Recommendations for Assessment and Management of Health-Related Quality of Life in Patients with Mucopolysaccharidoses in Latin America

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Abstract

Mucopolysaccharidoses (MPS) constitute a heterogeneous group of rare genetic disorders caused by enzymatic deficiencies that lead to the accumulation of glycosaminoglycans (GAGs). Clinical observations suggest a health-related impairment in quality of life in patients with MPS. Professionals with extensive experience in the care of patients with inborn errors of metabolism, such as MPS, held a meeting in April 2017 to discuss and propose recommendations for the evaluation and management of quality of life in MPS patients in Latin America. In the light of this scenario, the present work summarizes the content of the discussions and presents the recommendations produced at the meeting. The panel had suggested the use of the following tools for the assessment of health-related quality of life (HRQoL): Children's Health Assessment Questionnaire (CHAQ) for children and patients unable to express their feelings, Health Assessments Questionnaire (HAQ) and EuroQol 5 Domains (EQ-5D) scales for adult patients. Based on the scores verified in these scales, the panel proposes interventions that aim reducing the impairment of the quality of life in patients with MPS disorders.

Keywords

lysosomal storage diseases, MPS, quality of life, ADL, cognition, mobility, pain.

Background

The term "quality of life" (QoL) refers to the general well-being of individuals and societies and involves a wide variety of aspects, such as life satisfaction, physical health, family life, education, employment, material comfort, religious beliefs, finances and the environment in which one lives. A more recent and specific concept, which has been increasingly addressed in the scientific literature is the so-called *health-related* quality of life (HRQoL). The evaluation of the HRQoL is effectively an evaluation of QoL and its relation to health, including physical, mental, emotional and social aspects. The Centers for Disease Control and Prevention (CDC) defined HRQoL as "an individual's or group's perceived physical and mental health over time"[1]. Remarkably, HRQoL is usually measured by self-assessment; nevertheless when patients are unable to express themselves (in attribution to young age or very sick stage or severe cognitive impairment), a caregiver and/or a parent can serve as substitute for the evaluation, responding the tool by proxy.

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Mucopolysaccharidoses (MPS) comprise of a heterogeneous group of rare genetic diseases of lysosomal storage, which result in severe morbidity and reduced life expectancy[2]. New treatments for these disorders have led to a search for clinically relevant biomarkers and clinical markers associated with therapeutic efficacy in populations and individuals. However, biomedical measures fail to capture all aspects of a complex chronic disorder such as MPS. HRQoL instruments that use patient-reported outcomes (PROs) to address symptomatic parameters (pain, fatigue, psychological health) and functional parameters (activities and limitations) or the quality of life itself are used to complement the traditional biomedical outcomes. Many of these HRQoL measurement instruments demonstrate reduced quality of life in patients with MPS[2]. Thus, the standardization and validation of HRQoL instruments for patients with MPS becomes particularly relevant[3].

To discuss their clinical experience in the field of evaluation and management of HRQoL in patients with MPS in Latin America, the authors held a meeting sponsored by BioMarin Pharmaceutical Inc. in April 2017 (Campinas, São Paulo, Brazil). In the light of the discussion, the current work aimed to present the recommendations for evaluation and management of HRQoL in patients with MPS throughout their life, regardless of whether they are under enzyme replacement therapy or not, including other therapies as hematopoietic stem cell therapy.

Meeting Organization and Debate

All authors are health professionals with extensive experience in lysosomal storage diseases (LSD) and discussed in a face-to-face meeting clinical aspects related to HRQoL in MPS patients.

MPS cause a broad spectrum of chronic and progressive, life-threatening symptoms, and researches so far have focused mainly on physical manifestations, with little attention to psychological characteristics. As long as the assessment the quality of life of these patients has not an equalized standard in all reference centers in Latin America, the group discussed the importance of this domain in patients and family's health.

Although the work of Hendriksz et al.[3] have pointed to the importance of a standardization and validation of HRQoL instruments for use in patients with MPS, there are relatively few established guidelines that steer health professionals on how to deal with aspects of HRQoL in patients affected by this disease.

Methodology

Previously to the meeting, the authors had received articles retrieved from a search in Medline and Lilac platforms. The terms used included "mucopolysaccharidoses", "MPS disorders" and "quality of life". Notably, six articles were found regarding the assessment of quality of life and only two of these had discussed the importance of measuring the activity of daily living.

The authors had discussed instruments and tools of measurement of HRQoL that can be used in these conditions and possible measures to improve the HRQoL, with the purpose of formulating recommendations to health professionals who deal with this patient population. Any divergences were resolved by discussion until the members of the panel reached a consensus.

Impact on HRQoL in Patients with MPS

MPS manifestations in multiple organs can lead to reduced physical resistance and mobility, often associated with pain, limited range of motion (ROM), low energy levels, fatigue, which negatively affects HRQoL and activities of daily life (ADL). MPS patients may show increased physical and emotional dependence on family and close relatives, reduced participation in educational and professional activities and social life, as well as low self-esteem. Thus, psychological, behavioral, mental health conditions, such as anxiety and depression can also be negatively influenced[4]. Visual and hearing impairments and frequent surgeries can further reduce physical activity and adversely affect the ability to live independently[5,6,7,8].

Mobility impairment is also prevalent in patients with MP; most require walking aids or a wheelchair[8,9,10,11]. Mobility difficulties may be due to skeletal and joint abnormalities, spinal cord compression, lower extremity pain and reduced energy levels caused by cardiorespiratory problems[2]. Joint abnormalities may result in poor ROM, weakness, stiffness or changes in wrist mobility, which in turn affect the performance of simple ADL tasks, such as dressing, personal care and eating[12]. Pain can arise from joint defects, infections, such as otitis media, neurological involvement and neuropathic signs from the brain, increased intracranial pressure, spinal cord compression or carpal tunnel syndrome[11,12,13]. Fatigue resulting from impairment of cardiopulmonary functions can produce distress, frustration and, potentially, depression[14].

PRO are collected through standardized questionnaires, designed to measure symptomatic parameters (pain, fatigue, psychological health), functional parameters (activity limitations) and HRQoL[15]. Thousands of tools designed for assessment of PROs have already been described, including generic and disease-specific questionnaires[16,17]. The most important advantage of generic questionnaires lies in a wide range of applications in different types of diseases, severity, medical interventions and also across diverse demographic and cultural groups, allowing a comparison among different studies and diseases[18]. Specific questionnaires target a given patient population, with issues considered relevant, significant and acceptable for the affected population and they can be used to measure the effectiveness of interventions and treatments.

From the best of our knowledge, there is no specific tool to measure HRQoL for MPS disorders validated to Latin America[3]. The MPS HAQ and HS-FOCUS were adapted for

testing self-care, mobility skills, extent of caregiver assistance in performing activities and functionality impact. Those tools were used on clinical trials of MPS I and MPS II, respectively. However, the scarcity of data, besides the standardization of tests in such patients, hinder the accurate analysis of the impact on QoL over time.

Evaluation of Functional Aspects

ADLs have been evaluated as an exploratory outcome in some clinical studies[19,20]. In several studies involving MPS II, IVA, VI patients, researchers evaluated ADLs during clinical studies and extension periods[8,11,21]. General mobility difficulties and self-care, which tend to increase with age, have been reported.

As reported by Shapiro[22], neurological manifestations are typical of some MPS types (I, II, III and VII) and can lead to progressive cognitive impairment, difficulties with language and speech, behavioral abnormalities and sleep problems that together can dramatically influence HRQoL of patients and their families. Thus, neurocognitive function can be employed as a sensitive indicator of disease progression and treatment outcomes. Within this context, there is a necessity of using appropriate neurocognitive tools sensitive to changes in cognitive ability in MPS patients. More specifically, the tests have to be adequate in difficult level, be sensitive to disease-specific abnormalities and progression and produce a score for all patients with the disease comparable to normative data in order to be applied globally.

In MPS II patients, cognitive decline negatively affects ADL. In fact, a study involving 96 patients with attenuated MPS II (5.0 to 30.9 years of age) reported impairment in domains of the Hunter Syndrome-Functional Outcomes for Clinical Understanding Scale (HS-FOCUS), as well as in domains of hygiene, personal care, reaching objects, dressing and grooming of the CHAQ questionnaire[23]. Functional scores in the HS-FOCUS were lower in patients with better resistance in the 6-MWT and better joint mobility. Another smaller study (N = 29 patients, 2-29 years of age) suggested that difficulties in performing ADLs depend mainly on the cognitive status and age of the patients[24]. Younger patients with normal mental development were generally independent in terms of self-care, mobility and walking ability, but the need for help to perform ADLs is increased with age[3,23,24].

MPS III is characterized by a predominant neurodegenerative course. With rapid onset, both MPS IIIA and IIIB lead to loss of cognitive ability, language and motor function as well as behavioral abnormalities. Concurrently, tralesinidase alfa has been investigated as an enzyme replacement therapy for MPS IIIB (Sanfilippo Syndrome B). Patients with late onset commonly display epilepsy, sleep disorders, reduced ambulatory and to feed and toilet oneself[25,26].

MPS IVA and MPS VI have also been shown to significantly interfere with patients' ADL. In the International Morquio A registry of 326 MPS IVA patients, only 40–60% of patients were able to perform ADL independently. In the MorCAP study with 325 MPS IVA patients,20–40% reported self-care, ADL tasks (including the ability to wash or brush hair, tie shoelaces and cut fingernails) were affected by their disease. In the Survey Study of 121 MPS VI patients, the CHAQ disability index indicated a mild level of disability in patients aged >18 years and moderate disability in those aged ≤18 years[7,10,11].

Before the early 2000s, MPS patients relied exclusively on supportive care. From 2001, enzyme replacement therapy became available for some MPS types I, II, IV and VI, bringing substantial improvement in disease progression[27]. Unfortunately, the treatment cost is high and the access and reimbursement schemes for orphan drugs vary geographically[28]. In association, a considerable proportion of patients demand help in performing ADL, which is generally obtained by parents or close family members. Such demand of attention leads to a reduction in caregivers' workload and consequently, to a decreased family income[29]. Considering that patients need a multidisciplinary care, it is plausible to assume that HRQoL is also influenced by the financial status of the families. Thus, the impact on HRQoL is mainly dependent upon the patient's ability to remain independently mobile and that even slight improvements in mobility dramatically improve quality of life[4].

HRQoL Assessment Scales in Patients with MPS

CHAQ (Children's Health Assessment Questionnaire)

To evaluate the quality of life in children from infancy to adolescence, the panel recommends the use of the CHAQ (Childhood Health Assessment Questionnaire), an adaptation of Stanford's HAQ-DI (Health Assessment Questionnaire – Disability Index)[30–32]. It is a questionnaire to be applied to one of the parents and/or the patient, designed to measure the health condition in children of one year of age and older. In the development of the CHAQ, a number of new issues were added and other existing ones were modified to include at least one relevant issue for children of all ages in each functional domain of the instrument. CHAQ has already been validated for use in patients with juvenile rheumatoid arthritis and dermatomyositis and has been applied in studies of children with spina bifida, chronic juvenile oligoarticular and polyarticular arthritis and juvenile arthritis. Since its introduction, the instrument has shown excellent psychometric properties and has already been translated into several languages, including Brazilian Portuguese and Latin American Spanish[32].

HAQ (Health Assessments Questionnaire)

In its short and most widely used two-page version, the HAQ (Health Assessment Questionnaire) is composed of a "Disability Index" (HAQ-DI), a visual analogue scale (VAS) for assessment of pain intensity and a VAS for the patient's general health

status[30]. Pain, as a single symptom, negatively impacts QoL and should be measured routinely in MPS patients, as recommended by a group of Latin American experts[33].

The Inability Index (HAQ-DI) assesses the patient's level of functionality involving questions about fine movements of the upper extremities, locomotor activities of the lower extremities and activities involving upper and lower extremities. There are 20 questions in eight functional categories, which include activities such as dressing, getting up, eating, walking, personal care, reaching and grasping objects and usual activities. The questionnaire is available in Portuguese[34] and Spanish[35].

The HAQ pain VAS was developed to assess the presence or absence of pain related to arthritis and its intensity. The goal is to get information about pain throughout the week prior to the examination. The pain scale is defined by a graduated horizontal line from 0 (no pain) to 3 (severe pain) or, alternatively, from 0 (no pain) to 100 (severe pain). This pain VAS has been widely used in experimental, observational and clinical studies[36,37].

MPS-HAQ

The MPS-HAQ is a 52-question instrument originally developed to assess self-care and mobility in patients with MPS I. Domains covered by the MPS-HAQ are self-care (27 questions related to eating/drinking, dressing, bathing, grooming, tooth brushing and toileting), mobility (12 questions related to dexterity, mobility, walking, stair climbing and gross motor skills), and the extent of required caregiver assistance in the performance of these activities (13 questions)[3,19].

EQ-5D (EuroQol 5 Domains)

For adult patients, the authors recommend the EQ-5D questionnaire, an instrument developed as a generic measure of HRQoL. There is a youth version, a child-friendly EQ-5D-version in general, can be applied in younger than 16 years old (Table 1). The instrument defines health through a descriptive system divided into five dimensions (mobility, personal care, habitual activities, pain/discomfort and anxiety/depression), each with three (EQ-5D-3L) or five (EQ-5D-5L) severity levels: no problems or moderate or extreme problems in the EQ-5D-3L and no problems or minor, moderate, severe or extreme problems in the EQ-5D-5L. Health states are indicated by a five digit numerical code, which represents the severity level in each dimension. Thus, the state 11111, for example, represents the absence of problems in all dimensions, while the state 12345 represents no mobility problems, mild problems for personal care and dressing, moderate problems to carry out usual activities, serious problems of pain and extreme anxiety or depression in the EQ-5D-5L version. The EQ-5D is designed for self-completion and consists of a two-page questionnaire. The first page records the self-reported level of the problem in each of the five dimensions. The second part of the questionnaire contains a visual analogue scale of 20 cm, graded from 0 to 100, corresponding to the worst and the best imaginable state of health, respectively. The instrument has already been officially translated into more than 120 languages, including a version in Portuguese validated for use in Brazil and approved by the EuroQoL Group Translation Committee. It is probably the most

Table 1. Recommended tools for the assessment of HRQoL in MPS disorders

Name questionnaire	Acronym	Expert panel comment	Age range (yrs)	Details/time it takes to apply the tool	Reference
Children's Health Assessment Questionnaire	CHAQ	Indicated for children and patients unable to express their feelings	>=8 years old (by interviewing or self-report. <8 y: parents can answer as proxy.	Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status (functional ability). Takes arond 10 minutes.	[3, 30]
Health Assessments Questionnaire	HAQ	Indicated for adults	>= 18 years old (patients in transition from paediatric into adulthood, consider using CHAQ). Can be used in adolescents >12 years old).	Consists of 20 questions, which assess the ability in performing activities of daily living during the previous week. Is usually self-administered, but can also be given face-to-face in a clinical setting or in a telephone interview format by trained outcome assessors. The full HAQ takes 20 to 30 minutes to complete.	[3]
MPS - Health Assessments Questionnaire	MPS-HAQ	indicated for adults (for patients unable to express their feelings by proxy)	>= 18 years old (patients in transition from paediatric into adulthood, consider using CHAQ).	a 52-question instrument originally developed to assess self-care and mobility in patients with MPS I. Can take almost 1 hour.	[3,19]
EuroQol 5 Domains	EQ-5D	Indicated for adults, but there is a version for children/adolescents*	>= 16 years: adult version, .= 8 years: use EQ-5D- Y version*	EQ-5D-5L/ EQ-5D-3L: assessments of physical and mental health in 5 levels or in 3 levels. Takes around 20 minutes.	[3,36,37, 38]

Relevant studies are listed where available; however, as limited clinical evidence has been published, recommendations are based on the clinical experience of the authors in MPS disorders. Table has been adapted from Hendriksz et al. [3].
*EQ-5D- Y (Youth version)

widely used generic measure of health for clinical and economic appraisal, with a wide variety of applications and it has been incorporated into population health research[38–40]. Table 1 summarizes the tools above.

Interventions for improvement of HRQoL in MPS

It was a consensus among the experts that any damage related to quality of life should be immediately discussed with the family and the multidisciplinary team as psychologists, psychiatrists, physiotherapists and social workers to try to mitigate the deleterious impact both in the patient's life and in their families. Some patients may benefit from using adjuvant medications such as anti-depressants, anxiolytics more suitable for each case. Regular therapy can also be beneficial. Attention should also be focused on the functionality of daily life as well as civil rights ensured such as education and employment laws.

Even after many years of experience in the treatment of MPS few studies have focused on the QoL of this type of disorders. There are no specific free access tools for each type of MPS, so in this context, further studies should be done to better understand what tools to use in the follow-up of these patients.

Comments

MPS are genetic disorders, thus leading to chronic and complex clinical manifestations that challenge clinicians, patients and caregivers. Clinical presentation, severity and progression patterns may vary not only among the distinct types of the disorder but also among patients with the same type of MPS. However, the common denominator is the burden of the illness in the patient's life regarding emotional, psychological and socioeconomic development and independency. Thus, clinical manifestations as skeletal and joint deformities, restricted range of motion, pulmonary and cardiac impairments, fatigue and possible cognitive deficits negatively affect the quality of life of the patients.

The PRO tools to evaluate both HRQoL and ADL are strongly needed to draw a panorama from the baseline condition of the patient and the putative effects of the current treatments, such as enzyme replacement therapy and hematopoietic steam cell transplant. Therefore, the use of PRO instruments is gathering information concerning what a patient with MPS has to face daily[4].

Two pillars in designing the evaluation of HRQoL in patients with MPS are the age of the patient and the cognitive impairment promoted by this disorder as both factors can negatively influence ADL. Concerning age, although patients at younger ages are more independent in their self-care, assistance is progressively needed in attribution to increasing difficulty with motion and walking[22].

Clinical observations strongly suggest that patients with MPS suffer from chronic pain that affects all types of MPS[33,41]. As pain is able to negatively impact on HRQoL in adults and children is widely know[4,42,43], medical attention to this parameter is vital. In this regard, experts have proposed recommendations the management of pain in patients with MPS in Latin America[33,43] that are in accordance with the recommendations proposed herein.

To allow for data comparisons across published studies and as an auxiliary tool in the evaluation of HRQoL in MPS, the panel recommends the CHAQ for children and patients unable to express their feelings and the EQ-5D scale for adult patients. The HAQ may also be applied for adults, including the MPS HAQ if possible. The expert panel recommends using simpler tools periodically, both at baseline and throughout life, regardless of whether therapy is ongoing. Together with medical attention to precocious diagnosis and treatment when applicable, multidisciplinary care of the patient is critical for hindering the disease progression and reduce its impact not only on the life of the patients but also in the patients' family. Thus, the proposal of instruments to accurately evaluate health-related quality of life is needed to individually understand the physical and psychological state of the patient before and throughout the clinical and/or pharmacological assistance.

Another decisive aspect on evaluating the HRQoL of the MPS patients is to assure and evaluate the quality of life of their parents and/or caregiver. Within this context, Somanadhan and Larkin[44] have pointed out important issues faced by parents and/or caregivers, as the experiencing a of tardive diagnosis, receiving the diagnosis of a progressive and limiting disease, the stigma of a rare condition, intensive care, physical distress and coping with a uncertain future. Thus, evaluation of the psychological health of the family and/or caregivers is also critical for ensure the quality of life o the patient. For Latin America, Monteiro et al.[45] had proposed the validation of the Informal Caregiver Burden Assessment Questionnaire (QASCI) after its semantic adaptation to Brazil, a tool that could contribute to a complete assessment of quality of life of patients with MPS and their families.

Conclusion

MPS disorders are chronic diseases that generate a large burden on patients and family members' life. The expert panel drew attention to the measurement of HRQoL as routine in clinical practice, it is believed that standard measures can generate more accurate information in general health, optimizing resources in the health system.

Abbreviations

HRQoL: Health-related quality of life
CHAQ: Children's Health Assessment Questionnaire
HAQ: Health Assessments Questionnaire
EQ-5D: EuroQol 5 Domains
EQ-5D-5L: EuroQol 5 Domains 5 levels
EQ-5D-3L: EuroQol 5 Domains 3 levels
PRO: Patient-reported Outcomes
ROM: Range of motion

ADL: Activities of daily life
VAS: Visual analogue scale

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