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Health-related quality of life in children and adolescents with sickle cell disease

Qualidade de vida relacionada à saúde em crianças e adolescentes com doença falciforme

Calidad de vida relacionada a la salud de niños y adolescentes con enfermedad falciforme

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Abstract

To assess the health-related quality of life of children and adolescents with sickle cell disease (SCD). This is a cross-sectional study carried out with 97 male and female patients aged 5 to 18 years with clinical and laboratory diagnosis of SCD, seen at the Hematology and Hemotherapy Hospital of Pernambuco. The Pediatric Quality of Life Inventory™ questionnaires, version 4.0 – child/adolescent report – were applied. Most patients were female (76.3%), had sickle cell anemia (89.7%) and mixed race (59.8%). There was a significant association in the psychosocial domain between age groups 5 to 7 (72.10) and 8 to

12 years (p≤0.05), the latter of which had the worst quality of life score (65.36). There were significant differences between sexes only in patients aged 13 to 18 years for physical functioning and for the overall mean of the domains. The means in both cases were higher in female patients than in male ones (70.89 x 56.88 for physical functioning and 71.72 x 59.77 for the overall mean of the domains). Poor quality of life was observed among children and adolescents with SCD, with negative impacts according to age and sex.

Keywords: Sickle cell disease; Quality of life; Child; Adolescent.

Resumo

Analisar a qualidade de vida relacionada à saúde de crianças e adolescentes com doença falciforme (DF). Trata-se de um estudo transversal realizado com 97 pacientes na faixa etária entre cinco e 18 anos com diagnóstico clínico e laboratorial de DF, de ambos os sexos, atendidos no Hospital de Hematologia e Hemoterapia de Pernambuco. Foram aplicados os questionários Pediatric Quality of Life Inventory, versão 4.0 - relato da criança/adolescente. A maioria dos pacientes era do sexo feminino (76,3%), apresentava anemia falciforme (89,7%) e de etnia parda (59,8%). Houve associação significativa na dimensão psicossocial entre a faixa etária 5 a 7 (72,10) e de 8 a 12 anos (p≤0,05), esta última com um pior score de qualidade de vida (65,36). Em relação ao sexo, as únicas diferenças significativas ocorreram na faixa etária de 13 a 18 anos na variável de dimensão física e na média das dimensões, sendo as médias nos dois casos mais elevadas no sexo feminino do que no masculino (70,89 x 56,88 na dimensão física e 71,72 x 59,77 na média das dimensões). A qualidade de vida das crianças e dos adolescentes com DF encontra-se prejudicada, podendo haver interferências negativas de acordo com a faixa etária e o sexo.

Palavras-chave: Doença falciforme; Qualidade de vida; Criança; Adolescente.

Resumen

Analizar la calidad de vida relacionada a la salud de niños y adolescentes con enfermedad falciforme (EF). Este es um estudio transversal realizado con 97 pacientes de entre 5 y 18 años con diagnóstico clínico y de laboratorio de EF, de ambos sexos, atendidos en el Hospital de Hematología y Hemoterapia de Pernambuco, Brasil. Se aplicaron los cuestionarios del Pediatric Quality of Life Inventory, versión 4.0 - Informe del niño / adolescente. La mayoría de los pacientes fueron de sexo femenino (76,3%), presentaban anemia de células falciformes (89,7%) y pertenecian a un grupo etnico mixto (59,8%). Hubo una asociación significativa en la dimensión psicosocial entre el grupo de edad de 5 a 7 años (72,10) y el de 8 a 12 años

(p≤0,05) – este último presentó una peor puntuación de calidad de vida (65,36). En cuanto al sexo, las únicas diferencias significativas se dieron en el grupo de edad de 13 a 18 años en la variable dimensión física y en la media de las dimensiones, siendo los promedios en ambos casos superiores en mujeres que en hombres (70,89 vs. 56,88 en la dimensión física y 71,72 vs. 59,77 en la media de las dimensiones). La calidad de vida de los niños y adolescentes con EF se encuentra deteriorada y perjudicada, pudiendo haber interferencias negativas según la edad y el sexo.

Palabras clave: Enfermedad falciforme; Calidad de vida; Niño; Adolescente.

1. Introduction

Sickle cell disease (SCD) is one of the most common inherited hemoglobinopathies worldwide. It is caused by a single nucleotide substitution, converting a glutamic acid codon to a valine codon at position 6 of the β-globin subunit. This amino acid substitution causes some changes in the physical properties of the globin chain, leading to hemoglobin S (Hb S) polymerization during physiological stress (especially hypoxia), causing erythrocytes to take on a sickle shape. This intracellular event also induces the expression of several cell adhesion molecules that facilitate the physical interaction of sickle-shaped erythrocytes with leukocytes and endothelium, leading to vaso-occlusive events and hemolytic anemia, which play a central role in the clinical complications associated with SCD (Raghunathan *et al*., 2018).

This disease comprises a generic term that encompasses a group of inherited hemolytic anemias (Felix *et al*., 2010). Notwithstanding the markedly distinct features of sickle cell diseases, their clinical and hematologic manifestations are similar (Brasil, 2014).

Sickle cell anemia (SCA) is the genetic disorder with the most severe clinical and hematologic presentation and also the one with the highest prevalence (Naoum, 2000). In Brazil, SCA is highly prevalent and considered a public health problem (De Sousa & Silva, 2017).

As far as the physiology of this disease is concerned, red blood cells containing polymerized Hb S are rigid and non-deformable, contributing to microvascular occlusion, which eventually leads to tissue ischemia and organ dysfunction (Madigan & Malik, 2006; Vekilov, 2007). Interestingly, SCD is characterized by many acute and chronic complications, including anemia, serious infections, hemolytic and vaso-occlusive crises, bouts of recurrent pain, stroke, acute chest syndrome, pulmonary hypertension, and chronic organ damage (Steinberg, 2009; Therrel *et al*., 2015). In addition to systemic symptoms, clinical oral signs

commonly described in the literature include mucosal pallor, delayed tooth eruption, enamel and dentin demineralization, hypercementosis, dental pulp calcifications, changes in the superficial cells of the tongue epithelium, and bone alterations, causing maxillary protrusion and formation of a dense trabecular pattern (Pithon, 2011).

As patients with SCD are at a greater risk for severe comorbidities associated with vascular occlusion, hemolysis, and infection, in addition to oral disorders, their quality of life could be compromised (Fernandes *et al*., 2016). Hemoglobinopathies are often severe, present difficult management, and have a remarkable psychosocial impact on patients and on their families (Dahmani *et al*., 2017).

Therefore, the aim of the present study was to assess the health-related quality of life of children and adolescents with SCD.

2. Methods

This was a quantitative cross-sectional study (Pereira *et al*., 2018). The census sample was compound of 97 male and female patients aged 5 to 18 years with clinical and laboratory diagnosis of SCD, seen between March and July 2019 at the Hematology and Hemotherapy Hospital of Pernambuco (HEMOPE), a referral center for the treatment of these patients. As a result of the specificity of the study population and the difficulty associated with random selection of patients with SCD, we used a nonprobability (convenience) sample.

Those children and adolescents whose parents and/or legal guardians signed the free informed consent form were included in the study. An assent form was signed by adolescents aged 10 to 18 years. Patients with other systemic diseases, psychiatric disorders, neurologic disorders, and other special needs, and whose general health status did not allow the application of the questionnaire were excluded from the study.

The Pediatric Quality of Life Inventory^{TM} (PedsQL^{TM}) – child/adolescent report version 4 was used (Varni *et al*., 1999). This questionnaire evaluates the quality of life of healthy children and adolescents and of those with chronic diseases (Menezes *et al*., 2013). The questionnaire was validated and translated into Portuguese (Klatchoian *et al*., 2008). It should be underscored that the questionnaires were applied by conducting interviews targeted at children and adolescents, in the presence of the research team only.

The instruments comprise 23 items involving the following dimensions: physical (8 items), emotional (5 items), social (5 items) and scholar (5 items), and were developed through focus groups, cognitive interviews, pre-testing and field testing measurements (Varni

et al., 2001). The assessment includes the following age groups: five to seven, eight to 12 and 13 to 18. The items for each of the questionnaires are similar, differing in developmentally appropriate language and the use of first or third person tense (Klatchoian *et al*., 2008). Approximately 5 minutes are necessary to complete the application (Varni *et al*., 2001).

The questions investigated how much of a problem each item was for the children and adolescents in the past month, with three answer options for children aged 5 to 7 years (0 – never; 2 - sometimes; 4- almost always) and five answer options for those aged 8 years and older (0 – never; 1 – almost never; 2 – sometimes; 3 – often; 4 – almost always). Even though PedsQL™ was designed to be applied to children and adolescents aged 8 to 18 years as a self-administered questionnaire, it can be administered by the interviewer. Negative questions are reversed scored on a 0–100 scale (0–100; 1–75; 2–50; 3–25; 4–0); hence, higher scores indicate better quality of life. The domain scores can be computed as the sum of the items divided by the number of answered items, but if more than 50% of the items are missing, the domain score is not computed (Klatchoian *et al*., 2008). The summary score for physical health (eight items) is the same as that used for the physical domain. To create a summary score for psychosocial health (15 items), the mean is computed as the sum of the answered items on the scales for emotional, social, and school functioning divided by the number of items (Klatchoian *et al*., 2008). Permission for the use of PedsQL™ quality of life modules was granted by the MAPI Research Trust.

This study was approved by the Research Ethics Committee of HEMOPE (CAAE: 91720618.2.3001.5195 and process number: 2.934.364).

Mean, median, and standard deviation of the numerical variables were estimated. One of the following tests was used for comparison of numerical variable categories: Student's t test with equal variances, Student's t test with unequal variances in case of two categories, or the F test (ANOVA) in case of more than two categories. If the F test (ANOVA) showed significant difference between the categories, the least significant difference method was used as multiple comparison test. Student's t and F (ANOVA) tests were chosen for comparisons in which data were normally distributed (in each category). The normality of data was checked by the Shapiro-Wilk test and equal variance was determined by Levene's F test.

The significance level was set at 5% for all statistical tests. The data were entered into an EXCEL spreadsheet and the statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 23.

3. Results

The sample analyzed in this study consisted of 97 patients. Table 1 shows that most children and adolescents were female (76.3%), were in the age range of 8 to 12 years (47.4%), had SCA (89.7%), and were of mixed race (59.8%).

Table 1 – Characteristics of the sample of children and adolescents. Recife, Brazil, 2019.

Variable	n	%
Total	**97**	**100.0**
Sex		
Male	23	23.7
Female	74	76.3
Age (in years)		
5 to 7	27	27.8
8 to 12	46	47.4
13 to 18	24	24.7
Type of disease		
Sickle cell anemia	87	89.7
Beta thalassemia	6	6.2
SC hemoglobinopathy	4	4.1
Ethnicity		
White	10	10.3
Mixed	58	59.8
Black	29	29.9

Source: Authors.

Table 2 shows that the only significant difference between the age groups was observed in psychosocial functioning ($p < 0.05$). Note that this variable had the highest mean for children aged 5 to 7 years (72.10) and the lowest mean for those aged 8 to 12 years (65.36). The remaining domains were not statistically significant in terms of age.

Table 2 – Statistics for the quality of life domains in patients with sickle cell disease, according to age. Recife, Brazil, 2019.

Variable	Age (in years) 5 to 7 (n = 27) Mean ± SD (median)	8 to 12 (n = 46) Mean ± SD (median)	13 to 18 (n = 24) Mean ± SD (median)	p value
Physical functioning	64.12 ± 16.41 (68.75)	64.33 ± 14.26 (62.50)	67.97 ± 13.27 (67.19)	$p^{(a)} = 0.561$
Psychosocial functioning	72.10 ± 9.39 (70.00) **(A)**	65.36 ± 12.99 (64.17) **(B)**	70.49 ± 11.39 (73.33) **(AB)**	$p^{(a)} = 0.042^*$
Overall mean	68.11 ± 10.88 (66.25)	64.85 ± 11.48 (63.70)	69.23 ± 10.64 (69.11)	$p^{(a)} = 0.235$

* Significant difference at 5%
[a] F test (ANOVA) with LSD comparison test
Note: Different letters in brackets indicate significant difference between the corresponding age groups.
Source: Authors.

Table 3 demonstrates significant differences between sexes only in the 13–18 year age group for physical functioning and for the overall mean of the domain. The means in both cases were higher among female patients than among male ones (70.89 x 56.88 for physical functioning and 71.72 x 59.77 for the overall mean), indicating that male patients in that age range had a worse quality of life score.

Table 3 – Statistics for the quality of life domains in patients with sickle cell disease, according to sex and respective age group. Recife, Brazil, 2019.

Variable	Age (in years)	Sex Male Mean ± SD (median)	Female Mean ± SD (median)	p value
Physical functioning	5 to 7	62.50 ± 18.75 (62.50)	65.63 ± 14.45 (68.75)	$p^{(a)} = 0.630$
	8 to 12	63.13 ± 13.15 (59.38)	64.48 ± 14.54 (62.50)	$p^{(a)} = 0.843$
	13 to 18	56.88 ± 11.14 (62.50)	70.89 ± 12.42 (75.00)	$p^{(a)} = 0.032^*$
	Group total	61.41 ± 15.87 (62.50)	66.34 ± 14.09 (65.63)	$p^{(a)} = 0.158$
Psychosocial functioning	5 to 7	72.56 ± 11.48 (70.00)	71.67 ± 7.37 (71.67)	$p^{(a)} = 0.810$
	8 to 12	71.67 ± 12.02 (76.67)	64.59 ± 13.03 (63.33)	$p^{(a)} = 0.255$
	13 to 18	62.67 ± 10.84 (61.67)	72.54 ± 10.88 (75.00)	$p^{(a)} = 0.084$
	Group total	70.22 ± 11.67 (70.00)	67.97 ± 12.10 (67.50)	$p^{(a)} = 0.435$
Overall mean	5 to 7	67.53 ± 12.82 (67.71)	68.65 ± 9.20 (65.52)	$p^{(a)} = 0.796$
	8 to 12	67.40 ± 10.76 (69.79)	64.54 ± 11.65 (63.54)	$p^{(a)} = 0.605$
	13 to 18	59.77 ± 6.95 (61.15)	71.72 ± 10.13 (71.25)	$p^{(a)} = 0.022^*$
	Group total	65.82 ± 11.40 (66.25)	67.16 ± 11.15 (65.36)	$p^{(a)} = 0.617$

* Significant difference at 5%
[a] Student's t test with equal variances
Source: Authors.

4. Discussion

SCD is one of the most prevalent inherited hematologic diseases worldwide, affecting a remarkable share of the Brazilian population and being recognized as a public health problem (Franco *et al*., 2007). SCD has several complications, including vaso-occlusive crisis, acute chest syndrome, stroke, and several other conditions that may significantly affect the patient's health-related quality of life (Oliveira *et al*., 2019).

This study assessed the quality of life of 97 patients with SCD, among whom 89.7% had SCA. Likewise, in another study, of 100 children diagnosed with SCD, 69% had SCA (Lim *et al*., 2012). SCA was the most common type of hemoglobinopathy detected (63.8%) in the study carried out by Felix *et al*. (2010).

SCD arose in Brazil with the forced displacement of African black peoples taken as slaves from 1550 to 1850. This disease is now widely spread around the world, with a predominance among black and mixed-race individuals (Brasil, 2009). This is in line with our study, in which mixed-race individuals accounted for 59.8%, followed by black (29.9%) and white (10.3%) people.

Significant difference was observed in this study for psychosocial functioning in the age ranges of 5 to 7 years and 8 to 12 years, exhibiting the lowest mean (65.36). By contrast, another study did not find any significant association between age groups for any domain (Menezes *et al*., 2013). According to Menezes *et al*. (2013), all domains had lower quality of life scores, which is in line with the findings of the present study. The literature reports a mean of 60.7 for the quality of life of children with SCD aged 8 to 12 years (Oliveira *et al*., 2019). This reveals that SCD is associated with limitations on different aspects of health-related quality of life, especially on physical, emotional, and school functioning (Menezes *et al*., 2013).

Another study that also applied PedsQL™ Generic Core version 4.0 compared the quality of life of children and adolescents with a chronic disease with that of healthy children and adolescents. The mean for the functioning scores in patients with a chronic disease ranged from 71.87 to 75.99, compared to 89.31 to 95.94 in healthy patients (Lim *et al*., 2012).

In agreement with the literature, studies described that adolescents living with SCD have a poorer health-related quality of life than do their healthy peers (Varni, *et al*., 2001;

Dale *et al*., 2011; Bakshi *et al*., 2017; Kambasu *et al*., 2019). Complications associated with SCD and hospital admissions significantly contribute to this outcome (Kambasu *et al*., 2019).

A study of 963 young individuals revealed that the mean quality of life score, in the absence of an acute or chronic condition, ranged from 78.63 to 87.42 (Varni *et al*., 2001). In the present study, the mean scores of patients with SCD according to age ranged from 64.85 to 69.23, demonstrating that these patients had a worse quality of life than did healthy individuals.

The negative impact, mainly on physical functioning, is associated with pain caused by SCD and with the healthcare demands from children and adolescents with this disease (Mcgrath & Finley, 2000). The scientific literature has shown generalized deterioration of quality of life, especially in those younger than 15 years, and pointed out pain as the major complication (Vilela *et al*., 2012).

Pain crises, hospital admissions, blood transfusions, and other morbidities associated with SCD had a strong impact on the quality of life of these patients (Pereira *et al*., 2013). Therefore, appropriate pain management in SCD is a current concern and a parameter that should be used to assess quality of life (Cordeiro *et al*., 2015).

There was significant difference in physical functioning between sexes in the present study among patients aged 13 to 18 years, with a higher mean among female patients than among male ones (70.89 x 56.88). On the other hand, Dampier *et al*. (2016) demonstrated that female patients reported significantly sharper pain, fatigue, depressive symptoms, and worse scores for physical functioning than did male patients. Similarly, in another study, patients with chronic pain had worse physical functioning of upper limbs, anxiety and depression, whereas female patients had a worse quality of life score, with an increase in the demand for healthcare (Badawy *et al*., 2018). Conversely, the scientific literature has also revealed that male patients present with musculoskeletal disorders and impaired locomotion activity more frequently than do female patients (Cordeiro *et al*., 2015).

Studies on the quality of life of patients with chronic diseases are of utmost importance, as quality of life should be viewed as a determining health factor for the development of policies and measures targeted at the specific characteristics and social context of the disease, and implementation of interventions that could improve vitality, manage pain, and preserve mental health. This could help patients with SCD maintain a high quality of life (Vilela *et al*., 2012; Pereira *et al*., 2013). Given this context, it is suggested further research to be carried out in order to assess the health-related quality of life in patients with SCD compared to healthy patients. In addition, access to multidisciplinary treatment with updated medications is

increasingly feasible and this may reflect in healthy-related quality of life improvements in patients with SCD, showing thus the importance of developing more research in this area.

5. Conclusion

SCD is an inherited hemoglobinopathy that negatively affects the quality of life of children and adolescents. Male patients and those aged 8 to 12 years tend to have a worse quality of life. The most frequently affected domains are psychosocial and physical functioning. Thus, these patients should be given special attention and be followed up early on by a multidisciplinary team for implementation of preventive measures and efficient treatment options that can improve the quality of life of these patients.

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