int J Ment Health 23:24–56

Ware JE Jr, Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30:473–483

Ware JE, Snow KK, Kosinski M et al (1993) SF-36 health survey. Manual and interpretation guide. New England Medical Center, Boston

Weinreb N, Barranger J, Packman S et al (2007) Imiglucerase (Cerezyme) improves quality of life in patients with skeletal manifestations of Gaucher disease. Clin Genet 71:576–588

Wraith JE (2002) Lysosomal disorders. Semin Neonatol 7:75–83

Zimran A, Kay A, Gelbart T, Garver P, Thurston D, Saven A, Beutler E (1992) Gaucher disease. Clinical, laboratory, radiologic, and genetic features of 53 patients. Medicine 71:337–53