Tracking and considerations on the therapeutic management of neuropathic pain in adult patients with sickle cell disease

Rastreamento e considerações sobre a conduta terapêutica na dor neuropática em pacientes adultos com doença falciforme

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ABSTRACT

BACKGROUND AND OBJECTIVES: Sickle cell disease is considered the most common hereditary disorder in Brazil. The chronic pain resulting from some complications of sickle cell disease is still poorly understood, inadequately described, and under-researched. This study aimed to characterize chronic pain in individuals with sickle cell disease, evaluate its treatment, and discuss the importance of studying it as a distinct pathology.

METHODS: A cross-sectional study based on comparative analysis between two associations of sickle cell disease patients, one in Brazil and the other in France. The Pain Detect Questionnaire was used to assess neuropathic pain, and *Odds Ratio* was used to evaluate the strength of the association between opioid use and the recurrence of chronic painful crises.

RESULTS: In Brazil, the Pain Detect questionnaire revealed that 55% of patients had a probable neuropathic component, 23% negative, and 22% uncertain. In France, the application resulted in 51% for probable presence, 29% for negative, and 20% for uncertain. All patients reported constant pain. As for the frequent use of opioids, the results were 62% in Brazil and 32% in France. The Odds Ratio calculation results were: OR 15.14 (95% CI = 4.777- 41.4, p < 0.0001) in Brazil; and OR 7.5 (95% CI = 2.121- 25.74, p = 0.0013) in France.

CONCLUSION: While it is commonly believed that pain in sickle cell disease is primarily related to somatic and visceral tissue damage after vaso-occlusive events, this study indicated emerging evidence of neuropathic processes involved. Thus, there should be a significant concern about the management of chronic pain and particularly opioid dependence in Brazil.

Keywords: Chronic pain, Opioid, Sickle cell.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Dentre as alterações hereditárias, a doença falciforme é considerada a mais comum no Brasil. A dor crônica decorrente de suas complicações ainda é mal compreendida, inadequadamente descrita e pouco pesquisada. O presente estudo teve como finalidade caracterizar a dor crônica em indivíduos com doença falciforme, avaliar o seu tratamento e discutir a importância de seu estudo como uma doença em si.

MÉTODOS: Estudo transversal, baseado na análise comparativa entre duas associações de indivíduos acometidos pela doença falciforme, com sede no Brasil e na França. Foi aplicado o questionário *Pain Detect* para avaliação da dor neuropática e a *Odds Ratio* para avaliar a intensidade de associação entre o uso de opioides e a recorrência de crises álgicas de cunho crônico.

RESULTADOS: O questionário *Pain Detect* apontou que no Brasil 55% de pacientes da doença calciforme apresentam componente neuropático provável, 23% negativo e 22% incerto. Na França, os resultaram foram de 51% para componente provável, 29% negativo e 20% incerto. Dos acometidos pela doença, 100% relataram dores constantes, sendo que fizeram uso frequente de opioides 62% no Brasil e 32% na França. O cálculo do *Odds Ratio* apontou os seguintes resultados: OR 15,14 (IC 95% = 4,777- 41,4, p < 0,0001) no Brasil; e OR 7,5 (IC 95% = 2,121- 25,74, p = 0,0013) na França.

CONCLUSÃO: Embora haja uma crença de que a dor na doença falciforme seja primariamente relacionada à lesão tecidual a nível somático e visceral após os eventos vasoclusivos, o estudo apontou evidências emergentes de processos neuropáticos envolvidos. As-

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HIGHLIGHTS

- Sickle cell disease patients from two treatment centers in France and Brazil were selected.
- The presence of neuropathic pain and the relationship between opioid use and chronic pain crises were assessed.
- There is evidence of associated neuropathic processes and concern about the management of chronic pain in Brazil.

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sim, deve haver uma preocupação quanto ao manejo da dor crônica e em especial à dependência química pelos opioides no Brasil.
Descritores: Anemia falciforme, Dor crônica, Opioides.

INTRODUCTION

Sickle cell disease (SCD) is the most common monogenic hereditary disease in Brazil. Between the years of 2014 and 2020, the Brazilian National Newborn Screening Program diagnosed an annual average of 1087 new cases of children with SCD, which indicates an incidence of 3.78 per 10000 live births. Current estimates report a number of between 60000 and 100000 patients with SCD in the country[1-3]. Worldwide, it is estimated that 5% of the population has the disease and that an average of 275000 new SCD patients are born each year[4,5].

Considered one of humanity's oldest diseases, sickle cell hemoglobin (HbS) is the result of a point mutation in the beta globin polypeptide chain, in which the substitution of glutamic acid for valine is responsible for the electrochemical changes that give rise to a morphologically altered blood cell, which is called a drepanocyte. The term "sickle cell disease" is included in a family of hematological alterations in which the heterozygous form is represented by the association of an HbS with other alternative hemoglobins, while sickle cell anemia (SCA - HbSS) is its homozygous and more symptomatic representative[6]**.** Having been the focus of anthropological studies associated with biomolecular analysis, it is now believed that the abnormal allele for the synthesis of HbS arose in the Paleolithic and Mesolithic periods, approximately 50 or 100 thousand years ago, in central-west Africa, eastern Asia and India[1].

However, the first description in the literature of a physically different erythrocyte was done only in 1910, when cardiologist James Herrick reported the case of a young Caribbean patient, Walter Noel, treated at the Presbyterian Hospital in Chicago, with multiple complaints such as dyspnea and heart palpitations[2]. The clinical complications of this alteration have graduated levels of complexity, varying continuously between periods of well-being and periods of urgency and emergency. Of the many symptoms commonly observed, pain is the most frequent and stressful. According to authors[7], a large percentage of SCD adults report pain 95% of the time, suggesting that there is inadequate management of chronic pain (CP) and raising major concerns about the inappropriate use of therapeutic tools, especially chemical dependence on opioids.

Patients who have been treated with opioids on a daily basis may experience uncontrolled pain and withdrawal episodes[7]**.** Data from the International Association for the Study of Pain (IASP) states that CP associated with SCD is still poorly understood and different studies indicate that its characteristics are poorly described and researched[8]. Considering that the existence of the drugs that currently make up the treatment for SCD and the consequential increase in the life expectancy of its patients is a fairly recent reality, a study[9] highlights that the study of CP in these individuals is under-emphasized, justifying the great interest of researchers in the study of acute pain in SCD, especially in children. In addition, several authors report the scarcity of current references and relevant research on the treatment of CP in adults with SCD[10].

Thus, the present study's objective was to characterize CP in patients with SCD and evaluate the effectiveness of the treatments offered in order to survey not only the practices applied today in the clinic and their possible adverse effects, but also to discuss the importance of emphasizing the study of CP as a disease in itself, even when associated with a chronic disease such as SCD.

METHODS

The two largest associations of SCD patients located in Brazil and France were selected for this study. Their scope extends beyond the cities where they are based, including members living in other locations. This is an analytical, comparative study that used a cross-sectional design, considering a single point in time. A representative sample of members of the two associations was randomly selected, with a total sample size of 200 participants.

The study included members aged over 14 affected by SCD, who were given the validated Pain Detect Questionnaire, adapted for the Google Forms electronic platform, and an identification form with questions about treatment. Incomplete questionnaires and members who did not sign the Free and Informed Consent Term (FICT) were disregarded. Reports of pain crises in the month before the questionnaires were counted and the positive and negative reports were taken for statistical analysis using the Odds Ratio (with a 95% confidence interval) to calculate the strength of the association between opioid use and the recurrence of chronic pain crises. Individuals whose pain crises required blood transfusion were excluded from this calculation because they constituted acute, vaso-occlusive pain crises resulting from the underlying disease.

This study was approved by the Research Ethics Committee in Brazil, under number CAAE 67486617.8.0000.0093 and received a positive evaluation from the European Committee for the Protection of Persons.

Statistical analysis

The results of the Odds Ratio calculation were analyzed using the GraphPad Prism software version 7, considering a 95% confidence interval.

RESULTS

The Pain Detect questionnaire showed that in Brazil 55% of affected individuals had a probable neuropathic component, while 23% had negative results and 22% had uncertain results. In France, the same questionnaire resulted in 51% of individuals with a probable neuropathic component, 29% negative and 20% uncertain (Figure 1).

Of the studied individuals, 100% reported constant pain, and 62% in Brazil and 32% in France made frequent use of opioids. The Odds Ratio calculation results were: OR 15.14 (95% CI = 4.777- 41.4, $p < 0.0001$) in Brazil; and OR 7.5 (95% CI = 2.121- 25.74, $p = 0.0013$) in France (Table 1).

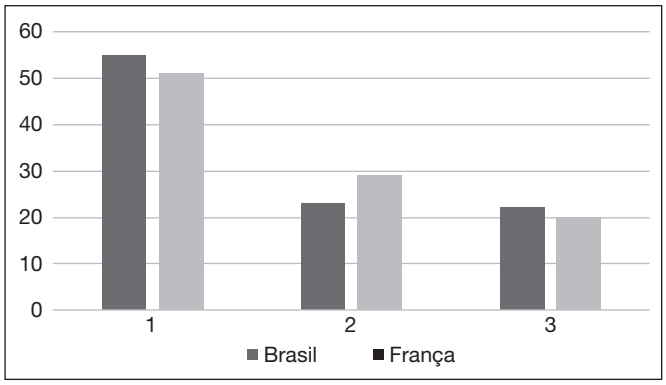

Figure 1. Pain Detect results.

Table 1. Odds Ratio values in Brazil and France

Sickle cell patients who tested positive on the Pain Detect questionnaire	Odds Ratio	95% CI	p-value
Brazil	15.14	4.777 a 41.4	<0.0001
France	7.5	2.121 a 25.74	0.00013

CI = confidence interval

DISCUSSION

The clinical manifestations associated with SCD have varying levels of complexity, ranging from periods of well-being to periods of urgency and emergency. The acute pain caused by the vaso-occlusive crises of SCD is the main cause of hospitalization. The persistence of this stimulus in SCD activates secondary mechanisms that give rise to different types of chronic pain. Pain of different types has already been identified in individuals with SCD: acute pain, caused by blockage of blood flow and other causes; CP from bone damage and other causes, and chronic neuropathic pain (NP)[11]**.** NP is a pain syndrome, usually chronic, in which the mechanism responsible for the onset of pain is found somewhere in the nociceptive pathways, causing a change in the nervous system with consequent hypersensitivity, either in the area of the lesion or in the surrounding tissue, without initially stimulating the nociceptors, contrary to what happens with nociceptive pain.

Therefore, NP is described by the IASP as a consequence of a lesion or disease in the somatosensory system, which can be classified as central or peripheral - depending on the affected nervous system location. NP can also be identified as possible, probable or definite. The diagnostic criteria for this classification include: (I) pain with compatible anatomical distribution; (II) historic that suggests injury or disease affecting the somatosensory system; (III) compatible anatomical distribution in at least one confirmatory test and (IV) confirmation of disease or injury in at least one confirmatory test. NP is definitive when it meets criteria I to IV; probable when criteria I and II are met with confirmation of III or IV; and possible when criteria I and II are met, but without confirmation of III or IV.

Because it has several etiologies and pathophysiological mechanisms that still are not well comprehended, NP is considered a complex disease and its diagnosis is a major clinical challenge, as not all symptoms are always well defined[12,13], even though there are no verbal descriptors for defining symptoms. Individuals affected by SCD complain of burning, shock sensation, painful cold sensation, stinging, tingling and itching. These terms are characteristic of NP, as is the presence of allodynia and hyperalgesia[13]. Although the diagnosis of NP is eminently clinical and is based on physical examination and a careful anamnesis, some tools have been proposed to help identify the disease. A simple screening tool, with a positive predictive value, sensitivity and specificity close to 80%, is the Pain Detect questionnaire, used in this study to differentiate NP from non-neuropathic pain in individuals with SCD. Initially developed to detect NP in patients with low back pain, Pain Detect was validated in individuals with SCD[11]**.**

A study carried out in the state of Wisconsin/USA with individuals with SCD using Pain Detect as an assessment tool found that more than 40% of patients had a score compatible with NP, a value similar to that obtained in this study for members of the two associations[14]. The report of constant pain by the interviewees in both associations, with an increase in frequency and intensity as age progressed, was consistent with the hypothesis raised about the presence of chronic pain in this group. However, the significant difference in the reported use of morphine sulphate (62% in Brazil and 32% in France), despite the similarity of treatment protocols for pain crises, points to an erroneous assessment and inadequate management of CP in Brazil[15].

The Brazilian Ministry of Health's manual of basic guidelines related to SCD states that pain crises should be assessed, their causes researched, as well as risk factors studied and laboratory investigations completed. The analgesics of first choice are dipyrone, diclofenac and codeine, depending on the degree of pain on the measured by an visual analog scale. Patients whose pain is not alleviated 6 hours after starting therapy should be hospitalized and treated according to the hospitalization protocol, in which strong opioids are at the bottom of the analgesic scale[6] (Table 2).

The opioid main mechanism of action is the stimulation of specific receptors located in the central and peripheral nervous system, which are classified as mu, delta and kappa receptors, although it is believed that these are not the only existing targets. Studies have shown that one possible target is the N-methyl--D-aspartate (NMDA) receptor, whose main excitatory neurotransmitter is glutamate, which is part of the propagation and sensitization of pain at a central level. The short and long-term use of opioids increases the activity of this receptor by directly interfering with the regulatory activity of glutamate[16], promoting the exacerbation of pain. There is no doubt about the efficacy of opioids for analgesia of acute pain resulting from the underlying disease, but there are controversies about the use of these drugs for the control of CP in SCD [11].

The calculation of the Odds Ratio associating frequent use of morphine sulphate and recurrence of pain crises points to a major concern about inappropriate use of therapeutic tools, especially chemical dependence on opioids. The sensation of uncontrolled pain and withdrawal episodes are frequent conditions in patients treated with opioids on a daily basis, as well as the possibility of developing drug-induced hyperalgesia, with ex-

Table 2. Sickle cell disease pain crises treatment protocol

Pain from 1 to 6 Home treatment was correctly done?		Pain from 6 to 9 Home treatment was correctly done?	
NO	YES	NO	YES
Switch from dipyrone to IV and diclofenac to IM.	Switch from diclofenac to IM and dipyrone to IV and add codeine (1mg/kg/dose).		Replace codeine with IV morphine (0.1mg/kg/dose); repeat if no improvement after 30 minutes and continue with morphine every 4 hours.
In case of improvement after 6 hours, discharge with: dipyrone + diclofenac	In case of improvement after 6 hours, discharge with: dipyrone + diclofenac + codeine		In case of improvement after 6 hours, discharge with: dipyrone + diclofenac + codeine
In case of no improvement after 1 hour, add OR codeine and hospitalize.	In case of worsening after 6 hours, replace codeine with morphine and hospitalize.		If case of worsening after 6 hours, hospitalize and evaluate morphine in continuous infusion.

IV = intravenous; IM = intramuscular; OR = oral route.
Source: Brazilian Ministry of Health

pansion of the receptive field, reduction in pain threshold and increased response to noxious stimuli[17]. Multiple factors seem to be associated with the development of hyperalgesia, such as the activation of NMDA receptors and the modification of glial cells. The difficulty in controlling CP, with exacerbation of the intensity and increase of the frequency of pain crises, is due to these mechanisms[18]**.** At this point, it is important to remember that SCD is the disease with the highest prevalence among the Afro-descendant population, a group that has been documented as being affected by discrimination and who are victims of historical exclusions, and which still suffers directly and in all social spheres from the impacts of racism and prejudice[4].

Different studies present in the literature show that various health professionals are unprepared when it comes to SCD. The treatment of pain episodes has not changed substantially for decades and is based on relieving acute events, without using strategies to address CP. As noted by the study[19], scientific production has not been silent about sickle cell disease, as it has been widely studied, but the silence and omission about people affected by the disease and the associated suffering is recurrent. Therefore, more studies focused on CP related to SCD are needed to advance comprehension and treatment methods so that those affected can improve their psychosocial potential and not remain continually debilitated by pain[20]. While some believe that pain in SCD is primarily related to tissue damage at the somatic and visceral level following vaso-occlusive events, the present study pointed to emerging evidence of neuropathic processes involved and a relevant concern regarding the management of CP, especially chemical dependence on opioids in Brazil.

Diagnostic difficulties in distinguishing the different types of pain that affect individuals with SCD result in the inadequate use of therapeutic resources and greater suffering for these individuals, since different treatments are necessary for the management of nociceptive pain, but are ineffective for NP. This study therefore points to the importance of emphasizing the treatment of NP as a disease in itself, even when associated with an underlying disease such as SCD.

Considering the epidemiological reality of the disease and the present study's results, which draws comparisons with an European country, the conclusion is that, in Brazil, individuals with SCD also suffer an important type of pain, which is not the result of erythrocyte sickle cell crises, nor of the different mechanisms of central sensitization, but rather of the historical invisibility of the disease, prejudice and lack of knowledge on the part of health professionals.

CONCLUSION

The present study has shown that there is a neuropathic component to the pain associated with SCD, both in Brazil and in France. In addition, the frequency of opioid use in Brazil points to a significant concern regarding pain management in individuals with this disease. Diagnostic difficulties in characterizing types of pain contribute to the inappropriate use of therapeutic resources and increased suffering in these patients. These findings highlight the importance of identifying and better comprehending CP in SCD and the disparity between the results found in both countries regarding the use of opioids, indicating the emerging need for an appropriate treatment which considers all complexities related to SCD.

AUTHORS' CONTRIBUTIONS

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Statistical analysis, Data Collection, Conceptualization, Resource Management, Project Management, Research, Methodology, Writing - Preparation of the original, Writing - Review and Editing, Supervision, Visualization
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