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QUALITY OF LIFE (QOL) IN CHILDREN AND ADOLESCENTS WITH MUCOPOLYSACCHARIDOSIS

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ABSTRACT

Objective: To assess quality of life (QOL) of children and adolescents with mucopolysaccharidosis, seen at a treatment center for innate errors in metabolism in Recife-PE. **Method:** Descriptive, cross-sectional study with a quantitative and analytical approach. The instrument (Peds-QL) was applied to caregivers of children and adolescents with Mucopolysaccharidosis. Quality of life scores were correlated with numerical variables (Pearson's correlation coefficient) and median scores associated with clinical and sociodemographic variables (Kruskall Walls test). **Results:** 29 patients were included in the study, of these 8 had a diagnosis of mucopolysaccharidosis II and 21 with Mucopolysaccharidosis VI. Children (2-10 years) had better QoL scores in physical capacity and total QOL ($p = 0.008$; $p = 0.033$) when compared to adolescents (> 10 to <18 years). Participants with Mucopolysaccharidosis VI had better QOL scores in physical ($p = 0.042$) and psychosocial ($p = 0.003$) aspects compared to those with Mucopolysaccharidosis II. Individuals diagnosed earlier had better QOL scores ($r = -0.54$; $p = 0.003$). **Conclusion:** it is important to raise the awareness of the scientific community about the advent of rare diseases. Mucopolysaccharidosis, when diagnosed early, allows treatment to begin sooner, minimizes complications and in this study was shown to guarantee better QOL scores.

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INTRODUCTION

According to the National Institute of Neurological Disorders and Stroke (2020) mucopolysaccharidosis (MPS) is a group of rare and hereditary metabolic diseases, characterized by the accumulation of the mucopolysaccharide, today called glycosaminoglycan (GAG), in various tissues, due to deficiency of lysosomal enzymes involved in its degradation (Sun A, 2018; Kondo, H .; Maksimova, N .; Otomo, T .; Kato, H .; Imai, A *et al*., 2017; Cancino CMF; Sasada INV; Souza CFM ; Oliveira M, 2016; Neufeld E; Muenzer J, 2001), whose prevalence is 3.72 cases for every 100 thousand live births (Cardoso A; Azevedo AC; Fagondes S *et al*., 2008), while its incidence varies from 1.9 to 4.5 cases in 100 thousand births worldwide (Deepak TA; Krishna S; Taretia R, 2010). Due to the various known clinical and phenotypic forms of MPS, it is classified, according to the deficient enzyme, into 11 types (I; II; IIIA, IIIB, IIIC, IIID, IVA, IVB, VI, VII and IX) and each type corresponds to a different disease (Vasilev F; Sukhomyasova A; Otomo T, 2020; Sainz CM; Muños CZ; Monteagudo AG, 2012).

The progressive accumulation of glycosaminoglycans (GAGs) has negative consequences for different organs and systems. In all types of MPS, macrocephaly, hepatosplenomegaly, umbilical and inguinal hernia, bone dysplasia, delayed motor development, hypoacusis, respiratory distress, facial and dental changes, bulky tongue, heart disease and joint mobility are common (Barth AL; Magalhães TSPC; Reis ABR *et al*., 2017; Cardoso A; Azevedo AC; Fagondes S *et al*., 2008). In most cases, the disease presents in childhood, occurring mainly in children between 2 and 4 years old, being considered a progressive disease and the clinical symptoms are absent at birth. Life expectancy is usually short, with most patients being children or adolescents (Vasilev F; Sukhomyasova A; Otomo T, 2020; Bôas FS; Filho DJ; Fernandes DJ; Acosta AX, 2011). Recognition of the initial symptoms of the disease should be a priority to guarantee the diagnosis, which is done through the measurement of GAGs in the urine (Jones AS; Breen C; Heap F *et al*., 2016; Marshall NR; Hassiotis S; King B *et al*., 2015) and by genetic studies (Bicalho CG; Rezende MM; Nogueira AMCM; Paulon RMC; Acosta AX, 2011). The

accurate diagnosis also guarantees the genetic monitoring of the family, which is important because it allows early diagnosis and genetic counseling in future pregnancies (Romãoa A; Simonb PE; Góes JE; Pintoc L, 2017). Treatment is palliative and consists of weekly enzyme replacement therapy (ERT), intravenously with the specific enzyme deficient in the patient and multidisciplinary follow-up (Giugliani R, Federhen A, Munoz RM, Vieira TA *et al*., 2010). Mucopolysaccharidosi is a group of chronic, serious, progressive diseases with high mortality before adulthood (Neufeld E; Muenzer J, 2001). It is important that patients with these characteristics, have their quality of life (QOL) measured using scales, so that, knowing their weaknesses, health professionals can offer assistance care geared to their needs and qualifying the child's clinical management sick with a chronic condition (Lecce TM; Casarim ST; Santos B, 2017). The interest in the concept of QOL in the health area is recent and results from new paradigms such as the increase in the prevalence of chronic-degenerative diseases and advances in treatment, with the possibility of controlling these diseases, allowing for a longer life expectancy (Lecce TM; Casarim ST; Santos BP, 2017). It is also noticed an increase in the number of studies that seek to measure the QoL of children in the child's own perception. This measurement is important because it has a multidimensional character, involving social, psychological and health issues of individuals (Souza JG; Pamponet MA; Souza TC; Pereira AR *et al*., 2014). Thus, the aim of this study was to assess the QOL of children and adolescents with mucopolysaccharidosis treated at a treatment center for inborn errors of metabolism in city the in Recife-PE.

MATERIALS AND METHODS

Descriptive, cross-sectional study with a quantitative approach and analytical component. Data collection was carried out from June to December 2013 with all patients who met the inclusion criteria that were met at the Treatment Center for Inborn Metabolism Errors (CETREIM) of the Instituto de Medicina Integral Prof. Fernando Figueira (IMIP) in Pernambuco, which was the only Treatment Center in the North / Northeast and the second largest in Brazil. Children (2 - 10 years) and adolescents (> 10 to <18 years) with a diagnosis of MPS using ERT were included. Data collection was performed through interviews with patients' caregivers and patients, using a form containing sociodemographic and clinical questions, and the health-related QL questionnaire "Pediatric Quality of Life Inventory (Peds-QL)" divided by range age group (2-4, 5-7, 8-12 and 13-18). This questionnaire has 21 items (age group 2-4) and 23 items for other age groups, covering: 1) physical dimension (eight items), 2) emotional dimension (five items), 3) social dimension (five items), and 4) school dimension (five items). The form of scoring of all items varies from zero to four, being: (0) never, (1) almost never, (2) sometimes, (3) often, (4) almost always.

The data were analyzed using the Stata 12.1 software. Descriptive analysis and frequencies, measures of central tendency, and dispersion (standard deviation and percentiles) were calculated. The results of the QOL questionnaire were scored inversely and transposed linearly to a scale of 0 - 100 (0 = 100; 1 = 75; 2 = 50; 3 = 25; 4 = 0); thus, the higher the score, the better the health-related QOL. The scores of the scales were computed as the sum of the items divided by the number of items answered (which solved the missing data question) and presented as medians and intervals between the first and third quartiles.

The Kruskall Walls test and the Pearson's correlation coefficient were used to compare the medians, to correlate some numerical variables with the quality of life scores, considered a significance level of <5%. The study was approved by the Research Ethics Committee of IMIP, protocol n ° 3477-13 in Ordinary Meeting of March 13, 2013.

RESULTS

During the study period, there were 29 children and adolescents with MPS II and VI who underwent ERT and were included in the study. The study had a summarized sample because it is a rare disease in Brazil and worldwide. The patients' age ranged from two to 18 years with a mean (SD) of 9.0 (± 4.4) years. Table 1 describes the sociodemographic and clinical characteristics. Children had higher QOL scores in terms of physical dimension (p = 0.008) and overall quality of life (p = 0.033) when compared to adolescents. Individuals who lived in the countryside had higher QoL scores in the physical dimension when compared to those who lived in the Metropolitan Region of the Pernambuco state (p = 0.037). The first symptoms of the disease appeared when the child was 18 ± 15 months old on average. Among these symptoms, 75.9% (n = 22) had some type of bone deformity; macrocrania and the presence of umbilical and / or inguinal hernias was noticed in 20.7% (n = 6).

The patients had an average (SD) 42 months (± 29) when the disease was diagnosed and waited an average (SD) 28 months (± 28) after diagnosis to start the ERT. Limitations during activities involving finger movement were reported in 69.0% (n = 20) and the presence of claw hands was present in 93.1% (n = 27). Most participants did not have difficulties in walking 79.3% (n = 23). Participants had a mean (SD) of 2.8 (± 3,3) hospitalizations in their lifetime and performed an average (SD) 1.0 (± 1.4) surgeries from birth to the day of the interview. Of the participants included, eight had MPS II and the rest MPS VI. Table 02 shows the association between clinical variables and QOL scores. Patients diagnosed with MPS VI had higher medians of QOL scores in all aspects than patients with MPS II in physical capacity (p = 0.042), psychosocial (p = 0.003), and overall quality of life (p = 0.004). The presence of neurological changes was associated with the lowest quality of life score in all aspects: physical (p = 0.010), psychosocial (p = 0.000) and general QOL (p = 0.001). Participants with a history of two or more hospitalizations in their lifetime had lower median QOL scores than participants with less than two hospitalizations for physical appearance (p = 0.008) and general QOL (p = 0.035).

In Table 2, the quality of life scores of physical capacity had the lowest median among all aspects (53,1). In addition, the aspect related to social functioning, presented the highest medians of quality of life scores among all domains (65,0). The figure 1 shows dispersion diagrams and Pearson's correlation coefficients for the associations of the general quality of life score with the variables current age of the patient, age of the patient at diagnosis, time of treatment with ERT and time between diagnosis and treatment. start of treatment. Significant inverse correlations were found between the participants' age and the general quality of life scores, indicating that the younger the patient was, the better his quality of life was (r = -0.63; p = 0.001). Another important finding was the inverse relationship between the patient's age at diagnosis and QOL scores.

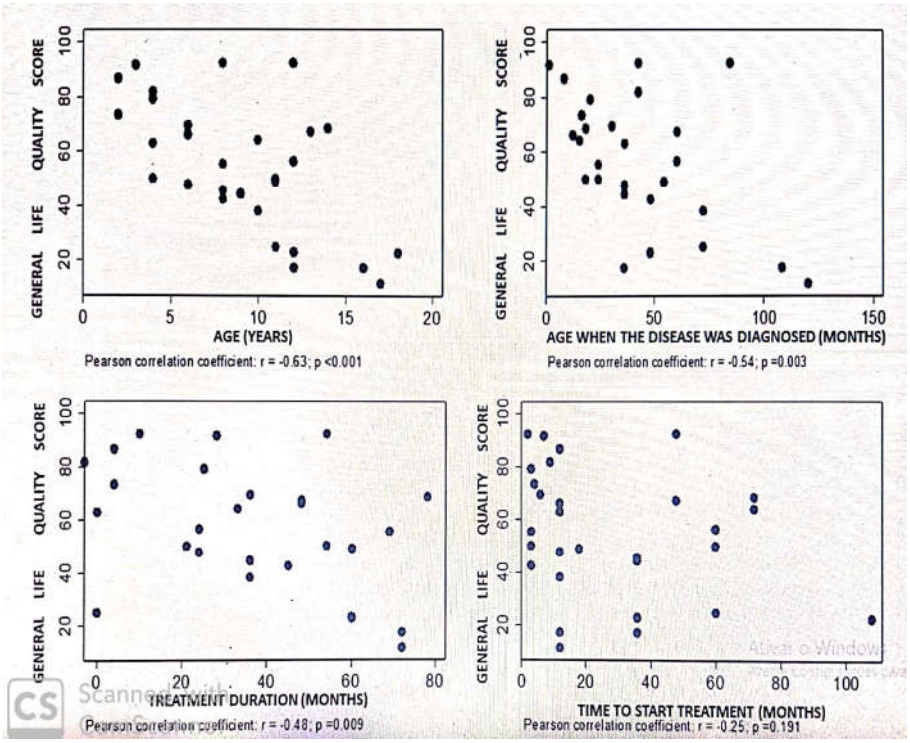

Figure 1. Dispersion diagrams and Pearson's correlation coefficients for associations of general quality of life score with age, age at diagnosis, duration of treatment and time to start of treatment, Pernambuco, Brazil, 2013

Table 1. Physical, psychosocial and general quality of life aspects, according to the sociodemographic and clinical characteristics of patients with Mucopolysaccharidosis, Pernambuco, Brazil, 2013

		Physical aspect		Psychosocialaspect		Overall quality of life	
Feature	N	Median (Q1-Q3)	p[a]	Median (Q1-Q3)	p[a]	Median (Q1-Q3)	p[a]
Age (years)			0,008		0,063		0,033
2 a 10	17	68,8(40,6-81,3)		65,6(51,7-77,5)		64,1(47,8-79,2)	
11 a 18	12	25,0(9,4-51,6)		48,3(30,2-66,7)		37,0(20,1-62,0)	
Gender			0,345		0,509		0,396
Male	20	48,4(18,8-70,3)		58,3(37,7-75,4)		52,7(31,5-69,0)	
Feminine	9	62,5(34,4-81,3)		60,0(51,7-75,0)		63,0(48,9-73,4)	
Frequent school			0,964		0,322		0,472
Yes	18	51,6(34,4-62,5)		59,2(51,7-73,3)		56,0(47,8-67,4)	
No	11	71,9(9,4-81,3)		45,0(30,0-80,6)		44,6(17,3-81,9)	
Origin			0,037		0,706		0,298
Countryside	17	62,5(40,6-81,3)		58,3(51,7-77,5)		56,5(45,7-79,2)	
RMR[b]	12	37,5(12,5-53,1)		60,0(40,0-71,7)		52,2(24,0-67,4)	
Caregiver			0,796		0,636		0,667
Mother	27	50,0(21,9-78,1)		58,3(43,3-77,5)		50,0(38,0-73,4)	
Other	2	53,1(53,1-53,1)		65,8(58,3-73,3)		61,4(56,5-66,3)	
Diagnosis			0,042		0,003		0,004
MPS II	8	15,6(9,4-46,9)		30,2(25,0-45,8)		24,0(17,3-41,3)	
MPS VI	21	53,1(40,6-78,1)		65,6(56,7-77,5)		64,1(50,0-73,4)	
Age at diagnosis			0,129		0,158		0,090
Up to 24 months	10	57,8(50,0-81,3)		71,7(63,3-78,3)		67,4(55,4-79,2)	
Between 25 and 48 months	10	54,7(9,4-71,9)		51,7(35,0-70,0)		46,2(23,1-69,6)	
More than 48 months	8	28,1(15,6-53,1)		51,7(25,2-66,7)		43,5(21,2-62,0)	
Time between diagnosis and start of treatment			0,228		0,316		0,198
Up to 12 months	16	65,6(32,8-81,3)		64,5(49,2-79,0)		64,7(45,1-80,6)	
Between 13 and 36 months	5	21,9(9,4-34,4)		45,0(30,0-56,7)		44,6(23,1-45,7)	
Between 37 and 60 months	5	53,1(46,9-53,1)		58,3(51,7-75,0)		56,5(50,0-67,4)	
More than 60 months	3	50,0(0,0-53,1)		70,0(35,0-78,3)		64,1(22,8-68,5)	
Neurological alteration			0,010		0,000		0,001
Yes	6	12,5(9,4-15,6)		30,0(20,0-30,4)		20,2(17,3-25,0)	
No	23	53,1(40,6-81,3)		65,6(51,7-78,3)		64,1(48,9-79,2)	
Limitation in the moments of the fingers			0,090		0,282		0,056
Yes	20	43,8(21,9-60,9)		57,5(38,5-71,7)		49,5(40,2-65,2)	
No	8	75,0(56,3-87,5)		73,8(54,5-79,4)		71,5(59,2-83,0)	
Nunber of hospitalization			0,008		0,098		0,035
≤ 2	19	62,5 (40,6 – 81,2)		63,3 (46,7 – 80,6)		63.0 (44.6 -81.9)	
> 2	10	28,1 (9,4 – 50,0)		54,2 (30,0 – 70,0)		46,7 (17,3 -64,1)	
Walking patient			0,005		0,010		0,005
Can walk without help	23	53,1(40,6-81,3)		63,3(51,7-78,3)		63,0(47,8-79,2)	
Walk with help	2	31,3(9,4-53,1)		60,0(45,0-75,0)		45,2(23,1-67,4)	
Don't wander	4	7,8(3,1-12,5)		25,0(20,0-32,5)		17,3(14,4-20,1)	

[a]Kruskal Wallis test. [b]metropolitan Recife region

Table 2. Medians of Quality of life scores in the physical, emotional, social, school and psychosocial health aspects of patients with Mucopolysaccharidosis, Pernambuco, Brazil, 2013

Aspects	Median	Minimum	Maximum
Physical ability	53,1	0,0	100,0
Emotional aspect	58,3	35,0	100,0
Social	65,0	15,0	100,0
School activity	55,0	15,0	85,0
Psychosocia	58,3	20,0	91,7
Overall quality of life	55,4	11,5	92,4

Thus, study participants who were diagnosed early had better quality of life scores (r = - 0.54; p = 0.003). No significant correlations were found between the time variables between the diagnosis of the disease and the beginning of treatment with TRE, although a tendency for better QoL scores to be associated with the shorter time taken between diagnosis and treatment has been observed (r = -0.25; p = 0.191). The value of the coefficient (r = - 0.48), indicates an inverse relationship between QOL and the time of treatment with ERT, with higher quality of life scores in patients with shorter treatment with ERT (p = 0.009).

DISCUSSION

The mucopolysaccharide patients had significantly lower QoL scores in all aspects compared to healthy children and adolescents. This is perceived by comparing the QOL scores of patients with MPS in this study with the scores of healthy children in a study conducted in São Paulo, where the PedsQL QL form (Klatchoian DA; Len CA; Terreri MT; Silva was validated for Brazil). M; Itamoto C; Ciconelli RM *et al*., 2008). In this comparison, general QOL scores were verified (Patients with MPS = 53.1; healthy patients = 97.86), showing the damage that this disease brings to the quality of life of patients with MPS (Klatchoian DA; Len CA; Terreri MT; Silva M; Itamoto C; Ciconelli RM *et al*., 2008). The lowest quality of life score was the physical aspect, which may be associated with the impairment of several joints that compromise the individual's ability to perform activities of daily living (Cardoso A; Azevedo AC; Fagondes S; Burin MG; Giugliani R; Schwartz IV, 2008), given this, also evidenced in a national research (Amaral IABS; Filho RLO; Neto JAR; Reis MCS, 2017). Another more recent study also shows that patients with MPS present a significant reduction in the functional capacity and strength of the respiratory muscles, corroborating the results found in this study (Figueirêdo BB; Magalhães PA; Andrade LB; Bezerra; Duarte MC, 2018).

The mucopolysaccharide VI does not course with cognitive alterations or interfere with intelligence (Mizuno CA; Figueiredo JB; Teza IT; Silva TA *et al*., 2010), justifying the majority of the individuals in the study attending school. However, some studies show that hospitalizations, due to the symptoms of the disease, such as joint pain, visual, hearing impairments, sleep apnea and heart disease, leading to the need for more medical appointments and consequently absences from school, which contributes to the delay and impairment of their learning (Regier DS, 2016; Holanda ER, Collet N, 2011), favoring the presentation of lower QOL scores in the aspect of school activity. The aspect that presented the best quality of life score was related to social functioning, this fact can be justified by the preserved mental health of most patients with MPS VI, a fact corroborated by a similar study with another instrument, where in the aspects of mental health, patients had the best average among the other scores of the quality of life assessment (Costa BGS; Ferreira TTC; Freitas SEO *et al*., 2017). However, the relatives of children with chronic diseases reveal the young people's concern with the self-image modified by the disease and report situations of exclusion driven by prejudice and lack of solidarity from colleagues in the face of falling ill, which can be barriers to the school inclusion of these patients (Pedroso ML; Motta MG, 2010).

The predominant type of MPS in this study was VI (n = 21), which despite being one of the rarest types in the world, is the most frequent in Brazil, a fact that is in agreement with other studies (Federhen A; Pasqualim G; Freitas TF *et al*., 2020; Cardoso A; Azevedo AC; Fagondes S *et al*., 2008). Although the explanation for this finding is unknown, the existence of a common mutation (1533del23) in the ARSB gene is described, which was present in Brazilian patients with MPS VI and which are distributed in 18 Brazilian states, the vast majority in the Northeast with 50%, followed by Southeast with 37.28% (Bochernitsan AN, 2013).

Most patients with MPS II in this study had neurological changes, contributing to low QoL scores in all aspects. The clinical presentation of MPS II involves clinical features such as heart disease, restrictive lung disease, joint contractures and neurological changes. Furthermore, in severe forms of MPS II, cognitive impairment progresses during childhood (Schwartz IV; Pinto LL; Breda G; Lima L; Ribeiro MG *et al*., 2009). Patients diagnosed with early disease had higher QOL scores. However, the average age at diagnosis of the disease was high (on average 42 months), higher than that found in the south of the country, approximately 28.5 months (Horovitz DD; Magalhães TS; Acosta A; Ribeiro EM; Giuliani LR *et al*., 2013). In this study, the long time for diagnosis is probably due to the fact that there is no reference center for these patients at the time when most were diagnosed, as CETREIM in Pernambuco was opened in 2013. The long period between diagnosis and start of treatment may be related to the difficulty encountered by patients in obtaining enzymes for treatment, as they receive it via an expanded access program (subsidized by the industry), or as commercial use financed by state governments or Union through judicialization (Diniz D; Medeiros M; Schwartz IV, 2012; Medeiros M; Diniz D; Schwartz IV, 2013). Another fact associated with the long period between diagnosis and the start of treatment is related to the lack of treatment when the disease was diagnosed in several patients, as the TRE was approved for use in Brazil in 2008 for MPS II and 2009 for MPS VI, receiving registration from ANVISA (Giugliani R, Federhen A, Munoz RM, Vieira TA *et al*., 2010). The beginning of treatment before the age of five, can improve some aspects of the disease and slow its progression, in children with MPS type VI (Horovitz DD, Magalhães TS, Acosta A, Ribeiro EM, Giuliani LR *et al*., 2013). In patients with MPS II, early diagnosis and treatment can bring some benefits, such as reduced urinary GAG excretion and hepatosplenomegaly, as well as improved joint mobility (Alegra T; Eizerik DP; Cerqueira CC; Pereira TV; Dornelles AD; Schwartz IV, 2013). Patients who had longer treatment with TRE did not have better QOL scores compared to other patients. It is suggested that this may be related to the presence of the age variable acting as a confounder, since the longer the treatment time, the greater the patient's age, which has already been verified, is related to lower QOL scores. However, ERT has been shown to be effective, safe and capable of providing clinical and quality of life improvement

for patients (Alegra T; Eizerik DP; Cerqueira CC; Pereira TV; Dornelles AD; Schwartz IV, 2013).

Conclusão

The results suggest that the QOL of patients with MPS is impaired mainly in the physical dimension. Lower age, MPS type VI and early diagnosis were variables associated with higher QOL scores, reinforcing the importance of raising awareness and disseminating degrees in rare diseases in the scientific community, such as mucopolysaccharidosis, so that they acquire the ability to recognize signs and symptoms. symptoms of the disease, favoring diagnosis and early treatment, in order to contribute to a better QOL for people with this disease.

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