Medicina Clínica 163 (2024) 449–457

MEDICINA CLINICA

www.elsevier.es/medicinaclinica

Original article

Identification of patient-reported outcomes measures (PROMs) and patient-reported experiences measures (PREMs) in Gaucher disease in Spain

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ARTICLE INFO

Article history:
Received 23 December 2023
Accepted 4 June 2024
Available online 1 August 2024

Keywords:
Gaucher disease
Patient reported outcomes
PRO
Patient reported experience
PRE
PREM
PROM

ABSTRACT

Background: Patient-reported outcome measures (PROMs) and patient-reported experiences measures (PREMs) are crucial for understanding the impact of GD on quality of life and patient's perceptions on care, but also to guide decision-making processes. Nevertheless, no specific PREMs in GD have been published, neither PROMs for Spanish GD patients have been developed.
Methods: Two project coordinators selected key-points to be included in a PROMs/PREMs questionnaire, and the scientific committee and a group of expert patients contributed to the initial draft. Then, 9 meetings with experts were held to discuss controversial points. After, a questionnaire with 103 items regarding symptomatology, aspects of daily life and care experience was developed. Finally, it was conducted a Delphi survey among a multidisciplinary group of experts in GD.
Results: Consensus was reached on 85 out of the 103 items. Recommendations on PROMs and PREMs regarding symptomatology, aspects of daily life and care experience were obtained. Consensus was reached on the importance of considering fatigue, concentration problems, and communication issues in GD patients using 5-step analog scales. Panelists recommended asking GD patients about the impact on social functioning and work/school performance. Finally, consensus was reached on considering care experiences, such as treatment satisfaction, treatment interruptions or transitions and healthcare professionals involved in patient's management to perceive patient's perceptions.
Conclusion: This expert consensus may help developing GD-specific PROMs/PREMs for improving GD management. Properly developed and validated PROMs/PREMs may help decision-making, establishing patient-tailored therapeutic and follow-up goals.

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https://doi.org/10.1016/j.medcli.2024.06.006

Identificación de medidas de resultados comunicados por el paciente y medidas de experiencias comunicadas por el paciente en la enfermedad de Gaucher en España

Palabras clave:
Enfermedad de Gaucher
Resultados comunicados por los pacientes
PRO
Experiencia comunicada por los pacientes
PRE
PREM
PROM

R E S U M E N

Antecedentes: Las medidas de resultados informadas por los pacientes (PROM) y las medidas de experiencias informadas por los pacientes (PREM) son cruciales para comprender el impacto de la enfermedad de Gaucher (EG) en la calidad de vida y las percepciones sobre la atención, pero también para guiar los procesos de toma de decisiones. Sin embargo, no se han publicado PREM específicas en la EG, ni se han desarrollado PROM para pacientes españoles con EG.

Métodos: Dos coordinadores del proyecto seleccionaron los puntos clave a incluir en un cuestionario de PROM/PREM, y el comité científico y un grupo de pacientes expertos contribuyeron al borrador inicial. A continuación, se celebraron 9 reuniones con expertos para debatir los puntos controvertidos. Después, se elaboró un cuestionario con 103 ítems sobre sintomatología, aspectos de la vida diaria y experiencia asistencial. Por último, se realizó una encuesta Delphi entre un grupo multidisciplinar de expertos en la EG.

Resultados: Se alcanzó consenso en 85 de los 103 ítems. Se obtuvieron recomendaciones sobre PROM y PREM relativas a sintomatología, aspectos de la vida diaria y experiencia asistencial. Se alcanzó un consenso sobre la importancia de tener en cuenta la fatiga, los problemas de concentración y los problemas de comunicación en los pacientes con EG. Los panelistas recomendaron preguntar a los pacientes con EG sobre el impacto en el funcionamiento social y el rendimiento laboral/escolar. Por último, se llegó a un consenso sobre la importancia de tener en cuenta las experiencias asistenciales, como la satisfacción con el tratamiento, las interrupciones o transiciones del tratamiento y los profesionales sanitarios implicados en el tratamiento del paciente para percibir los efectos de la enfermedad.

Conclusiones: Este consenso de expertos puede ayudar a desarrollar PROM/PREM específicos de la EG para mejorar el manejo de la misma. Unas PROM/PREM adecuadamente desarrolladas y validadas pueden ayudar a la toma de decisiones, y a establecer objetivos terapéuticos y de seguimiento adaptados al paciente.

Introduction

Gaucher disease (GD) (OMIM 230800, 230900, 231000) is a rare autosomal recessive disease caused by mutations in the gene encoding for glucocerebrosidase (*GBA*) (EC 3.2.1.45, OMIM 606463). This enzyme deficiency leads to the accumulation of glucosylceramide within lysosomal macrophages, causing a systemic and heterogeneous disease.[1–4] The spectrum of phenotypes associated with GD varies widely, ranging from intrauterine fatalities to asymptomatic individuals in their eighties.[4] Main GD signs and symptoms include anemia, thrombocytopenia, splenomegaly, hepatomegaly, and bone disease. In addition, pulmonary involvement, coagulation abnormalities and neurologic disease have also been described.[1,2,4] Beyond its impact on overall functioning, GD also impairs general health-related quality of life (HRQoL), i.e., physical, psychological, cognitive, and social factors that affect an individual's performance of daily activities and self-perceived well-being.[5]

Traditionally, GD has been classified into three subtypes: non-neuronopathic or GD type 1 (GD1), which accounts for >90% of all GD cases; acute neuronopathic, or GD type 2 (GD2), and chronic neuronopathic disease or GD type 3 (GD3).[3,6] Treatment options for GD are limited and include enzyme replacement therapy (ERT) and substrate reduction therapy (SRT), both effective for GD1.[7–9] Although these treatments improve patients' QoL and disease prognosis, treatment options for GD2 and GD3 patients are still limited, and no cure for the disease has been found so far.[10]

Given the wide phenotypic heterogeneity, the few therapeutic alternatives, the limited understanding of the disease, and the geographical dispersion of patients, there is a need for new and personalized management approaches. Patient-reported outcome measures (PROMs) comprise tools, primarily questionnaires, designed to directly obtain information from patients regarding disease outcomes, treatment effectiveness, clinical progression and information about the patient's QoL.[11] Patient-reported experience measures (PREMs) seek to capture patients' perceptions during their healthcare journey.[11] PROMs allow a more personalized follow-up, measuring treatment evolution and adherence to medical recommendations.[11] When analyzed together with clinical data, PROMs and PREMs support appropriate decision-making. PROMs can be classified as generic or disease-specific measures. Condition-specific measures provide greater validity and credibility than general QoL questionnaires because consider disease-specific particularities. Although most GD studies use generic measures of QoL,[12] two versions of an specific PROM questionnaire for GD1 have been recently developed: a 24-item version for routine clinical practice and a 17-item version for clinical trials.[13]

In Spain, GD affects approximately 342 patients,[14] but no specific PROMs for GD have been developed. Furthermore, no specific national or international studies of PREMs in GD have been published. Thus, the aim of the present study was to identify and define which items should be included in future PROM and PREM tools for patients with GD in Spain using a Delphi survey to define consensus among a multidisciplinary group of experts.

Material and methods

We used a modified Delphi method[15] to obtain a consensus on PROs and PREs in patients with GD in Spain. Two project coordinators (PG and MM) selected the key-points to be included in the questionnaire based on a literature review and their clinical expertise. Then, a group of expert patients and a multidisciplinary scientific committee (SC) created ad hoc for this project made their contributions to the initial draft. The SC included 7 multidisciplinary experts in GD management, and expert patients were recruited from the AEEFE (Spanish Association of Patients and Relatives of Gaucher's Disease).

A total of 9 regional meetings with 10 experts and a moderator consisting of talks and participative workshops were held from

October to December 2022. In these meetings, PROMs and PREMs in GD were discussed and controversial points were identified. The project coordinators designed the final questionnaire for the Delphi survey on the basis of the meeting results, relevant literature and their clinical expertise.

The final questionnaire included 103 items on the role of PROMs and PREMs on GD:

27 items regarding PROs on symptomatology, 37 items regarding PROs on aspects of daily life and 39 items regarding care experience. The Delphi questionnaire was written in Spanish and it was translated into English for this manuscript. The original items of the questionnaire can be found as Supplementary material 1.

For panel composition, healthcare providers with expertise on GD management from different medical specialties from all over Spain were invited to participate. The survey was administered through an online platform and was held to two rounds of voting, between 16th March 2023 and 17th April 2023 (first wave), and from 5th May 2023 to 28th May 2023 (second wave).

Descriptive analysis of the results was performed for the Likert-type questionnaire's items with a 9-position scale: 1–3 (disagreement), 4–6 (neither disagreement nor agreement), and 7–9 (agreement). Median score, average score, interquartile range and percentage of panelists whose score was outside the median were calculated for each item. When <33.3% of panelists ranked a statement outside of the median value, an item was considered to have reached "consensus" (66.7%). It was considered "consensus on agreement" with median values ≥7, and "consensus on disagreement" with median values ≤3. When ≥33.3% of panelists ranked a statement outside of the median value, the level of consensus for that item was considered as "undetermined". When a third or more panelists ranked a statement as "agreement" and a third or more panelists as "disagreement", the level of consensus for that item was considered as "discrepancy". All items with an "undetermined" level of consensus or with an interquartile range ≥4 on the first round were sent for a second round of vote.

Results

A total of 56 panelists from across Spain participated in the first round of the Delphi survey, and 55 participated in the second round. Demographic and clinical specialty characteristics of participants can be found in Table 1. After two rounds, consensus was reached on 85 out of the 103 items included in the questionnaire, with 84 showing "agreement" and 1 "disagreement". The remaining 18 items were considered "undetermined".

Patient-reported outcomes on symptom implications

In the first section, consensus was reached on 16 out of 27 items. Regarding limitations caused by fatigue, panelists recommended asking GD patients about the frequency with which they encounter difficulties in performing basic activities of daily living (BADLs) (90.9%), their ability to fulfill daily life obligations (90.9%), and the need to give up desired activities (89.1%), using a 5-step analog scale (87.3%) (Table 2). To estimate fatigue in GD patients, the use of the Short Form Health Survey (SF-36) (67.3%) questionnaire and the Functional Assessment of Chronic Illness Therapy (FACIT) scale (78.2%) was recommended, while the Barthel Index was not considered suitable (76.4%). There was no consensus on using the 6-minute walk test (6MWT), Piper fatigue scale (S-PFS-R), or MPN-10 scale for estimating fatigue in GD patients (Table 2).

Panelists recommended asking GD patients about the degree of difficulty in activities that require concentration (81.8%), the frequency of interruptions in attention-holding activities (80.0%) and the frequency with which they forget things (72.7%), using 5-step analog scales (Table 2). However, there was no consensus on using specific scales for estimating concentration in GD patients (Table 2).

Table 1
Characteristics of participant experts.

	N = 56
Gender, n (%)	
Male	27 (48.2%)
Female	29 (51.8%)
Geographical distribution, n (%)	
Andalusia	5 (8.9%)
Aragon	1 (1.8%)
Asturias	2 (3.6%)
Balearic Islands	2 (3.6%)
Basque Country	4 (7.1%)
Canary Islands	6 (10.7%)
Castile – La Mancha	2 (3.6%)
Castile and León	1 (1.8%)
Catalonia	5 (8.9%)
Community of Madrid	6 (10.7%)
Extremadura	2 (3.6%)
Galicia	7 (12.5%)
La Rioja	1 (1.8%)
Navarre	1 (1.8%)
Region of Murcia	2 (3.6%)
Valencian Community	9 (16.0%)
Healthcare specialty	
Hematology	26 (46.4%)
Internal medicine	16 (28.6%)
Nurse	8 (14.3%)
Hospital pharmacy	5 (8.9%)
Oncology	1 (1.8%)

To assess communication problems in GD patients, the panelists recommended the use of a 5-step analog scale to measure the degree of communication difficulties (83.6%). They agreed on inquiring GD patients about the difficulty in making their ideas and thoughts understandable (67.3%), but no consensus was reached regarding asking about the difficulty of finding words during a conversation (60.0%) or difficulty in written communication (63.6%). Panelists agreed on the importance of asking the caregiver or companion about the patient's ability to communicate his ideas in an understandable way (72.7%), using a 5-step analog scale to measure it (Table 2).

Patient-reported outcomes on daily life aspects

In the second section, consensus was high, including 36 out of 37 items. Panelists recommended asking GD patients about sleep problems (i.e.: falling asleep, maintaining continuous sleep and frequency of rest periods during daily activity) and anxiety levels using 5-step analog scales (Table 3). Most panelists recommended asking GD patients about worries of the future course of the disease (83.6%) and anxiety arising from possible complications (78.2%). The Pittsburgh Sleep Quality Scale (PSQI) was recommended for estimation of sleep-related problems (69.1%), and both the Hamilton Scale and the Hospital Anxiety and Depression Scale (HADS) for estimation of anxiety. In addition, panelists agreed that the HADS is suitable for measuring depression in GD patients (Table 3).

Regarding the impact of GD on patients' social life, panelists recommended asking about the disease effect on the patient's circle of relationships (85.5%), and on sexual and couple relationships (70.9%), as well as the level of family and social support received (76.4%), and support from associations (72.7%), using 5-step analog scales (Table 3). Moreover, panelists agreed on assessing concerns on possible disease transmission to offspring (87.3%) and limitations in reproductive decisions, both to be measured using 5-step analog scales (Table 3).

Table 2
Patient reported outcomes on the implications of symptomatology.

Item	Median (1: disagree – 9: agree)	% of consensus	Result
1. To assess the limitations in daily activities caused by fatigue, we should ask about the frequency with which the patient has difficulties in performing basic activities of daily living (BADLs) (e.g.: climbing stairs, cooking, cleaning, carrying shopping bags, getting dressed, etc.).	9	90.9%	Agreement
2. To assess the limitations in daily activities due to fatigue, we should ask about the frequency with which the patient has had to fulfil their daily living obligations due to fatigue (e.g. work, student activities, etc.).	8	90.9%	Agreement
3. To assess the limitations in daily activities caused by fatigue, we should ask about the frequency with which the patient has had to give up activities that they wanted to do (e.g. travel, sports, social life activities, etc.).	8	89.1%	Agreement
4. To measure how often limitations in daily activities have occurred due to fatigue in the last month, we should use a 5-step analogue scale (e.g. "1: never", "2: rarely", "3: occasionally", "4: frequently", "5: always").	8	87.3%	Agreement
5. To measure the degree of difficulty in communication, we should use a 5-step analogue scale (e.g.: "1: none", "2: little", "3: some", "4: quite a lot", "5: a lot").	7	83.6%	Agreement
6. Patients with Gaucher disease should be asked about the degree of difficulty in activities that require concentration (e.g. reading, playing cards, etc.).	8	81.8%	Agreement
7. Patients with Gaucher disease should be asked about the frequency with which they interrupt activities that require attention for a long time (e.g. films, lectures, radio programs, etc.).	7	80.0%	Agreement[a]
8. The FACIT scale enables to estimate the fatigue variable in the patient with Gaucher disease.	7	78.2%	Agreement
9. To measure the degree of difficulty in concentration, we should use a 5-step analogue scale (e.g.: "1: none", "2: little", "3: some", "4: quite a lot", "5: a lot").	7	78.2%	Agreement
10. The Barthel Index enables to estimate the fatigue variable in the patient with Gaucher disease.	3	76.4%	Disagreement[a]
11. To measure the frequency with which the patient with Gaucher disease has interrupted activities requiring attention and immediate forgetfulness in the last month, a 5-step analogue scale should be used (e.g.: "1: never", "2: rarely", "3: occasionally", "4: frequently", "5: always").	8	76.4%	Agreement
12. To assess concentration problems, patients with Gaucher disease should be asked how often they forget things immediately (e.g. leaving their keys behind, etc.).	7	72.7%	Agreement[a]
13. To assess communication problems in patients with Gaucher disease, we should ask the caregiver or companion about the extent to which the patient communicates their ideas in an understandable manner.	7	72.7%	Agreement
14. To measure the patient's communication problems from the caregiver's point of view, we should use a 5-step analogue scale (e.g.: "1: he/she is understood perfectly", "2: he/she is well understood", "3: he/she is understood with some difficulty", "4: he/she is quite difficult to understand", "5: he/she cannot be understood").	7	72.7%	Agreement
15. The SF-36 enables to estimate the fatigue variable in the patient with Gaucher disease.	8	67.3%	Agreement
16. To assess communication problems in patients with Gaucher disease, one should ask about the degree of difficulty they encounter in making their ideas and thoughts understandable.	7	67.3%	Agreement
17. To assess communication problems in patients with Gaucher disease, one should ask about the degree of difficulty they encounter in communicating in writing (e.g.: e-mail, social media chats, etc.).	7	63.6%	Undetermined[a]
18. The Piper fatigue scale (S-PFS-R) enables to estimate the fatigue variable in the patient with Gaucher disease.	6	61.8%	Undetermined[a]
19. To assess communication problems in patients with Gaucher disease, one should ask about the degree of difficulty they encounter in finding the words with which to express themselves in conversation.	7	60.0%	Undetermined[a]
20. The MPN-10 quality of life scale in polycythemia vera enables to estimate the fatigue variable in the patient with Gaucher disease.	5	58.2%	Undetermined[a]
21. Scales for patients with ADHD such as the DSM-IV criteria enable to estimate the concentration variable in the patient with Gaucher disease.	5	58.2%	Undetermined[a]
22. The Toulouse-Piéron test enables to estimate the concentration variable in the patient with Gaucher disease.	6	58.2%	Undetermined[a]
23. The 6-minute walk test (6MWT) enables to estimate the fatigue variable in the patient with Gaucher disease.	5	54.6%	Undetermined[a]
24. Geriatric assessment scales enable to estimate the concentration variable in the patient with Gaucher disease.	3	54.6%	Undetermined[a]
25. The MPN-10 quality of life scale in Polycythemia Vera enables to estimate the concentration variable in the patient with Gaucher disease.	5	49.1%	Undetermined[a]
26. Folstein's Mini-Mental State Examination (MMSE) test enables to estimate the concentration variable in the patient with Gaucher disease.	5	43.6%	Undetermined[a]
27. The Pfeiffer's questionnaire (Short Portable Mental Status Questionnaire, SPMSQ) enables to estimate the concentration variable in the patient with Gaucher disease.	5	38.2%	Undetermined[a]

[a] Items that underwent a second round of vote.
FACIT: Functional Assessment of Chronic Illness Therapy; SF-36: Short Form Health Survey.

Regarding concerns about performance at work or at school, panelists recommended asking GD patients, or parents or guardians of children with GD, about the frequency of absenteeism from work or school due to disease-specific symptoms or treatment, using a 5-step analog scale to measure absenteeism in the last month (78.2%) (Table 3). Questions on professional limitations and anxiety about job loss due to GD were recommended, with 5-step analog scales for measurement (Table 3). The Work Productivity and Activity Impairment Questionnaire (WPAI) was suggested for assessing GD's impact on work (70.9%). Panelists agreed on asking about the influence of GD-specific symptoms on work or school tasks and recommended a 5-step analog scale for measurement (81.8%).

Care experience

In the final section, consensus was reached for 33 out of 39 items. Panelists recommended asking GD patients about the care provided by healthcare professionals throughout the care process

Table 3
Patient reported outcomes on aspects of daily life.

Item	Median (1: disagree – 9: agree)	% of consensus	Result
1. Parents or guardians of patients with Gaucher disease should be asked about the frequency with which the symptoms of the disease have led to absenteeism from school.	8	92.7%	Agreement
2. Parents or guardians of patients with Gaucher disease should be asked about the frequency with which factors associated with the treatment have caused absenteeism from school.	8	92.7%	Agreement
3. Patients with Gaucher disease should be asked about the frequency with which factors associated with the treatment have caused absenteeism from work.	8	90.9%	Agreement
4. Patients with Gaucher disease should be asked about the degree of concern they feel about the possible transmission of the disease to their offspring.	8	87.3%	Agreement
5. Patients with Gaucher disease should be asked about the frequency with which the symptoms of the disease have led to absenteeism from work.	8	87.3%	Agreement
6. To measure the frequency of sleep and rest impairment in the patient with Gaucher disease in the last month, a 5-step analogue scale should be used (e.g.: "1: never", "2: rarely", "3: occasionally", "4: frequently", "5: always").	8	85.5%	Agreement
7. To assess the impact of Gaucher disease in the patient's social life, we should ask about the extent to which this affects the patient's circle of relationships.	8	85.5%	Agreement
8. To assess the level of anxiety about Gaucher disease in patients, patients should be asked about their level of concern about the future course of the disease.	8	83.6%	Agreement
9. Patients with Gaucher disease should be asked the extent to which the disease affects their decision to have offspring.	8	83.6%	Agreement
10. Patients with Gaucher disease should be asked about the extent to which the symptoms of the disease have affected the performance of the tasks required in their work activity.	8	83.6%	Agreement
11. Patients with Gaucher disease should be asked about how often they need periods of rest during daily activity.	8	81.8%	Agreement
12. To measure the level of anxiety generated by Gaucher disease in patients, a 5-step analogue scale should be used (e.g.: "1: none", "2: little", "3: some", "4: quite a lot", "5: a lot").	8	81.8%	Agreement
13. Patients with Gaucher disease should be asked about the extent to which their physical condition may place limitations on their ability to undertake pregnancy, childbirth and breastfeeding.	8	81.8%	Agreement
14. Parents or guardians of patients with Gaucher disease should be asked about the extent to which the disease-specific symptoms have affected their school performance.	8	81.8%	Agreement
15. To measure the degree to which the symptoms of the disease have affected the patients' school/work performance, a 5-step analogue scale should be used (e.g.: "1: none", "2: little", "3: some", "4: quite a lot", "5: a lot").	8	81.8%	Agreement
16. Patients with Gaucher disease should be asked about how often they have problems maintaining continuous sleep due to their disease.	8	78.2%	Agreement
17. Patients with Gaucher disease should be asked about their level of anxiety about the occurrence of possible complications.	8	78.2%	Agreement
18. The Hospital Anxiety and Depression Scale (HADS) allows for an estimation of the level of anxiety generated by the disease in patients with Gaucher disease.	7	78.2%	Agreement[a]
19. To measure the impact of Gaucher disease in the patient's social life, a 5-step analogue scale should be used (e.g.: "1: none", "2: a little", "3: some", "4: quite a lot", "5: a lot").	8	78.2%	Agreement
20. To measure the frequency with which the symptomatology or treatment of Gaucher disease has caused absenteeism from work or school in the last month, a 5-step analogue scale should be used (e.g.: "1: never", "2: rarely", "3: occasionally", "4: frequently", "5: always").	8	78.2%	Agreement
21. Patients with Gaucher disease should be asked about how often they have problems falling asleep due to their disease.	8	76.4%	Agreement
22. To measure the degree to which Gaucher disease conditions decisions to have offspring and the degree to which the patient's physical condition can pose limitations to pregnancy, childbirth and breastfeeding, a 5-step analogue scale should be used (e.g.: "1: none", "2: little", "3: some", "4: quite a lot", "5: a lot").	8	76.4%	Agreement
23. The patient with Gaucher disease should be asked about the level of support they have in their family and social environment with regard to their disease.	8	76.4%	Agreement
24. To measure the degree to which Gaucher disease affects relationships with a partner, and the support perceived by the patient in the family and social environment and patient associations, a 5-step analogue scale should be used (e.g.: "1: none", "2: a little", "3: some", "4: quite a lot", "5: a lot").	8	74.6%	Agreement
25. Patients with Gaucher disease should be asked about the extent to which the disease has limited their professional possibilities (e.g.: employment contracts, promotions, etc.).	7	74.6%	Agreement
26. To measure the degree of concern or guilt generated by the possibility of transmission of Gaucher disease to offspring, a 5-step analogue scale should be used (e.g.: "1: none", "2: little", "3: some", "4: quite a lot", "5: a lot").	8	72.7%	Agreement
27. The patient with Gaucher disease should be asked about the level of support they have in patient associations with regard to their disease.	7	72.7%	Agreement
28. To measure the degree to which Gaucher disease has limited the patient's professional possibilities, a 5-step analogue scale should be used. (e.g.: "1: none", "2: little", "3: some", "4: quite a lot", "5: a lot").	7	72.7%	Agreement
29. The Hamilton Anxiety Scale allows for an estimation of the level of anxiety generated by the disease in patients with Gaucher disease.	7	70.9%	Agreement[a]
30. The HADS allows for an estimation of the degree of depression generated by the disease in patients with Gaucher disease.	7	70.9%	Agreement[a]
31. Patients with Gaucher disease should be asked about the extent to which their mental or emotional state may place limitations on their ability to undertake pregnancy, childbirth and breastfeeding.	8	70.9%	Agreement

Table 3
(*Continued*)

Item	Median (1: disagree – 9: agree)	% of consensus	Result
32. The patient with Gaucher disease should be asked about how their disease affects their sexual relationships or relationships with their partner.	7	70.9%	Agreement
33. The Work Productivity and Activity Impairment (WPAI) Questionnaire enables to measure the impact of Gaucher disease on the work or professional activity of patients.	7	70.9%	Agreement
34. The Pittsburg Sleep Quality Index (PSQI) allows for an estimation of sleep-related problems in patients with Gaucher disease.	7	69.1%	Agreement
35. Patients with Gaucher disease should be asked how anxious they are about the possibility of losing their job because of the disease.	7	69.1%	Agreement
36. To measure the level of anxiety generated by the possibility of the patient losing their job because of the disease, we should use a 5-step analogue scale (e.g.: "1: none", "2: little", "3: some", "4: quite a lot", "5: a lot").	7	69.1%	Agreement
37. Patients with Gaucher disease should be asked about the degree of guilt they feel about the possible transmission of the disease to their offspring.	7	54.6%	Undetermined[a]

[a] Items that underwent a second round of vote.

(74.6%), and the degree to which patients preferences were taken into account when making clinical and therapeutic decisions (76.4%) (Table 4).

Regarding changes in healthcare professionals, panelists recommended inquiring GD patients about the extent to which changes in the healthcare professionals impact the disease management (67.3%) and the quality of care (67.3%), and use a 5-step analog scale to measure it (78.2%), but did not reach consensus on asking GD patients about the frequency of change of health professionals (Table 4).

Panelists recommended asking GD patients about their perception of the degree of coordination between healthcare professionals (76.4%) and commitment to reduce hospital visits (72.7%); however, no consensus was reached on whether the Person-Centered Coordinated Care Questionnaire (P3CEQ) could assess professional coordination from a patient's perspective in GD management (Table 4).

Panelists agreed on asking about the appropriate age for transitioning from pediatric to adult care, with an age range of 12–18 years recommended (Table 4). They also recommended questions on the transition process's continuity and transfer of information quality, assessing it with a 5-step analog scale. There was consensus on asking whether patients had experienced any treatment interruptions during transition, using a two-response options question ("yes" or "no"). There was no consensus on inquiring about the similarity of care in pediatric and adult settings (Table 4).

Panelists agreed on asking GD patients about their perceptions of healthcare professionals' language use (74.6%); ease of access to healthcare professionals (85.5%); access to psychological support, support and guidance (87.3%); satisfaction with the treatment received (94.6%), and the conditions of hospital administration of the treatment (83.6%). In addition, inquiries about satisfaction with genetic counseling (89.1%); and on the level of satisfaction with the attention received from the hospital pharmacy regarding treatment-related doubts (92.7%) were recommended. However, there was no consensus about satisfaction on the amount of time spent in the physician's office (65.5%), neither on asking about the effect of sharing waiting and treatment administration areas with other types of patients (63.6%) (Table 4).

Panelists recommended asking GD patients about the frequency with which the hospital offered them facilities to reconcile their daily and professional activities with consultations and treatment administration, measuring this with a 5-step analog scale (Table 4).

Regarding treatment satisfaction, consensus was reached to ask GD patients about the effectiveness of the treatment on symptoms, and the impact of adverse effects of treatment on their quality of life using a 5-step analog scale (Table 4). The TSQM scale (Treatment Satisfaction Questionnaire for Medication) was recommended for assessment of treatment satisfaction in GD patients (Table 4).

Finally, experts agreed to include an open field for patient opinions on care process improvements in the PROMs and PREMs questionnaire for GD patients.

Discussion

In this study a consensus on recommendations for PROMs and PREMs in GD management from a Delphi panel of nurses and physicians experienced on GD care in Spain is presented.

It is well-described that adults with GD1 experience poorer HRQoL than healthy counterparts[5,16]; however, no consensus on the use of particular QoL instruments for GD patients exists. Currently, QoL measurements in GD patients are generally performed through generic instruments, such as SF-35 or EQ-5D.[12] Nevertheless, these instruments have not been validated for use in patients with GD. As in many other rare diseases, the small number of patients, the high geographical dispersion and the cost of developing new tools hampers the development of rare-disease-specific PROMs and PREMs.[17] Even so, it has recently been developed an specific GD1-PROM questionnaire, with a 24-item version for routine clinical practice (rmGD-1 PROM) and a 17-item version for clinical trials (ctGD-1 PROM).[13]

PROMs and PREMs are considered essential tools for a comprehensive evaluation of disease impact and treatment efficacy; however, these instruments have been little researched in rare diseases such as GD. This first GD-1 PROM questionnaire was developed in three countries: US, France, and Israel, with three language versions available: Hebrew, Arabic, and English.[13] Given that biological and cultural factors such as phenotype, anthropological perception of disease, educational level or language may have an influence on PROMs and PREMs; this cannot be extrapolated to other settings.

In the present study it was necessary to identify social, psychological, emotional, physical, and cognitive factors affecting performance of daily activities and impacting on self-perceived well-being and healthcare process. The outcomes reaching more consensus where those regarding impact on work/school, satisfaction with treatment and limitations in daily activities due to fatigue. Although fatigue is a non-specific disease symptom, is commonly reported by GD patients, significantly interfering in physical and cognitive functioning (school, job and social activities).[16] GD negatively impacts on work, career, school, and recreational activities in both children and adults.[16,18] Besides, moderate to severe psychological complications are frequently reported in GD patients.[19] Thus, experts agreed on considering items regarding psychological distress and cognitive functioning with wide consensus.

Table 4
Care experience.

Item	Median (1: disagree – 9: agree)	% of consensus	Result
38. The patient with Gaucher disease should be asked about the efficacy of the treatment in relieving their symptoms.	9	98.2%	Agreement
39. The patient with Gaucher disease should be asked about the extent to which the adverse effects of treatment affect their quality of life.	9	98.2%	Agreement
40. Patients with Gaucher disease should be asked about their overall satisfaction with the treatment received (symptom relief, side effects, improvement in quality of life).	9	94.6%	Agreement
41. The patient with Gaucher disease should be asked about their degree of satisfaction with the attention received from the hospital pharmacy with regard to doubts about the treatment.	8	92.7%	Agreement
42. The PROMs and PREMs questionnaire of the patient with Gaucher disease should include an open field to collect the patient's opinion on possible improvements in the care process.	9	92.7%	Agreement
43. The patient with Gaucher disease should be asked whether the transition between care centers has resulted in a temporary interruption of treatment.	8	89.1%	Agreement
44. The patient with Gaucher disease should be asked about their degree of satisfaction with the genetic counselling provided by the professionals.	8	89.1%	Agreement
45. To measure the degree of coordination of the different healthcare professionals, we should use a 5-step analogue scale (e.g.: "1: none", "2: little", "3: some", "4: quite a lot", "5: a lot").	8	87.3%	Agreement[a]
46. Patients with Gaucher disease should be asked about the ease of access to guidance, psychological support and counselling.	8	87.3%	Agreement
47. To measure the efficacy in symptom relief and the impact of adverse effects on the patient's quality of life, a 5-step analogue scale should be used (e.g.: "1: none", "2: a little", "3: some", "4: quite a lot", "5: a lot").	8	87.3%	Agreement
48. To measure the degree of satisfaction of the patient with Gaucher disease with the continuity of care and handover of information in the transition from pediatric to adult care, a 5-step analogue scale should be used (e.g.: "1: none", "2: little", "3: some", "4: quite a lot", "5: a lot").	7	85.5%	Agreement[a]
49. Patients with Gaucher disease should be asked about the ease of access to the professionals who care for them in the hospital (doctors, nurses, hospital pharmacists, etc.).	8	85.5%	Agreement
50. The patient with Gaucher disease should be asked how often the hospital has provided facilities to reconcile their daily professional activities with treatment consultations and administration.	8	85.5%	Agreement
51. The Treatment Satisfaction Questionnaire for Medication (TSQM) enables to estimate the degree of satisfaction with treatment in the patient with Gaucher disease.	7	85.5%	Agreement
52. In order to establish whether the transition from pediatric to adult care has resulted in a temporary interruption of treatment, the options of yes and no should be considered as mutually exclusive.	8	83.6%	Agreement[a]
53. Patients with Gaucher disease should be asked about their degree of satisfaction with the conditions of the hospital administration of the treatment (sufficient time range, adequate administration space, waiting time, etc.).	8	83.6%	Agreement
54. The patient with Gaucher disease should be asked whether the transition from pediatric to adult care has resulted in a temporary interruption of treatment.	8	80.0%	Agreement
55. To measure the extent to which changes in the healthcare professionals impact on the quality of care for patients with Gaucher disease, we should use a 5-step analogue scale (e.g.: "1: none", "2: a little", "3: some", "4: quite a lot", "5: a lot").	7	78.2%	Agreement[a]
56. The patient with Gaucher disease should be asked if they felt accompanied and had good continuity of care during the transition from pediatric to adult care.	8	78.2%	Agreement
57. In order to establish whether the transition between care centers has resulted in a temporary interruption of treatment, the options of yes and no should be considered as mutually exclusive.	8	78.2%	Agreement[a]
58. Patients with Gaucher disease should be asked about their perception of the degree of coordination between the different healthcare professionals providing their care.	8	76.4%	Agreement
59. Patients with Gaucher disease should be asked about the degree to which their healthcare professionals pay attention to their preferences when making clinical and therapeutic decisions.	8	76.4%	Agreement
60. To measure the frequency with which the hospital provides facilities to reconcile the patient's daily and professional activities with treatment consultations and administration, a 5-step analogue scale should be used (e.g.: "1: never", "2: rarely", "3: occasionally", "4: frequently", "5: always").	8	76.4%	Agreement
61. Patients with Gaucher disease should be asked about their perception of the degree of care provided by healthcare professionals throughout the care process.	8	74.6%	Agreement
62. Patients with Gaucher disease should be asked whether they consider the language used by professionals in the medical practice to be appropriate.	8	74.6%	Agreement
63. Patients with Gaucher disease should be asked about their perception of the degree of commitment of their healthcare professionals to coordinating the performance of tests and thus reducing hospital visits.	7	72.7%	Agreement
64. To measure the age at which the transition from pediatric to adult care would be most appropriate, age ranges between 12 and 18 years should be used (e.g.: 12–14 years old, 15–17 years old).	7	72.7%	Agreement
65. The patient with Gaucher disease should be asked whether they consider that the transfer of information between professionals from pediatric to adult care has been of good quality.	8	72.7%	Agreement
66. A 5-step analogue rating scale should be used to measure the patient's experience of the clinical environment and treatments (e.g.: "1: none", "2: a little", "3: some", "4: quite a lot", "5: a lot").	7	70.9%	Agreement[a]
67. To measure the frequency of changes in the healthcare professionals caring for the Gaucher patients, a 5-step analogue scale should be used (e.g.: "1: none", "2: little", "3: some", "4: quite a lot", "5: a lot").	7	69.1%	Agreement[a]
68. The patient with Gaucher disease should be asked about the age that, from their personal experience, would be the most appropriate for the transition from pediatric to adult care.	7	69.1%	Agreement[a]
69. Patients with Gaucher disease should be asked about the extent to which changes in the healthcare professionals who care for them impact on the management of their disease.	8	67.3%	Agreement

Table 4
(*Continued*)

Item	Median (1: disagree – 9: agree)	% of consensus	Result
70. Questions should be asked about the extent to which changes in the healthcare professionals impact on the quality of care for patients with Gaucher disease.	7	67.3%	Agreement
71. Patients with Gaucher disease should be asked whether they consider the time spent on their care in the medical practice to be appropriate.	7	65.5%	Undetermined[a]
72. Patients with Gaucher disease should be asked about the frequency of changes in the healthcare professional attending them at the different levels of care (e.g.: specialists, primary care, nursing, etc.).	7	63.6%	Undetermined[a]
73. The Person-Centered Coordinated Care Experience Questionnaire (P3CEQ) allows for the coordination of the different healthcare professionals in the management of Gaucher disease to be assessed from a patient-oriented perspective.	7	63.6%	Undetermined[a]
74. The patient with Gaucher disease should be asked about the degree to which they are affected by sharing treatment waiting and administration areas with other types of patient in the day hospital (e.g.: cancer patients, chronic illnesses, degenerative diseases, etc.).	7	63.6%	Undetermined[a]
75. In order to measure comparatively the care received by the Gaucher patient in adult and pediatric care, a 5-step value scale should be used (e.g.: 1: "much worse, 2: "worse", 3: "the same", 4: "better", 5: "much better").	7	58.2%	Undetermined[a]
76. The patient with Gaucher disease should be asked whether they consider that the care received in adults is similar in dedication and time to that received in pediatric care.	7	54.6%	Undetermined[a]

[a] Items that underwent a second round of vote.

Apart from information on QoL, PROMs and PREMs also provide data to support appropriate decision-making regarding treatment administration (ERT or SRT). Timely treatment administration may prevent or reverse diagnostic delays or complications such as vascular necrosis, serious bleeding or bone pain, among others.[20] Moreover, PROMs and PREMs also provide information for analyzing whether treatment is necessary in asymptomatic cases. Revel-Vilk et al. showed that asymptomatic or mildly affected untreated GD1 patients have good functional status and HRQoL using GD-specific PROMs; thus, not all patients with GD1 would require disease-specific therapy according to self-reported experiences.[21] Finally, PROMs and PREMs may also help on choosing the best treatment (SRT or ERT) for each patient. Wagner et al. reported a range of behaviors toward SRT, and that one particular treatment may not be ideal for all GD patients, because it depends on individual perceptions of convenience, invasiveness, or side effects, as per PROMs results.[22] Even so, pharmacological treatment has demonstrated a positive impact on patients' QoL, both children and adults.[16,23–26] Finally, it must be taken into account that this is a hypothesis or an option to be included as another factor in the decision-making process; however, for the moment, it cannot be considered a factor to be communicated to the authorities until the instrument is validated.

The questions included in the present survey are based on extensive clinical expertise of all members involved in the study: project coordinators, SC, moderators, panelists and expert patients. Furthermore, the multi-step design of the study, with participative talks and meetings allowed us identifying important issues from both healthcare experts and GD patients' point of view. GD is a disease with multiple clinical manifestations, diverse initial presentation, heterogeneous disease course, complications, exacerbations, and affecting people from all ages. Thus, translating this variability into PROMs and PREMs is a challenging undertaking. Moreover, the broad consensus reached is the main strength of this study.

This study has some limitations. It should be recognized that the results represent the opinion of experts, and conclusions do not derive from prospective or retrospective data. Nevertheless, a sample of answers from 56 experts in GD gives good reliability to these results. It has to be noted that panelists are healthcare professionals practicing in Spain and results may not be extrapolated to other countries with different healthcare settings.

Conclusion

Pending the development or validation of questionnaires in our setting; here, we present a prospection for further developing a thorough Spanish questionnaire for GD. The results of this expert consensus are the basis for developing GD-specific PROMs and PREMs tool in a future phase. Properly developed and validated tools would improve not only clinical outcomes, but also would allow establishing personalized therapeutic approaches and follow-up, thus improving GD management.

Ethical considerations

Not applicable.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest

PG reports personal fees for lectures, advisory boards and research project from the following pharmaceuticals: Alexion, Amicus, Chiesi, Pfizer, Sanofi-Genzyme, and Takeda. The financial contributions are dedicated to research on Gaucher and other lysosomal diseases through the Spanish Foundation for the Study and Therapeutics of Gaucher and other Lysosomal Diseases (FEETEG).

MM reports personal fees for consultancy, support for research projects and transport for conference attendance from the following companies: Genzyme Corporation, Alnylam and Takeda.

EM reports personal fees for lectures and consultancy from the following companies: Pfizer, Sanofi-Genzyme, Novartis, BMS, GSK, Blueprint, Incyte, Amgen.

DI reports personal fees from Sanofi genzyme.

MC, PCA, EG-C, SL and MPVC report no conflicts of interest.

Acknowledgements

The authors wish to thank Sanofi and Luzan5 for their collaboration with the logistics of the meetings and the assistance with the

medical writing. The authors wish to thank all the panelists who participated in the Delphi survey.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.medcli.2024.06.006.

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