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REVIEW

Assessment of the quality of life in patients with LGMD. The case of transportinopathy

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The Quality of Life (QOL) is influenced by several disease-related factors, support, resources, expectations, and aspirations, within the disease-related concepts. The Individualized Neuromuscular Quality of Life (INQoL) is a validated muscle disease-specific measure of the QoL developed from the experiences of patients with muscle disease and can be used for people or large cohorts. This review of QoL in transportinopathy cases reports adjustments in an autosomal dominant (AD) LGMD, and a comparison is made with autosomal recessive (AR) LGMD evaluated by INQoL. The locus for this form of LGMD with AD inheritance was found on chromosome 7, and then identification of the gene and its encoded protein (transportin-3) was obtained in 2013. A large three-generation family with several branches in Spain and Italy was previously reported and described in detail. Some patients had an early onset weakness, but others had an adult onset of the disease, as late as 58 years. The severity of the appearance of the phenotype is correlated with QoL and progresses with age. Assessing the impact on their QoL is particularly relevant to know whether the treatment is reducing their suffering.

Key words: quality of life, transportin-3, limb-girdle muscular dystrophy, caregivers

Introduction

There is a lack of high-quality randomized evidence in the treatment of Limb-girdle Muscular Dystrophy (LGMD) and of their Quality of Life (QoL). Health status can be measured using QoL questionnaires, in general, chronic diseases and often neuromuscular disorders (NMD) lead to reduced QoL, the comprehensive study of QoL in Muscular Dystrophies (MDs) captures 3 broad domains of QOL: physical, psychological, and social, including factors influencing self-reported QOL disease factors, support, resources, and expectations, and places these concepts within the context of the disease course.

QoL has been studied in some muscular dystrophies [1-6]. It is also important to evaluate the caregiver's role. In a cohort of 502 MDs including Duchenne, Becker patients, or Limb-Girdle MDs (LGMDs) key relatives, Magliano et al. [7] reported that, despite the difficulties associated with caregiving, relatives identify valuable benefits in their experience and activities. These findings confirm that home management of patients with LGMDs may be demanding for patients and relatives, especially when social and professional resources are poor and patients present decreased functional abilities. Aspects that most affect QoL in patients with LGMD are mobility, difficulty in performing daily activities (ADLs), limitations in social interaction, and emotional impact. Efforts are needed, both at the level of health policies and professional training, to help caregivers and patients face the difficulties of MDs and value such complex family experiences.

QoL studies done in recessive forms of LGMD might not reflect the importance of the genetic type of inheritance on affected caregiver/affected patient impact.

We analyze such impact with a focus on a dominant LGMD-TNPO3 related or LGMD-D2.

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Transportinopathy clinical characterization (LGMD1F/D2)

Transportinopathy produces early and late-onset phenotypes and has been identified in familial and sporadic cases [8]. There is high variability in age and symptom onset, a common sign is the development of generalized atrophy of muscle mass.

A large three-generation family with several branches in Spain and Italy was previously examined and described in detail [9-10]. The clinical history of 29 patients was collected. There were early onset patients who became wheelchair-bound around 30 years of age, while in milder cases, walking ability was preserved up to 65 years of age. Some patients had an early onset weakness while others had the adult onset of the disease, as late as 58 years. The phenotype severity appearance does not always increase in successive generations, at different from what was originally reported by Gamez et al. [9]. Anticipation phenomenon is generally seen in triplet expansion disorders, such as myotonic dystrophy or Huntington Chorea rather than in this disorder. In this LGMD, the main clinical features were dysphagia, dysarthria with bulbar, and distal and axial involvement, variably occurring in the family members. The weaker muscles were at onset in the lower limbs and then weakness spread to upper girdle muscles, especially the triceps. Abnormal long fingers (arachnodactyly) characterize also the clinical phenotype. There was a prominent neck axial weakness (flexor more than extensor).

A typical clinical sign was observed when patients were lying in bed: they were able to raise their arms horizontally, but in a standing position, they were not able to fully lift their arms over the head, because of scapular winging. The locus for this form of LGMD with autosomal dominant inheritance was identified on chromosome 7, through clinical and genetic analysis of a large Spanish family.

The identification of the gene and its encoded protein (transportin-3) was obtained in 2013 [10]. Transportin-3 protein is involved in HIV and associated with other proteins allowing its transport in the nucleus. The genetic mutations that cause transportinopathy make the patients immune to AIDS, holding promise for research in this field and reassuring the patients regarding a possible HIV infection risk. The mutation could block the activity of the HIV-1 intasome and make it unable to interact with cargo protein causing a block of nuclear import of proteins involved in lentiviral replication: CD3 and CD28 peripheral blood cells from transportinopathy patients of the Italo-Spanish family
show lower production of viral proteins in patients than in control (Alcami, personal communication).

Methodology used for QoL study in LGMD

As it will be discussed later, therapeutic options for these diseases are often limited and with limited life expectancy for some of them. In this case, long-term preservation of QoL is often the main focus of medical care [11].

Different tools can be found to measure QoL, such as the SF-36 [12], the EQ-5D [13], the WHOQOL [14], and there are even specific tools to assess this concept in certain diseases, such as the ALSAQ-40 [15] for Amyotrophic Lateral Sclerosis (ALS), the MG-QOL [16] for Myasthenia Gravis, among others. These tools are mainly focused on assessing this variable in adults, however, it is also possible to find tools aimed at assessing QoL in children, such as the PEDSQL [17] or the KIDSCREEN-52 [18].

A QoL questionnaire for NMD was constructed and validated in the United Kingdom in a sample of adult patients with a variety of muscle disorders [19]. Previous studies suggested it could be a more relevant and practical measure of QoL in muscle diseases than generic health measures of QoL. The symptom-specific QoL questionnaire called the Individualized Neuromuscular Quality of Life (INQoL), was validated in Italy in a cohort of more than 1000 patients with different muscle disorders with various MDs, with various progression of muscle symptoms and disability [1].

INQoL is recommended to assess QoL in muscle diseases because of its ability to capture physical limitations that are specifically relevant to the muscle condition.

We have formally validated the Italian version of INQoL confirming and extending
data obtained in the United Kingdom. In addition to good results in terms of reliability, and criterion validity, a comparison with the SF-36 scales showed a stronger association between INQoL total index and SF-36 regarding the progression of muscle symptoms and disability [1].

INQoL consists of 45 questions within 10 sections. Four of these refer to the impact of common muscle disease symptoms like weakness, locking, pain, and fatigue. Five sections examine the degree and importance of the impact of muscle disease on particular areas of life: activities, independence, relationships, emotions, and body image. The last sections investigate treatment and its effects and expectations. Symptoms and impact of these are referred to as the perception of the disease, in general, with no reference to a specific time frame in the INQoL.

Patients respond using a seven-point scale giving their view of the degree of impact of a symptom or the degree of impact of muscle disease on an aspect of their life together with the importance that they attach to each item, thus allowing a patient-weighted score to be given for each section. The final score from each section is presented as a percentage of the maximum detrimental impact with a higher percentage, indicating greater symptom impact or worse QoL. A composite score can also be obtained from five preselected sections assessing the impact of the muscle disease on particular areas of life, representing overall QoL. The higher the INQoL index, the worse the perception of the patient's QoL, as it was corroborated in the validation process in Italy and other countries [1,20].

The results of this extensive survey suggested that the questions in the INQoL are more relevant to people with muscle disease than a generic questionnaire and more sensitive to the life changes that occur as the muscle condition progresses.

For these reasons, LGMD patients were asked to fill out or respond to the INQoL interview.

A recent QoL study [21] was performed utilizing the INQoL questionnaire on 6 patients affected by LGMD-D2 (3 males,3 females,18-66 years old) and 3 caregivers of LGMD-D2 (one healthy male, two affected women, 48-66 years old).

They were compared with 3 patients affected by recessive LGMD (LGMD-R2, or dysferlinopathy, M, 46-year-old, LGMD-R4, or be-

ta-sarcoglycanopathy, F, 42-year-old, LGMD-R5 or gamma-sarcoglycanopathy, F, 47-year-old), that presented fast evolution.
The recruitment of the sample was done from the hospital in Padova and the association of patients. This included collecting sociodemographic data, GSGC, MRC Scale, INQoL, and muscle MRI images [21].
The interview was done directly or by telemedicine using either the Italian, English, or Spanish INQoL-validated version.

The comparison between AR and AD LGMD

INQoL is useful for assessing QoL in muscle diseases because of its ability to capture physical limitations that are specifically relevant to the muscle condition.
It was observed that the means in the muscle weakness subscale and the independence subscale are particularly different in the LGMD course. The LGMD-D2 transportinopathy cases had a variable GSGC scale score.
A higher dependency in functional activity was observed in recessive LGMD forms and is also documented in the higher GSGC scale scores (GSGC score of 27).
In addition, in almost all areas of the INQoL scale, greater impairment, and a higher number of symptoms are observed in the recessive forms, as expected since recessive forms have a fast progression and are more severe. In general, muscle weakness and independence had a great impact on QoL in patients with a recessive form of LGMD. This is consistent with the fact that recessive forms may produce greater dependence due to associated symptomatology as reported by Zatz et al. [22].

Comparisons between other studies

Comparing results assessed with INQoL, the patients with LGMD-D2 are found to have higher scores on the impact of muscle pain and fatigue [13]. In another study in which patients with LGMD were assessed using INQoL, it was observed that several aspects of QoL have a strong association with disability. In fact Peric et al. [6], using both INQoL and SF-36 scale in recessive LGMD to evaluate QoL in patients with LGMD, tried to identify the most significant predictors of QoL. The study included 46 patients with a diagnosis of LGMD. QoL in patients was evaluated using two scales-SF-36 questionnaire and the INQoL and physical composite total INQoL score were 46.1 ± 20.4, with the worst results obtained for weakness, fatigue, and independence, while social relationships and emotions showed better results. Significant predictors of worse SF-36 score in LGMD patients were higher fatigue level and use of assistive devices It is of special interest that some of the identified factors that correlated with worse QoL in LGMD patients might be amenable to treatment.
The results obtained in LGMD-D2 patients show greater impairment in ADLs, express higher levels of fatigue, and suffer more from the consequences of blocking, which may be for contractures.
In the studies in which QoL has been assessed with other instruments in patients with recessive LGMD, as the one by Kovalchick et al. [23] the study determined the frequency and impact of symptoms on QoL in patients diagnosed with three types of LGMD. Participants with a diagnosis of LGMD due to Calpain-3 (LGMD R1), Dysferlin (LGMD R2), and FKRP (LGMD R9) completed a survey to report the frequency and relative impact of themes and symptoms of LGMD. Frequency, mean impact, and population impact scores were calculated, and responses were categorized by age, symptom duration, gender, employment status, use of assistive devices, and 134 LGMD participants completed the survey. The most prevalent themes included a 100% inability to do activities, limitation with mobility, and lower extremity weakness. Themes with the greatest impact were: limitations with mobility, lower extremity weakness, and an inability to do activities. Symptom duration and the use of assistive devices were associated with the presence of multiple themes. Employment was associated with the impact of several themes with no differences in frequency. In the LMGD population, the most prevalent and impactful themes were related to weakness, but additional concerns related to emotional challenges were also considered in a clinical setting since they might at large correlate with social problems and the impact on ADLs. In addition, fatigue and impact on independence and social relationships are also reported in the LGMD-D2 sample [22].

The comparison between the caregiver and the affected case

Descriptively, when we analyzed the differences between patient and caregiver reports, caregivers reported a greater impact of the disease on their QoL in all domains except muscle pain. Caregivers report higher scores in almost all spheres of QoL impact in LGMD-D2 [17]. This indicates that, in general, they consider that the patient has a worse QoL than the patient thinks.
Moreover, caregiver responses are relevant for a broader understanding of the impact of the disease, as some caregivers lived with the disease and often perceived the situation more objectively.
These findings confirm that home management of patients with MDs may be demanding for patients' relatives, especially when social and professional resources are scarce and patients' functional abilities decrease. Efforts are needed, both at the level of health policies and professional training, to help caregivers and patients face the difficulties of MDs and to value such complex family experiences.

Progression with age and QoL in LGMD

Another important aspect recognized in the study [21] is that age seems to correlate with an increased burden of illness on ADLs and emotional management.
The underlying explanation for this relationship seems to be that the specific pathophysiological mechanisms that cause clinical disorders are modified and increased by an aging process.
As a disability worsens and ambulation becomes increasingly difficult, patients may rely on assistive devices eventually requiring a wheelchair or motorized device. Additionally, patients using wheelchairs, motorized chairs, or multiple devices reported a greater impact of changed body image on quality of life than those using no devices or a cane or brace. Changed perception of body image is a form of psychological distress that often accompanies physical disability

along with decreased self-esteem, and patients may experience distress as they adapt to their disability and require more assistance. Additionally, the use of assistive mobility devices was associated with the frequency of several themes and their impact. The association of ambulation status with several important symptomatic themes and perceived impact on quality of life has also been found in patients with spinal muscular atrophy. Interventions that address difficulties with ambulation and the need for assistance may have a large effect on disease burden and perceived QoL.

Despite their different genetic mutations, LGMD subtypes share a similar profile of progressive symptoms, mainly proximal muscle weakness, with a similar impact on quality of life. Beyond the themes that are common across all subtypes, there is phenotypic heterogeneity and notable differences between subtypes

Duong et al. [30] assessed differences among LGMD subtypes and determined differences and associations in QOL measures and clinical endpoints. Assessments included muscle strength, motor function, cardiac and respiratory assessments as well as QOL questionnaires which included the InQoL [30]. In LGMD cases, a significant correlation was observed between the INQoL subcategory of ability to perform ADL and the 6-minute walk test (6MWT) distance. INQoL total scores also showed significant correlations with ankle dorsiflexion and total manual muscle testing scores. Other cardiac and respiratory function analyses and the ability to perform ADLs did not show significant relationships.

Unmet needs in LGMD

Currently, LGMD has no curative treatment. Although a few trials are underway, the perspectives are still limited, since they consist either of the use of corticosteroids in monotherapy for LGMDR5 contrary to its accepted use with Duchenne myopathy. However, it remains largely used in clinical trials in combination with genetic treatments. Given the fact that progressive proximal limb-girdle muscle weakness, wasting, respiratory deficiency, and retractions are frequently observed in LGMD cases, respiratory treatment of LGMD patients with a morning headache and dyspnea is mandatory. All these treatments are symptomatic, and it is necessary to consider that the symptomatology produced by the disease can limit life expectancy and reduce QoL [24-28]. Thus, patients typically report limitations in aspects such as mobility, difficulty in performing activities, limitations in social interaction, as well as emotional impact [29-31].

Furthermore, to generate or create new treatments aimed at improving the lives of these people, it is especially important

to know which aspects of their QoL are most affected, so that the treatment can be as specific as possible related to the outcomes.

Conclusions

NMD, and especially LGMD, generate a series of symptoms that lead to increased dependence and disability, which will eventually result in increased dependence on their environment, technical aids, and external people [30-31].

While this dependence in the later stages of the disease is generalized, certain signs will lead to greater disability than others.

Knowing the signs and how they affect life helps professionals to direct treatment optimally and effectively for the patient.

Also, in the current context of ongoing research aimed at creating new treatments, assessing the impact on their QoL is particularly relevant to know whether the treatment is reducing their suffering.

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Conflict of interest statement

The author declares no conflict of interest.

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Ethical consideration

This project has been approved by the Ethics Committee ofthe University of Deusto (Ref: ETK-39/18-19) and was conducted in accordance with the Declarationof Helsinki.

Authors' contributions

Author Contributions: Conceptualization, CA and AAR; resources, CA; writing—original draft preparation, CA; writing—review and editing, CA and AAR; supervision, CA and AAR All authors have read and agreed to the published version ofthe manuscript.

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