Original Article

Pain in children and adolescents with falciform disease: observational study

Dor em crianças e adolescentes com doença falciforme: estudo observacional

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ABSTRACT | INTRODUCTION: The most common symptom in sickle cell disease (SCD) is high-intensity pain that manifests in childhood. To be controlled, it is necessary to determine its type. OBJECTIVE: To outline the profile of pain in children and adolescents with sickle cell disease and analyze its impact on quality of life. **METHODS:** Cross-sectional study was con-ducted with children and adolescents aged 8 to 17 years and diagnosed with DF HbSS and HbSC (WHO criteria) in reference units (Salvador, Bahia, Brazil). The Adolescent Pediatric Tool (APPT) children's pain assessment scale and the PedsQL module DF quality of life questionnaire were applied. Associations and correlations between the items of the instruments were tested (Alpha 5%, Beta 20%). CAAE 57274516.8.0000.5544 and 09163419.3.0000.5544. **RESULTS:** Two samples, one with 46 and the other with 44 partici-pants, with about 60% of the HbSS type, confirmed the presence of high pain intensity (from 5.0 ± 0.00 to 9.94 ± 0.23 points on the scale pain intensity) throughout the body and systematic use of analgesics (95.5%). The greater the intensity of pain, especially in the case of neuropathic pain, the greater the total number of descriptors and the use of sensory, affective, and temporal terms ($p < 0.05$), with strong correlations ($r \geq 0.84$; $p < 0,05$) between intensity and sensory and evalua-tive descriptors. **CONCLUSION:** Pain in children and adolescents with SCD is high intensity, with the worst losses for those who report pain with neuropathic characteristics.

KEYWORDS: Sickle Cell Anemia. Pain, Child. Adolescent. Quality.

RESUMO | INTRODUÇÃO: O sintoma mais comum na Doença Falciforme (DF) é a dor de alta intensidade que se manifesta desde a infância. Para ser controlada, é necessária a determinação do seu tipo. **OBJETIVO:** Delinear o perfil da dor em crianças e adolescentes com doença falciforme e analisar o impacto do tipo desta na qualidade de vida. **METODOLOGIA:** Estudo transversal realizado com crianças e adolescentes com idade entre 8 e 17 anos e diagnóstico de DF HbSS e HbSC (critérios da OMS), em unidades de referência (Salvador, Bahia, Brasil). Foram aplicados a escala infantil de avaliação de dor *Adolescent Pediatric Tool* (APPT) e o questionário de qualidade de vida PedsQL módulo DF. Foram testadas associações e correlações entre os itens dos instrumentos (Alfa 5%, Beta 20%). CAAE 57274516.8.0000.5544 e 09163419.3.0000.5544. **RESULTADOS:** Duas amostras, uma com 46 e outra com 44 participantes, com cerca de 60% do tipo HbSS, confirmaram presença de alta intensidade da dor (de 5,0±0,00 a 9,94±0,23 pontos na escala de intensidade de dor) por todo o corpo e uso sistemático de analgésicos (95,5%). Quanto maior a intensidade da dor, principalmente no caso da dor neuropática, maior o total de descritores e o uso de termos sensoriais, afetivos e temporais ($p < 0,05$), com correlações fortes ($r \geq 0,84$; $p<0,05$) entre intensidade e descritores sensoriais e avaliativos. **CONCLUSÃO:** A dor em crianças e adolescentes com DF apresenta alta intensidade, com os piores prejuízos para os que referem dor com características neuropáticas.

PALAVRAS-CHAVE: Anemia Falciforme. Dor. Criança. Adolescente. Qualidade de Vida.

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Introduction

Sickle cell disease (SCD) is the most prevalent hereditary hematological disease in the world, which causes physical, psychological, social, and economic changes in those affected.[1] Approximately 7% of the world population has traits or anemias related to HbSS, HbSC, HbSD, and HbSE hemoglobins.[2] An incidence of SCD in the United States is estimated at one in 350 live births among people of African descent.[3] They estimate that about 3,500 children are born each year with DF in Brazil, the hollow region of Bahia with the highest number of new cases (ratio of 1: 314 live births).[4]

People with SCD, at some point in their lives, will experience the unpleasant experience of the painful crisis related to the vessel occlusion that is responsible for frequent hospitalizations and a high level of suffering in this population.[5] In addition to acute pain attacks, people with SCD also report the presence of Chronic Pain (CP), with daily or almost daily frequency, as the most striking feature of the disease.[6] CP is itself complex and multidimensional morbidity that requires an interdisciplinary approach.[7]

Much of the CP in SCD has been classified as a neuropathic type of pain with the involvement of dysfunctions in the somatosensory system or a consequence of central sensitization.[8] Neuropathic pain is more intense, does not respond well to common analgesics, is more difficult to control, and causes significant losses in the quality of life of the affected.[9] However, many pains can be nociceptive due to local ischemia, and after the crisis, they are remissible. Neuropathic and nociceptive pains respond to totally different behaviors[10], requiring clinicians to make an accurate assessment.

There are reports of manifestation of pain affecting children with SCD since the age of six months.[11] As the nervous system is still forming in childhood and adolescence, the presence of pain without adequate control can generate poorly adaptive plasticity. This brain dysfunction can, in turn, perpetuate pain for life. However, few studies have outlined pain in children and adolescents and evaluated its impact on quality of life, especially in a place with such a high incidence as Bahia.[12] The present study aimed to outline the profile of pain in children and adolescents with sickle cell disease and to assess the impact of the type of pain on the quality of life of this population.

Methodology

A cross-sectional, quantitative, and analytical study, with primary data, was carried out from March 2017 to July 2019 in reference units to monitor people with SC in Salvador, Bahia, and Brazil. The team responsible for the collection involved three nurses and a nursing student, properly trained. The data were obtained in two complementary collections in which both projects were approved by the research ethics committee involving human beings from Escola Bahiana de Medicina e Saúde Pública under the numbers CAAE 57274516.8.0000.5544 and 09163419.3.0000.5544. All the recommendations of the National Health Council and resolution 466/12 were strictly followed.

Children and adolescents aged 8 to 17 years, of both sexes, with a confirmed diagnosis of DF in the genotypes HbSS and HbSC were included according to the criteria of the World Health Organization (WHO), whose legal guardians have signed the free consent form and clarified, and the minors, the term of free and informed consent. Those with confounding comorbidities such as juvenile rheumatoid arthritis, trauma, and other inflammation less than fifteen days were excluded.

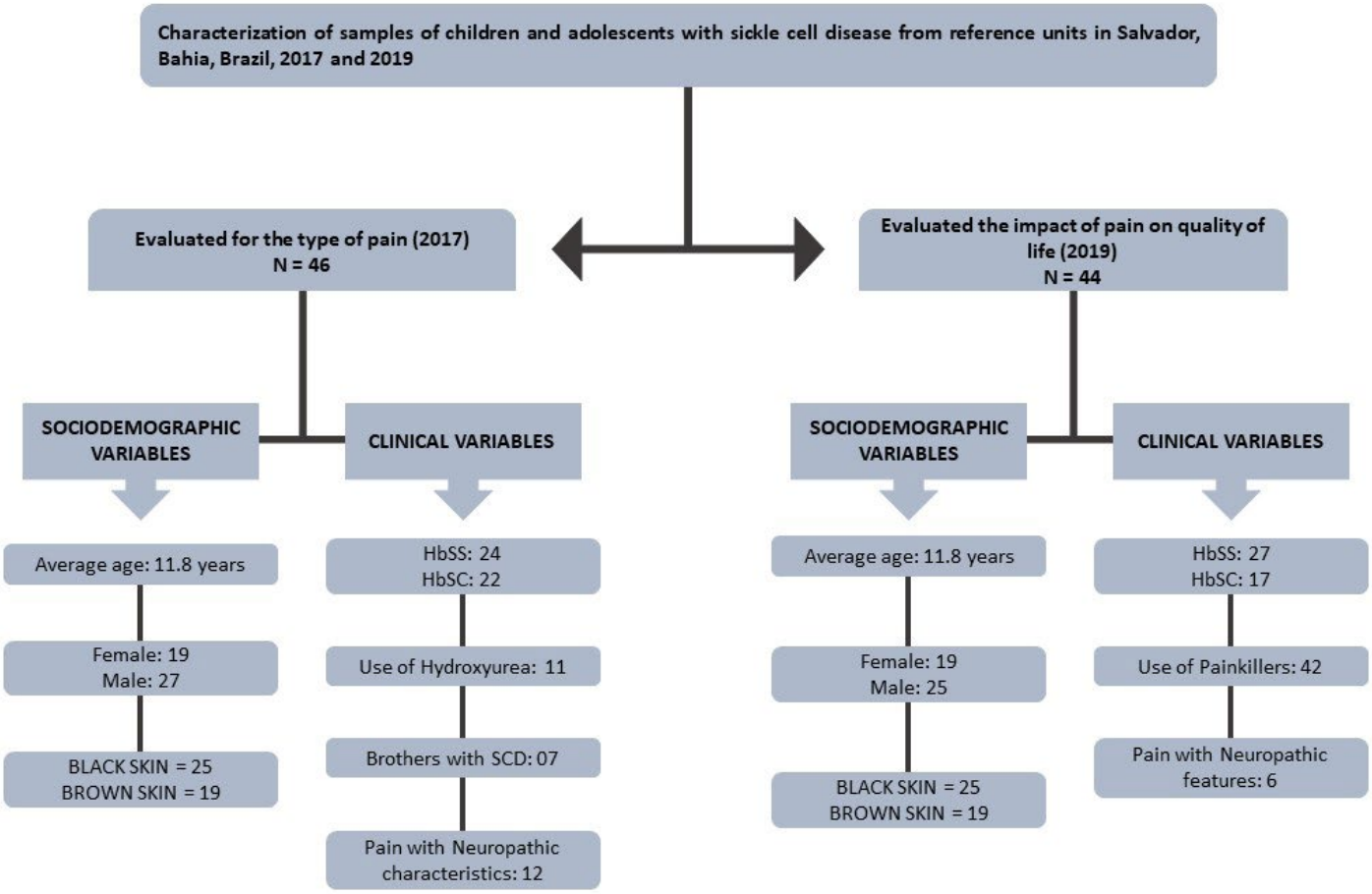
The instruments applied were the Adolescent Pediatric Pain Tool scale (APPT-P Brazil)[13] to assess the location, intensity, and descriptors for pain; and the PedsQL module SCD to assess Health-Related Quality of Life, the use of which was previously authorized by the Mapi Research Trust (http://www.mapi-trust.org/). All recommendations of the developers of these instruments have been followed. Due to the lack of an instrument capable of distinguishing the type of pain in people in this age group, APPT-p Brasil descriptors like those used by Doleur Neuropathic Pain DN-4[14] were used to classify neuropathic pain.

The data were tabulated and analyzed using the Social Package for Social Science (SPSS version 14 for Windows). Quantitative data were presented with central tendency and dispersion measures and categorical variables in absolute numbers and proportions. To test the hypothesis if the pain intensity was related to the APPT-P Brazil descriptors, the Kruskall-Wallis test was applied. The Chi-square test was applied, and with the intensity of the pain, the Mann-Whitney test the hypothesis of whether the type of disease (HbSS or HbSC) is related to the pain location and frequency. The same tests were used to compare the group that presented pain with neuropathic characteristics with the others. Spearman's correlation was also evaluated to compare the descriptors with the domains of quality of life in different types of pain. All tests adopted a power of 80% and a significance of 5%.

Results

For the first part of the analysis, the sample included 46 children and adolescents, while the second assessed the impact on quality of life in 44 participants (Figure 1).

Figure 1. Flowchart of the first part of the analysis



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The demographic and clinical data of the two samples are described in Table 1.

Table 1. Characterization of children and adolescents with sickle cell disease in reference units in Salvador, Bahia, Brazil, 2017 and 2019

Evaluated for the type of pain N = 46 (2017)		
Sociodemographic variables	**N**	**%**
Male	27	58,7
Self-reported skin color as Black	25	54,3
Self-reported skin color as Brown	19	41,3
	M	**DP**
Age	11,8	2,30
Clinical Variables	**N**	**%**
HbSS	24	52,2
HbSC	22	47,8
Use of Hydroxyurea	11	23,9
Brothers with SCD	7	13,0
Pain with Neuropathic Features	12	26,1
The impact of pain on quality of life was assessed N = 44 (2019)		
Sociodemographic variables	**N**	**%**
Male	25	56,8
Self-reported skin color as Black	25	54,3
Self-reported skin color as Brown	19	41,3
	M	**DP**
Age	11,8	2,73
Clinical Variables	**N**	**%**
HbSS	27	61,4
HbSC	17	38,7
Use of Painkillers	42	95,5
Pain with Neuropathic Features	6	13,6

Pain intensity was medium (5.00 ± 0.00) to severe (9.94 ± 0.23) according to the points of the APPT visual pain scale. The higher the intensity, the more descriptors were used by the participants. The pain intensity ($p < 0.001$), the total number of descriptors ($p = 0.003$), the effective descriptor ($p = 0.034$), and the evaluative descriptor ($p < 0.001$) of the APPT were related to the categorized "worst pain" intensity in three strata, Table 2.

Table 2. Continuous variables related to pain intensity in children and adolescents with sickle cell anemia, Salvador, Bahia, Brazil, 2017

	Moderate pain Md (IQ) **	Much pain Md(IQ)**	Worst pain Md(IQ)**	P-value
Pain intensity	5,0 (5,0–5,0)	7,0 (7,0–7,8)	10,0 (10,0–10,0)	**<0,001**
Total Descriptors	18,0 (13,0–22,0)	23,0 (18,2–29,5)	25,5 (22,7–32,2)	**0,003**
Sensory Descriptor	8,0 (5,0–11,0)	10,0 (5,5–14,5)	10,0 (8,0–16,0)	0,132
Affective Descriptor	4,0 (2,0–5,0)	5,0 (4,0–7,0)	6,0 (4,0–8,0)	**0,034**
Evaluative Descriptor	2,0 (1,0–3,0)	4,0 (2,2–5,0)	5,0 (4,0–6,0)	**<0,001**
Time descriptor	3,0 (3,0–5,0)	4,5 (3,0–5,7)	3,5 (3,0–6,2)	0,716

Kruskal-Wallis test ** Median and interquartile range

The most affected sites were the legs in the HbSS group and arms in the HbSC group. Most of them report that the pain affects them a few times a month. No significant associations were identified between the type of disease and the locations, frequency, and intensity of pain, Table 3.

Table 3. Relationship between the type of disease and some variables related to pain in children and adolescents with sickle cell anemia, Salvador, Bahia, Brazil, 2017-2019

	SS N=24	SC N=22	P-value
Pain location[a]			0,079
Abdomen	3(12,5)	4(18,2)	NA
Arms	3(12,5)	10(45,5)	NA
Legs	11(45,8)	6(27,3)	NA
Dorsal	3(12,5)	0(0,0)	NA
Joints	0(0,0)	1(4,5)	NA
Chest	1(4,2)	0(0,0)	NA
Low back	3(12,5)	1(4,5)	NA
Frequency of pain[a]			0,068
Almost every day	1(4,2)	2(9,1)	NA
Few days a week	2(8,3)	1(4,5)	NA
Few times a month	19(79,2)	11(50,0)	NA
No information	2(8,3)	2(9,1)	NA
Sporadic	0(0,0)	6(27,3)	NA
Pain intensity[b]	8,0 (7,0–10,0)	7,0 (5,0–10,0)	0,244

[a]Categorical variables expressed in N (%) and Chi-square test.

[b]Numerical variables expressed by the median and interquartile range and Mann-Whitney test.

NA = not applicable

Pain with neuropathic characteristics was associated with the total number of descriptors (p = 0.002), with the sensory descriptors (p <0.001), with the affective (p = 0.038) and with the temporal (p = 0.018), Table 4.

Table 4 – Statistical relationship between neuropathic pain and some pain descriptors in children and adolescents with sickle cell disease, Salvador, Bahia, Brazil, 2017

	Neuropathic pain indicator N = 12	Absence of neuropathic pain indicator N = 34	P-value
Pain intensity[b]	7,2 (7,0–10,0)	7,7 (5,0–10,0)	0,969
Pain frequency	NA	NA	0,093
Almost everyday	2 (16,7)	1 (2,9)	NA
Few days a week	0 (0,0)	3 (8,8)	NA
Few times a month	10 (93,3)	20 (58,8)	NA
No information	0 (0,0)	4 (11,8)	NA
Sporadic	0 (0,0)	6 (17,6)	NA
Total descriptors[b]	32,0 (21,2–40,2)	22,0 (16,7–25,2)	0,002
Sensory Descriptor[b]	15,5 (10,0–20,5)	8,0 (6,0–11,0)	0,000
Affective descriptor[b]	7,0 (4,5–8,0)	5,0 (4,0–6,0)	0,038
Evaluative descriptor[b]	4,0 (2,2–5,7)	4,0 (2,7–5,0)	0,713
Time descriptor[b]	5,5 (3,5–6,7)	3,0 (3,0–5,0)	0,018

[a]Categorical variables expressed in N (%) and Chi-square test

[b]Numerical variables expressed by the median and interquartile range and Mann-Whitney test

NA = not applicable

Children and adolescents in pain with neuropathic characteristics showed strong correlations (r ≥ 0.84) with the intensity of the pain (p = 0.015), with the sensory (p = 0.011) and evaluative (p = 0.034) descriptors in the domain "Pain and Damage" of PedQV-SCD. The temporal descriptors showed strong correlations with the domains "Impact of Pain" (p = 0.008) and module I of "Communication" (p = 0.013). At the same time, those who reported pain with nociceptive characteristics showed moderate to weak correlations between pain intensity and "Sensory Descriptors" in practically all PedQL-SCD domains, except in the "Treatment" domain. Table 5.

Table 5. Correlations of the type of pain, intensity, sensory descriptors, and evaluations with quality-of-life domains in a sample of children and adolescents with sickle cell disease in Salvador, Bahia, Brazil, 2019

	Intensity Pain *r (p)*	Sensory Descriptors *r (p)*	Affective Descriptors *r (p)*	Evaluative Descriptors *r (p)*	Time Descriptors *r (p)*
Pain with neuropathic characteristics					
Pain and Damage	**-0,899 (0,015)**	**-0,912 (0,011)**	-0,617 (0,192)	**-0,845 (0,034)**	-0,765 (0,076)
Impact of Pain	-0,603 (0,205)	-0,672 (0,144)	-0,235 (0,654)	-0,600 (0,208)	**-0,925 (0,008)**
Pain Control	-0,493 (0,321)	-0,500 (0,312)	-0,164 (0,756)	-0,359 (0,484)	-0,688 (0,131)
Concern I	-0,377 (0,461)	-0,618 (0,191)	0,278 (0,594)	-0,135 (0,798)	-0,588 (0,219)
Concern II	0,471 (0,346)	0,328 (0,525)	0,501 (0,311)	0,394 (0,439)	0,134 (0,800)
Emotions	-0,265 (0,612)	-0,448 (0,373)	0,235 (0,654)	0,000 (1,000)	-0,433 (0,391)
Treatment	0,377 (0,416)	0,265 (0,612)	0,463 (0,355)	0,338 (0,512)	0,235 (0,653)
Communication I	-0,564 (0,244)	-0,747 (0,088)	-0,317 (0,541)	-0,657 (0,156)	**-0,906 (0,013)**
Communication II	-0,308 (0,553)	-0,563 (0,245)	0,295 (0,570)	-0,144 (0,786)	-0,625 (0,184)
Physical Functioning	0,058 (0,913)	0,029 (0,956)	0,154 (0,770)	0,169 (0,749)	0,441 (0,381)
Emotional Functioning	-0,059 (0,912)	-0,164 (0,756)	0,736 (0,095)	0,394 (0,439)	0,000 (1,000)
Social Functioning	-0,339 (0,511)	-0,313 (0,546)	0,230 (0,662)	-0,072 (0,892)	0,063 (0,906)
School Functioning	-0,224 (0,670)	-0,409 (0,421)	0,429 (0,396)	0,052 (0,922)	-0,182 (0,730)
Total score	-0,174 (0,742)	-0,412 (0,417)	0,525 (0,285)	0,101 (0,848)	-0,383 (0,454)
Pain with nociceptive characteristics					
Pain and Damage	**-0,729 (0,000)**	**-0,558 (0,000)**	-0,171 (0,306)	-0,144 (0,389)	-0,079 (0,639)
Impact of Pain	**-0,644 (0,000)**	**-0,637 (0,000)**	-0,298 (0,069)	-0,269 (0,102)	-0,174 (0,297)
Pain Control	**-0,373 (0,021)**	**-0,323 (0,048)**	0,031 (0,854)	-0,291 (0,076)	-0,176 (0,290)
Concern I	-0,163 (0,327)	**-0,405 (0,012)**	-0,109 (0,516)	0,018 (0,912)	-0,104 (0,534)
Concern II	-0,180 (0,281)	**-0,326 (0,046)**	-0,149 (0,372)	-0,208 (0,210)	-0,154 (0,357)
Emotions	-0,210 (0,206)	**-0,336 (0,039)**	-0,220 (0,183)	-0,121 (0,468)	-0,134 (0,423)
Treatment	-0,071 (0,674)	-0,059 (0,725)	-0,079 (0,639)	-0,033 (0,844)	-0,045 (0,788)
Communication I	**-0,347 (0,033)**	-0,272 (0,099)	-0,037 (0,824)	-0,251 (0,129)	-0,186 (0,264)
Communication II	**-0,416 (0,009)**	**-0,345 (0,034)**	0,237 (0,153)	-0,002 (0,988)	-0,126 (0,453)
Physical Functioning	**-0,402 (0,012)**	**-0,426 (0,008)**	-0,209 (0,208)	-0,280 (0,088)	-0,295 (0,072)
Emotional Functioning	**-0,672 (0,000)**	**-0,495 (0,002)**	-0,175 (0,294)	**-0,430 (0,007)**	-0,254 (0,124)
Social Functioning	**-0,468 (0,003)**	**-0,458 (0,004)**	-0,123 (0,462)	-0,127 (0,448)	-0,212 (0,202)
School Functioning	**-0,338 (0,038)**	-0,284 (0,084)	-0,103 (0,539)	-0,186 (0,265)	-0,041 (0,809)
Total score	**-0,706 (0,000)**	**-0,642 (0,000)**	-0,196 (0,238)	-0,291 (0,077)	-0,260 (0,115)

Coeficiente de correlação de rô e p-valor do teste de Spearman (alfa 5%)

Discussion

This cross-sectional study sought to outline the pain in children and adolescents with sickle cell disease and found that pain with neuropathic characteristics affected 13.6 and 26.1% of the samples composed of 44 and 46 participants, respectively. Our findings allow us to consider that the central nervous system undergoes sensitization during the phase of neuropsychomotor development, which justifies the chronicity of pain in adults in this population. These data point to the imperative need for pharmacological and non-pharmacological pain control in children and adolescents with SCD.

The sociodemographic characteristics of the two samples confirm that people with Afro-descendant characteristics are the most affected by SCD.[3] In countries with a lower Human Development Index (HDI), where social inequality is greater, this is also the population that has the worst social determinants of health[16] and, for this reason, reinforces the need to implement public policies for protection and care permanent benefits for people with SCD.

As for the intensity, the pain in the sample was moderate to very severe with frequent use of analgesics, requiring urgent measures of attention and care. It can be considered inhumane not to offer protection, health promotion, and symptom relief measures in a condition that affects people in situations of social vulnerability.[16]

Many previous studies have reported the presence of neuropathic pain in people with SCD.[5,6,10-12] However, some authors report that nociceptive pain is the most common in this population.[9,17] Our findings demonstrate that although less prevalent, neuropathic pain has a greater impact on different reactive aspects and quality of life. Due to the absence of a specific instrument to distinguish the type of pain in children and adolescents, the APPT-P Brazil descriptors that correspond to the discriminative DN-4 descriptors were used for the classification. It was found that pain with neuropathic characteristics causes more negative impacts than nociceptive.

We observed that the greater the intensity of pain, the more children and adolescents use descriptors to express pain. In addition, those with greater intensity describe this pain with more evaluative and affective descriptors than sensory or temporal ones. These findings reinforce our hypothesis that the treatment for neuropathic pain should be as early and effective as possible since it easily affects cognitive and emotional aspects, increasing the level of suffering and the chance of chronification.[18]

There was no association between any aspect of pain and the type of hemoglobinopathy, whether HbSS or HbSC. That differs from what has been reported in studies involving adults.[5] A possible explanation for this finding is that pain may have a different longitudinal evolution in each type of SCD, leading adults to differentiate themselves. In addition, the inflammatory level may be more relevant than anemia to generate acute, but not chronic, pain.[19]

Participants in pain with neuropathic characteristics showed strong correlations with the intensity of pain, with the sensory and evaluative descriptors in the Pain and Damage domain of PedQV-SCD. That confirms that pain intensity is a relevant factor in evaluating this population in pain crises[6], but it should not be the only aspect to be considered in the treatment.[18] It is worth mentioning that, in the present sample, they also affected the communication domain. As communication implies several cognitive and relational aspects, quality of life can be severely impaired in the perception of children and adolescents. The expectations they use as a reference to assess the quality of life involve peers without SCD, which can be a factor of hopelessness and can even cause depression.[9,20]

Participants with nociceptive pain showed weak correlations between pain intensity and sensory descriptors in different domains of quality of life, except concerning treatment. It is possible that the fact of being in a service led the sample to consider the risk of damage to the treatment, influencing this result. Unlike what occurred with children and adolescents with nociceptive pain, neuropathic pain affected all domains of quality of life. This finding confirms the hypothesis that this type of pain brings more cognitive, psychological, and social damage to the quality of life of affected children and adolescents.[21-24]

The small sample size and the application in only one reference center prevent the generalization of the results. The low quality of the medical records limited the presentation of other relevant clinical data. However, this research helps to recognize the imperative need for a more accurate assessment of the type of pain in children and adolescents for effective control, especially of neuropathic pain. Future studies should follow this population longitudinally and test the efficacy and safety of pharmacological and non-pharmacological approaches to control neuropathic pain in this population.

Conclusion

We can conclude that pain in children and adolescents with sickle cell disease is distributed throughout the body, presents characteristics of nociceptive and neuropathic pain, with the worst losses for those who report neuropathic pain.

Author contributions

Machado RAF and Lima AGB participated in the elaboration of the project, submission to the ethics committee on research in human beings, data collection, tabulation and analysis, and literature review. De Carvalho ASS participated in data collection, literature review and drafting the database. Almeida HS participated in the literature review, interpretation of data and preparation of the manuscript. Sá KN participated in the preparation and coordination of the project, interpretation of results, preparation of the article and correction of the final version. All authors approved the final version of the submitted manuscript and are responsible for the veracity of the data.

Competing interests

No financial, legal or political competing interests with third parties (government, commercial, private foundation, etc.) were disclosed for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.).

References

1. Ministério da Saúde (Brazil), Secretaria de Atenção à Saúde, Departamento de Atenção Especializada. Doença falciforme: condutas básicas para tratamento [Internet]. Brasília: Ministério da Saúde; 2012. Available from: https://bvsms.saude.gov.br/bvs/publicacoes/doenca_falciforme_condutas_basicas.pdf

2. Silva RBP, Ramalho AS, Cassoria RMS. The sickle cell disease as a Public Health problem in Brazil. Rev. Saúde Pública, 1993;27(1):54-8. https://doi.org/10.1590/S0034-89101993000100009

3. Felix AA, Souza HM, Ribeiro SBF. Epidemiologic and social aspects of sickle cell disease. Rev Bras Hematol Hemoter. 2010;32(3):203–8. https://doi.org/10.1590/S1516-84842010005000072

4. Silva WS, Oliveira RF, Ribeiro SB, Silva IB, Araújo EM, Baptista AF. Screening for Structural Hemoglobin Variants in Bahia, Brazil. Int J Environ Res Public Health. 2016;13(2):13–8. https://doi.org/10.3390/ijerph13020225

5. Ballas SK. Current issues in Sickle Cell Pain and Its Management. Hematology Am Soc Hematol Educ Program. 2007;(1):97–105. https://doi.org/10.1182/asheducation-2007.1.97

6. Ballas SK, Gupta K, Adams-Graves P. Sickle cell pain: A critical reappraisal. Blood. 2012;120(18):3647–56. https://doi.org/10.1182/blood-2012-04-383430

7. Gilron I, Watson CPN, Cahill CM, Moulin DE. Neuropathic pain: a practical guide for the clinician. CAMAJ. 2006;175(3):265–75. https://doi.org/10.1503/cmaj.060146

8. Treede RD, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, et al. Neuropathic pain: Redefinition and a grading system for clinical and research purposes. Neurology. 2008;70(18):1630–5. https://doi.org/10.1212/01.wnl.0000282763.29778.59

9. Bakshi N, Lukombo I, Shnol H, Belfer I, Krishnamurti L. Psychological characteristics and pain frequency are associated with experimental pain sensitivity in pediatric patients with sickle cell disease. Pain. 2017;18(10):1216-28. https://doi.org/10.1016/j.jpain.2017.05.005

10. Brandow AM, Farley RA, Dasgupta M, Hoffmann RG, Panepinto JA. The Use of Neuropathic Pain Drugs in Children with Sickle Cell Diseases is Associated with Older Age, Female Gender and Longer Length of Hospital Stay. J Pediatr Hematol Oncol. 2015;37(1):10-5. https://dx.doi.org/10.1097%2FMPH.0000000000000265

11. Ballas SK, Darbari DS. Neuropathy, neuropathic pain, and sickle cell disease. Am J Hematol. 2013;88(11):927-9. https://doi.org/10.1002/ajh.23575

12. Antunes FD, Propheta VGS, Vasconcelos HA, Cipolotti R. Neuropathic pain in patients with sickle cell disease: a cross-sectional study assessing teens and young adults. Ann Hematol. 2017;96(7):1121-5. https://doi.org/10.1007/s00277-017-2984-z

13. Jacob E, Mack AK, Savedra M, Cleve LV, Wilkie DJ. Adolescent Pediatric Pain Toll (APPT) for Multidimensional Measurementof Pain in Children and Adolescents. Pain Manag Nurs. 2014;15(3):694-706. https://dx.doi.org/10.1016%2Fj.pmn.2013.03.002

14. Santos JG, Brito JO, Andrade DC, Kaziyama VM, Ferreira KA, Souza I, et al. Translation to Portuguese and validation of the Douleur Neuropathique 4 questionnaire. J Pain. 2010;11(5):484-90. https://doi.org/10.1016/j.jpain.2009.09.014

15. Pereira LMS. Desenvolvimento de um Instrumento Multidimensional para Avaliação de Dor em Crianças a partir de Descritores Observados em Narrativas Infantis [thesis] [Internet]. Recife: Universidade Federal de Pernambuco; 2015. Available from: https://repositorio.ufpe.br/handle/123456789/15485

16. Marmot M. Social determinants of health inequalities. Lancet. 2005;365(9464):1099-104. https://doi.org/10.1016/s0140-6736(05)71146-6

17. Cataldo G, Rajput S, Gupta K, Simone DA. Sensitization of nociceptive spinal neurons contributes to pain in a transgenic model of sickle cell disease. Pain. 2015;156(4):722-30. https://doi.org/10.1097/j.pain.0000000000000104

18. Antunes FD, Silva Junior CL, Cerqueira KS, Faro ML, Cipolotti R. Screening for neuropathic pain in patients with sickle cell disease: Is a single assessment scale sufficient? Orphanet J Rare Dis. 2019;14(108). https://doi.org/10.1186/s13023-019-1082-9

19. Guarda CC, Yahouédéhou SCMA, Santiago RP, Neres JSDS, Fernandes CFL, Aleluia MM, et al. Sickle cell disease: A distinction of two most frequent genotypes (HbSS and HbSC). PLoS One. 2020;15(1):e0228399. https://dx.doi.org/10.1371%2Fjournal.pone.0228399

20. Santos LFO, Guimarães MW, Baptista AF, Sá KN. Impact of neuropathic pain on quality of life in adults with sickle cell disease: observational study. Hematol, Transfus Cell Ther. 2020. https://doi.org/10.1016/j.htct.2020.03.010

21. Hardy SJ, Bills SE, Wise SM, Hardy KK. Cognitive Abilities Moderate the Effect of Disease Severity on Health-Related Quality of Life in Pediatric Sickle Cell Disease. J Pediatr Psychol. 2018;43(8):882-94. https://doi.org/10.1093/jpepsy/jsy019

22. Kambasu DM, Rujumba J, Lekuya HM, Munube D, Mupere E. Health-related quality of life of adolescents with sickle cell disease in sub-Saharan Africa: a cross-sectional study. BMC Hematol. 2019 May 14;19:9. https://doi.org/10.1186/s12878-019-0141-8

23. Ludwig NN, Sil S, Khowaja MK, Cohen LL, Dampier C. Executive Functioning Mediates the Relationship Between Pain Coping and Quality of Life in Youth With Sickle Cell Disease. J Pediatr Psychol. 2018;43(10):1160-9. https://doi.org/10.1093/jpepsy/jsy057

24. Román ME, Highland J, Retherford D, Pan AY, Panepinto JA, Brandow AM. Neuropathic pain is associated with poor health-related quality of life in adolescentes with sickle cell disease: A preliminar report. Pediatr Blood Cancer. 2020;67(12):e28698. https://doi.org/10.1002/pbc.28698