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Construction of a Quality of Life Questionnaire for slowly progressive neuromuscular disease

Antoine Dany[1,2,10] · Coralie Barbe[1,2] · Amandine Rapin[1,2] · Christian Réveillère[3] · Jean-Benoit Hardouin[4] · Isabella Morrone[1,2] · Aurore Wolak-Thierry[1,2] · Moustapha Dramé[1,2] · Arnaud Calmus[1,2] · Sabrina Sacconi[5] · Guillaume Bassez[3] · Vincent Tiffreau[6] · Isabelle Richard[7] · Benjamin Gallais[8] · Hélène Prigent[9] · Redha Taiar[1] · Damien Jolly[1,2] · Jean-Luc Novella[1,2] · François Constant Boyer[1,2,10]

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Abstract
Purpose To build a questionnaire to assess health-related quality of life (HRQL) in patients suffering from slowly progressive neuromuscular disease (NMD) using item response theory (IRT).
Methods A pool of 64 items and a validated questionnaire (WHOQOL-BREF) were administered to 159 patients recruited in eight NMD referral centers. Exploratory statistical analysis included methods derived from both IRT and classical test theory.
Results We constructed a questionnaire named QoL–NMD which is composed of two general items and 24 items classified in three domains: (1) "Impact of Physical Symptoms," (2) "Self-perception" and (3) "Activities and Social Participation." Each domain has good psychometric properties (Cronbach's alpha > 0.77, test–retest ICC > 0.81, Loevinger's $H > 0.41$) and meets IRT assumptions. Comparison with the WHOQOL-BREF enabled assessing similarities and discrepancies with a generic questionnaire.
Conclusion This study enabled the development of a new HRQL questionnaire specifically designed for slowly progressive NMD patients. The QoL–NMD is short enough to be used in clinical practice (26 items). The next steps will be to validate QoL–NMD by re-assessing psychometrics in an independent sample of patients and calibrate the IRT scoring system.

Keywords Item response theory · Neuromuscular disease · Outcome research · Patient outcome assessment · Quality of life

Introduction

Slowly progressive neuromuscular diseases (NMDs) involve a progressive loss of physical condition, ranging from difficulty walking long distances to a total inability to perform essential activities of daily living (e.g., walking, eating, body washing). The progression rate and severity of these deteriorations vary significantly according to the NMD. Since therapeutic options are limited for NMD patients, long-term preservation of health-related quality of life (HRQL) is one of the main goals of medical care. Thus, there is a need to measure it regularly and scrutinize its evolution [1, 2]. Prominent public organizations such as the European Medicines Agency and the Food and Drug Administration have made HRQL measurement a mandatory criterion in the assessment of new treatments [3, 4]. The use of generic tools to assess HRQL (e.g., SF36 and NHP)

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✉ Antoine Dany
antoine.dany@univ-reims.fr

1 University of Reims Champagne-Ardenne, Reims, France
2 Reims University Hospital, Reims, France
3 Henri Mondor Hospital, Créteil, France
4 University of Nantes, Nantes, France
5 Nice University Hospital, Nice, France
6 Swynghedauw Hospital, Lille, France
7 Angers University Hospital, Angers, France
8 Myology Institute, Paris, France
9 Raymond-Poincaré Hospital, Garches, France
10 Service de Médecine Physique et Réadaptation, Centre de Référence des Maladies Neuromusculaires, Hôpital Sébastopol, CHU de Reims, 48, rue de Sébastopol, 51092 Reims Cedex, France

among these patients does not enable specific aspects of life potentially impaired by NMD to be assessed and may include aspects of life that are irrelevant to NMD patients [5, 6]. As a result, generic HRQL questionnaires are unable to differentiate the wide range of HRQL levels among slowly progressive NMD patients. These tools are, however, useful to compare patients suffering from different pathologies or who have more than one disease or medical condition [7]. Thus, any study on HRQL in patients suffering solely from slowly progressive NMD would benefit from the availability of a specific questionnaire.

To date, there are few HRQL measurement tools specifically designed for patients suffering from slowly progressive NMD. In Sweden, Ahlstrom et al. were the first to work on this subject; they developed the Quality of Life Profile Questionnaire [8, 9], but it has never been formally validated. In 2007, Vincent et al. [10] validated a questionnaire designed to assess HRQL in patients suffering from acquired and genetic NMD, named Individualized Neuromuscular Quality of Life Questionnaire (INQoL). This questionnaire is composed of 45 items and was developed using only classical test theory (CTT).

The development of a questionnaire using advanced statistical methods derived from item response theory (IRT) enables scales to be calibrated. The measures generated by a calibrated scale are very useful in clinical assessment because they can be directly compared on a common metric (i.e., a unit of measurement can be associated). The development of a specific questionnaire using both CTT and advanced statistical methods derived from IRT was initiated by the French Muscular Dystrophy Association.

In a previous study, Boyer et al. [11] developed a pool of items following Question Appraisal System-1999 (QAS-99) guidelines [12], which was short enough to be conveniently administered to patients (64 items). The impact of NMD on HRQL was explored by interviewing patients using the focus group methodology [13]. Verbatim generated by the focus groups was used to develop a pool of items in the framework of the International Classification of Functioning, Disability and Health model [14]. The experts who developed the pool of items included both patients and experts, in order to explore a wide range of viewpoints. They reached consensus using the Delphi method [15]. We will refer to this stage of development of the questionnaire as the "qualitative stage." Since HRQL is a multi-dimensional concept, items were classified in four predefined domains on the basis of the literature and expert knowledge. These initial domains were named (1) "Impact of Physical Symptoms," (2) "Self-perception," (3) "Environment, Accessibility, Quality of Care" and (4) "Activities and Social Participation." Each item included 4–5 ordered response categories (Likert scale) giving a wide view of the degree of impact of NMD on the item content.

The purpose of this article is to describe the construction of the questionnaire from the pool of items. The questionnaire is named "Quality of Life in Neuromuscular Diseases" (QoL–NMD). The QoL–NMD will be freely accessible, and although its development was conducted in French, a translation with transcultural adaptation into English is given in Appendix 1 (Online Resource 1).

Methods

Participants

The pool of 64 items developed during the qualitative stage and the WHOQOL-BREF [16] were administered to patients recruited in eight NMD referral centers. All patients gave written consent. The Institutional Review Board of Reims approved the ethical aspects of the study. Eligible patients were to be suffering from a genetic neuromuscular disease, confirmed by molecular biology, complete genetic study or indisputable clinical and paraclinical arguments. The disease was a sole or predominant motor deficiency, and there was no symmetrical sensory deficiency nor auto-immune disease. Patients were also to be older than 18 years and were excluded if they could not read or speak fluently. The ability of patients to perform activities of daily living was evaluated using the Barthel index [17].

Data analysis

The items had been assigned to predefined HRQL domains by the expert group on the basis of medical and psychological arguments to ensure content validity. To be valid, IRT requires three strong assumptions that were to be assessed in each QoL–NMD domain independently. These assumptions are (1) unidimensionality (2) local independence and (3) monotonicity.

Unidimensionality implies that patient's answers to items are determined by a single latent trait. In our case, the latent trait corresponded to a measure of the impact of NMD on a HRQL domain. Monotonicity implies that the probability of choosing a response indicative of a lower impact of NMD does not decreases as patient HRQL increases. Local independence implies that, after adjusting to the latent trait value, there is no residual correlation between item responses. Local dependence can be observed, for example, when two items are very similar and behave as if the same question has been asked twice.

The nonparametric IRT model [18] verifies unidimensionality, local dependence and monotonicity if all items have a high scalability coefficient (criterion: $H_i > 0.30$). The analysis was guided by Mokken's item selection procedure which is described elsewhere [19]. Several values

were used for the lower bound c (from 0.2 to 0.4 by 0.01) to assess results stability. Unidimensionality was re-assessed using a principal component analysis on polychoric correlations, since the combined use of the two methods has been found beneficial [20]. When unidimensionality is investigated by principal component analysis, several rules of thumb exist to make the decision. We chose to use parallel analysis because there is a growing consensus that it is the most efficient method to determine how many components should be taken into account [21].

Reliability and validity of each domain were evaluated. Internal consistency was evaluated using Cronbach's alpha [22]. Cronbach's alpha is high if there is good item-interrelatedness and/or if the number of items is large (criterion: Cronbach's alpha > 0.70). Test–retest reliability evaluates the repeatability of a questionnaire result administered to the same patient in similar conditions. It measures the agreement between two time-spaced administrations of the same test using the intraclass correlation coefficient (criterion: ICC > 0.80). The period of time between the first and the second administration of the questionnaire should be short enough for the patient's health condition not to have evolved and long enough for the patient not to remember the questionnaire. In the case of slowly progressive NMD, a period of time of 1 month $\pm$ 7 days was chosen. Spearman's rank correlation coefficients between QoL–NMD and WHOQOL-BREF domain scores were computed to investigate similarities and discrepancies with a generic HRQL questionnaire.

Statistical software

Statistical analyses were performed using programming language R (R core development team [23]). The non-parametric IRT model and the Mokken's item selection procedure algorithm were applied using the *mokken* package [24]. We used the *pcaPA* package [25] to perform the principal component analysis and parallel analysis. Cronbach's alpha, multi-trait multi-method analysis and ICC were computed using the *psy* package [26].

Results

Clinical characteristics of the patients are presented in Table 1, a flow chart resuming item selection is presented in Fig. 1, psychometric properties are summarized in Table 2, and results from the multi-trait multi-method analysis are presented in Table 3.

Participants

A total of 159 patients were included. The ages ranged from 18 to 80 years. The majority of patients were men (58 %). Almost all patients reached at least high school (95 %), but only 43 % went to university. There were approximately as many married patients (43 %) as single patients (42 %).

Table 1 Clinical evaluation of patients

Characteristics	Value
Number of patients	159
Age (years)	
Mean (SD)	43 (14.9)
Range	18–80
Diagnosis, n (%)	
Myotonic dystrophy type 1	44 (27.7)
Dystrophinopathies	29 (18.2)
Facioscapulohumeral muscular dystrophy	26 (16.4)
Limb-girdle muscular dystrophy	24 (15.1)
Spinal muscular atrophy	14 (8.8)
Congenital muscular dystrophies	8 (5.0)
Metabolic myopathies	7 (4.4)
Congenital myopathies	5 (3.1)
Other muscular dystrophies	2 (1.3)
Barthel index, n (%)	
[0, 4]	12 (7.5)
[5, 9]	31 (19.5)
[10, 14]	23 (14.5)
[15, 19]	45 (28.3)
[20]	47 (29.6)
Omitted	1 (0.6)
Reported age when symptoms first appeared (years)	
Mean (SD)	20 (16.3)
Range	0–61
Walking status, n (%)	
Came to consultation walking	92 (57.9)
Did not come to consultation walking	67 (42.1)
Mechanical ventilation, n (%)	
None	118 (74.2)
Noninvasive	33 (20.8)
Invasive	8 (5.0)

The Barthel index measures performance in activities of daily living (a high score reflects good performance)

The clinical assessment of patients is summarized in Table 1. Patient pathologies included various slowly progressive NMDs among which the most frequent were myotonic dystrophy type 1 (Steinert disease), facioscapulohumeral muscular dystrophy and dystrophinopathies (Becker muscular dystrophy and Duchenne muscular dystrophy). Almost one-third of the patients were completely autonomous, with a Barthel index of 20, whereas less than 10 % of patients had to rely heavily on a third party with a Barthel index below 5. The mean age at NMD

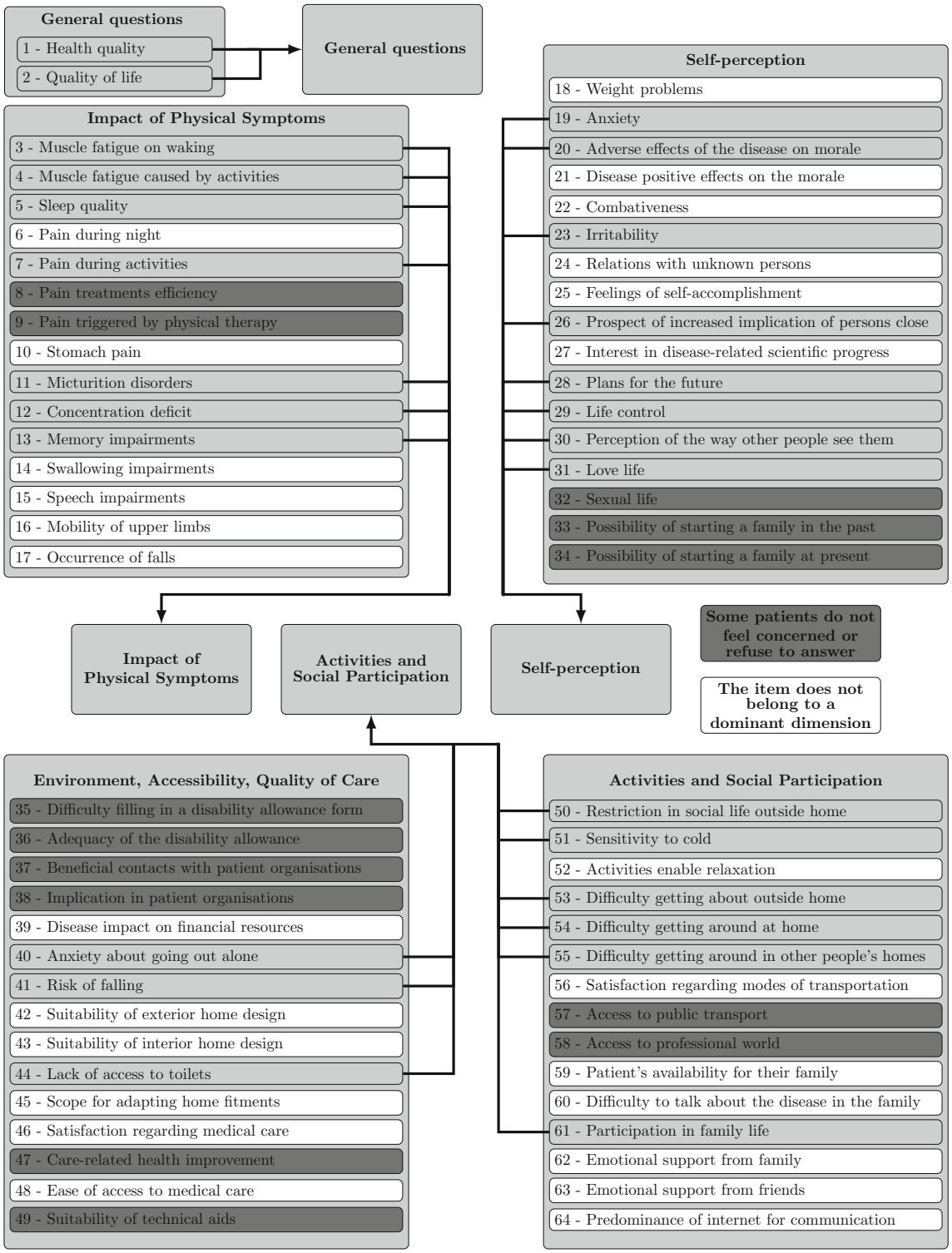

Fig. 1 Description of the item selection process. Dominant dimensions were determined using a Mokken scale analysis with lower bound $c = 0.3$

onset was 20 (SD = 16). The majority of patients came to the consultation walking (58 %). There were 21 % of the patients under noninvasive mechanical ventilation and 5 % under invasive mechanical ventilation. Our data contained few missing answers, as 55 items out of 64 had less than 2.5 % missing answers.

Table 2 Dimensionality assessment and internal consistency of each domain

Domain	Item	Item scalability coefficient	Domain psychometric properties
Impact of Physical Symptoms	Muscle fatigue on waking	0.462 ± 0.047	Scale scalability coefficient: 0.41 ± 0.05
	Muscle fatigue caused by activities	0.459 ± 0.048	
	Sleep quality	0.350 ± 0.059	
	Pain during activities	0.441 ± 0.056	Cronbach's $\alpha = 0.77$ ($N = 154$)
	Micturition disorders	0.316 ± 0.065	
	Concentration deficit	0.457 ± 0.058	Test–retest reliability: ICC = 0.81 ($N = 60$)
	Memory impairments	0.338 ± 0.073	
Self-perception	Anxiety	0.439 ± 0.052	Scale scalability coefficient: 0.45 ± 0.04
	Morale	0.536 ± 0.043	
	Irritability	0.375 ± 0.063	
	Prospect of increasing implication of persons close	0.443 ± 0.055	Cronbach's $\alpha = 0.83$ ($N = 154$)
	Plans for the future	0.468 ± 0.047	
	Life control	0.463 ± 0.048	
	Perception of the way other people see them	0.465 ± 0.046	Test–retest reliability ICC = 0.84 ($N = 60$)
	Love life	0.376 ± 0.051	
Activities and Social Participation	Anxiety about going out alone	0.456 ± 0.042	Scale scalability coefficient: 0.44 ± 0.04
	Risk of falling	0.486 ± 0.042	
	Lack of access to toilets	0.382 ± 0.050	
	Restriction in social life outside home	0.418 ± 0.052	Cronbach's $\alpha = 0.85$ ($N = 156$)
	Sensitivity to cold	0.469 ± 0.045	
	Difficulty getting about outside home	0.337 ± 0.060	
	Difficulty getting around at home	0.470 ± 0.043	Test–retest reliability ICC = 0.93 ($N = 60$)
	Difficulty getting around in other people's homes	0.455 ± 0.045	
	Participation in family life	0.454 ± 0.042	

ICC intraclass correlation coefficient. *N* number of patients for the analysis (if less than 159)

Impact of Physical Symptoms

Two items with high percentages of missing answers (14.5 and 6.3 %) were removed. These items investigated pain treatment efficiency and pain triggered by physical therapy, respectively.

The item investigating micturition disorders ("Have you been troubled by a frequent need to urinate because of your neuromuscular disease?") was modified because the wording was confusing: There was a notion of frequency in both the question and the response options. To solve this problem, the expert group decided to modify the response options. The item was dichotomized as follows: "Yes" ("Often" and "Very often") and "No" ("Sometimes" and "Never").

The response "Once a day" to the item investigating pain during activities ("How often have your daily activities been restricted because of pain linked to your neuromuscular disease?") was underused (7 % of the answers) in comparison with other responses "Never"(27 %), "Sometimes, but not every day"(48 %), "Several times a day"(18 %). This probably stems from the fact that the response "Once a day" is a very precise frequency, whereas the other response options correspond either to the norm ("Never") or to an imprecise frequency ("Sometimes, but not every day" and "Several times a day"). The expert group decided to combine the responses "Once a day" and "Several times a day" to create a new response option termed "Every day."

The multi-trait multi-method analysis (Table 3) showed that the item investigating sleep quality ("Given your neuromuscular disease, how have you been sleeping?") was comparably correlated with the domain "Self-

Table 3 Spearman's Item–Scale correlations

Item	Domain	0—general questions	1—Impact of Physical Symptoms	2—self-perception	3—Activities and Social Participation
Health quality	0	**0.65**	0.61	0.51	0.43
General perception of quality of life	0	**0.65**	0.51	0.47	0.38
Muscle fatigue on waking	1	0.45	**0.63**	0.42	0.36
Muscle fatigue caused by activities	1	0.48	**0.63**	0.41	0.30
Sleep quality	1	0.41	0.40	**0.41**	0.31
Pain during activities	1	0.48	**0.51**	0.44	0.36
Micturition disorders	1	0.35	**0.36**	0.28	0.20
Concentration deficit	1	0.38	**0.56**	0.37	0.28
Memory impairments	1	0.36	**0.42**	0.22	0.11
Anxiety	2	0.47	0.44	**0.56**	0.36
Morale	2	0.46	0.57	**0.69**	0.42
Irritability	2	0.33	0.36	**0.44**	0.27
Prospect of increasing involvement of persons close	2	0.41	0.38	0.52	**0.63**
Plans for the future	2	0.42	0.42	**0.59**	0.52
Life control	2	0.37	0.32	**0.61**	0.55
Perception of the way other people see them	2	0.35	0.37	**0.63**	0.48
Love life	2	0.15	0.20	**0.46**	0.28
Anxiety about going out alone	3	0.34	0.34	0.46	**0.63**
Risk of falling	3	0.34	0.38	0.45	**0.66**
Lack of access to toilets	3	0.26	0.23	0.36	**0.50**
Restriction in social life outside the home	3	0.34	0.35	0.42	**0.54**
Sensitivity to cold	3	0.35	0.35	0.54	**0.60**
Difficulty getting about outside home	3	0.26	0.17	0.29	**0.48**
Difficulty getting around at home	3	0.34	0.30	0.46	**0.63**
Difficulty getting around in other people's homes	3	0.25	0.17	0.46	**0.63**
Participation in family life	3	0.39	0.44	0.53	**0.62**

If the item belongs to the domain, the score does not include the item. In bold is the highest item–domain correlation

perception" (0.41) and the domain "Impact of Physical Symptoms" (0.40). This may result from the fact that sleep quality can be altered by poor self-perception. The expert group, however, decided to keep the item in the domain "Impact of Physical Symptoms," since sleep quality is indeed a physical symptom.

The Mokken analysis revealed a single dominant scale for all lower bounds from 0.2 to 0.4. The item assessing micturition disorders was dropped if $c \geq 0.32$, whereas the item investigating stomach pain entered the domain if $c \leq 0.22$.

A scale composed of seven items was used to form the first HRQL domain in the QoL–NMD. Table 2 shows that the domain had acceptable scalability, internal consistency and test–retest reliability ($H = 0.41$, Cronbach's alpha $= 0.77$, ICC $= 0.81$). The principal component analysis confirmed unidimensionality (Figure S1 in Online Resource 2).

Self-perception

Three items with a high percentage of patients who either did not answer or stated that they were not concerned (40, 53 and 6.3 %) were removed. These three items, respectively, investigated the possibility of starting a family in the past, the possibility of starting a family at present and satisfaction regarding sexual life.

Table 3 shows that the item investigating the prospect of increasing involvement by persons from the close circle ("Do you ever think that in the future, because of your neuromuscular disease, you are likely to rely more heavily on those around you?") was more correlated with the domain "Activities and Social Participation" (0.63) than with the domain "Self-perception" (0.52). These two dependent correlations were, however, not significantly

different ($p = 0.13$). This may result from the fact that the item investigates two concepts: the prospect of losing autonomy, which belongs to the intended domain ("Self-perception"), and the involvement of persons from the close circle, which belongs to social life. The expert group decided to keep the item in the domain "Self-perception" since the prospect of losing autonomy is the main concept that was to be explored.

The Mokken analysis revealed a single dominant scale for all lower bounds from 0.2 to 0.4. The item assessing love life was dropped if $c \geq 0.38$, whereas the item investigating weight problems entered the domain if $c \leq 0.27$.

A scale composed of eight items was used to form the second HRQL domain in the QoL–NMD. Table 2 shows that the domain had high scalability, internal consistency and test–retest reliability ($H = 0.45$, Cronbach's alpha $= 0.83$, ICC $= 0.84$). The principal component analysis confirmed unidimensionality (Figure S2 in Online Resource 3).

Environment, Accessibility, Quality of Care

There was no marked unidimensional set of items for this domain. It was therefore abandoned. However, the expert group decided that the items would be tested for re-assignment to the domain "Activities and Social Participation" because this domain is conceptually close.

Activities and Social Participation

Two items with a large percentage of patients who either did not answer or stated that they were not concerned (32 and 9 %) were removed. These two items, respectively, investigated access to public transport and access to the professional world.

The Mokken analysis revealed a single dominant scale for all lower bounds from 0.2 to 0.4. The item assessing difficulty getting about outside home was dropped if $c \geq 0.38$, whereas the item investigating satisfaction regarding modes of transportation entered the domain if $c \leq 0.27$.

A scale composed of seven items and three recycled items from the domain "Environment, Accessibility, Quality of Care" were used to form the third HRQL domain in the QoL–NMD. Table 2 shows that the domain had high scalability, internal consistency and test–retest reliability ($H = 0.44$, Cronbach's alpha $= 0.85$, ICC $= 0.93$). The principal component analysis confirmed unidimensionality (Figure S3 in Online Resource 4).

Comparison to a generic questionnaire

In the final version of the QoL–NMD, the items are thus classified into three main domains (1) "Impact of Physical Symptoms," (2) "Self-perception" and (3) "Activities and Social Participation."

All domains in the QoL–NMD were fairly well correlated with the domain "Physical health" in the WHOQOL-BREF ("Impact of Physical Symptoms": 0.72, "Self-perception": 0.61, "Activities and Social Participation": 0.65). The correlation between the domains "Self-perception" in the QoL–NMD and "Psychological" in the WHOQOL-BREF was modest (0.47). There was low correlation between the domains "Activities and Social Participation" in the QoL–NMD and "Social relationships" in the WHOQOL-BREF (0.27).

Discussion

The QoL–NMD is the first NMD-specific questionnaire with good psychometric properties that was constructed to meet IRT assumptions. The main advantage of these properties is that the QoL–NMD can be calibrated using an IRT model designed for a Likert-type scale, such as a partial credit model [27] or a graded response model [28]. Once calibrated, a questionnaire domain can produce measures on an interval scale. Only this property justifies the use of mathematical operations such as additions or subtractions, and as a result, it is possible to study score evolutions over a period of time or even calculate a mean score [29]. One other asset of IRT is that missing answers do not prevent estimation of a latent trait, whereas in CTT, when there are missing answers, the score estimation requires the use of an imputation technique. In addition, statistical methods derived from IRT are very useful to assess the reliability of a calibrated scale, as it provides a way to estimate its precision across patient profiles [30].

The International Classification of Functioning, Disability and Health (ICF) core set for NMD [31] can be used to assess whether QoL–NMD items include the concerns of patients. The ICF categories covered by the QoL–NMD are emotional functions, sensation of pain, muscle endurance functions, recreation and leisure, family relationships, energy level, sleep functions, attention functions, memory functions, urination functions, informal social relationships, moving around in different locations and intimate relationships.

The QoL–NMD and the INQoL have comparable psychometric properties, such as high internal consistency and test–retest reliability in each domain. However, the QoL–NMD differs from the INQoL on the following points: (1) It is shorter with 26 versus 45 items. (2) Its domains meet IRT assumptions. (3) It is specific to genetic NMD, whereas the INQoL was developed for both acquired and genetic NMD. The fact that the INQoL is long can be a limiting factor in clinical practice. The ICF categories

covered by the QoL–NMD but not covered by the INQoL are energy level, sleep functions, attention functions, memory functions, urination functions, moving around in different locations and intimate relationships. The ICF categories covered by the INQoL but not covered by the QoL–NMD are exercise tolerance functions, muscle power functions, muscle tone functions, remunerative employment, and health services, systems and policies.

The high correlation of each QoL–NMD domain with the domain "Physical health" in the WHOQOL-BREF could be explained by the fact that restrictions in both self-perception and social life stem mainly from the alterations in physical condition associated with NMD. The moderate correlation between the domains "Self-perception" in the QoL–NMD and "Psychological" in the WHOQOL-BREF demonstrated that NMD severity alone, despite being the main factor, is far from being sufficient to determine patient psychological well-being. The weak correlation between the domains "Activities and Social Participation" in the QoL–NMD and "Social relationships" in the WHOQOL-BREF could reflect the fact that NMD severity is a potentially misleading factor in determining a patient's degree of fulfillment in social life. Indeed, assessing a patient's social life and assessing how much NMD impacts it are two different things. If we take the example of an introverted patient with mild motor restriction, we would probably find a poor social life but a minor impact of NMD on social life. The reverse could be true for an outgoing patient in a wheelchair.

For each domain, there were little variations in the Mokken analysis results when varying lower bound *c*. The item assessing micturition disorders was the only item that would be easily dropped due to its low scalability. It was, however, considered as clinically very important by the expert group and thus kept in the final questionnaire.

The low scalability of the item on "pain during night" with the domain "Impact of Physical Symptoms" may seem counterintuitive since this domain contains an item assessing "pain" (during activities) and an item assessing "sleep quality." This is, however, not surprising since pain at rest (during night) and pain during activities are two very different things. Moreover, a poor sleep quality can result from other factors than pain notably the incapability to change body position without help.

Although genetic NMDs share a common pattern (i.e., a progressive loss of physical condition), they are also very heterogeneous on several criteria, such as the age of disease onset, which muscles are affected, the range of severity between the beginning and the end of the disease. Ideally, a questionnaire specific to each NMD should be developed. However, the large number of NMDs and the low prevalence of most of them is a limiting factor for the development of such questionnaires.

The QoL–NMD items were phrased following the "disease-attributed" approach [32] and require respondents to distinguish between potential causes for the symptom or outcome of interest and to identify the part of that symptom or outcome that is attributable to the NMD. Another alternative, which is being developed by the PROMIS® working group [33], would be the "universally relevant" approach, in which the symptom or outcome of interest is measured by items that are not related to the etiology. In the case of patients with several chronic pathologies (e.g., elderly patients), the causes of the symptom or outcome of interest are hard to identify and only the "universally relevant" approach seems appropriate. In the case of NMD patients, the two approaches are complementary. The "disease-attributed" approach enables a direct evaluation of NMD impact, whereas the "universally relevant" approach enables direct comparison with healthy persons or patients suffering from other pathologies.

Conclusion

This study led to the construction of the QoL–NMD, a new HRQL questionnaire specifically designed for slowly progressive NMD patients. It is composed of two general items and 24 items classified in three domains: (1) "Impact of Physical Symptoms," (2) "Self-perception" and (3) "Activities and Social Participation." All three domains showed good psychometric properties and met IRT assumptions. The next steps will be to validate QoL–NMD by re-assessing psychometrics in an independent sample of patients and calibrate the IRT scoring system.

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