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Chronic osteo-articular changes in patients with sickle cell disease

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Abstract

Background: Sickle cell disease (SCD) is an autosomal recessive genetic disease in which a mutation occurs in the β-globin chain gene, resulting in abnormal hemoglobin levels. In an environment with reduced oxygen concentration, red blood cells change their conformation, resulting in chronic hemolysis and consequent anemia and vaso-occlusive crises with injuries to several organs, with a significant impairment of the osteoarticular system. This study aimed to verify the chronic osteoarticular alterations and their association with clinical and laboratory characteristics of patients with SCD with a more severe phenotype (SS and $S\beta^0$), on a steady-state fasis.

Methods: Fifty-five patients were referred to a medical consultation with a specialized assessment of the locomotor system, followed by laboratory tests and radiographic examinations.

Results: In total, 74.5% patients had hemoglobinopathy SS; 67.3% were female; and 78.2% were non-whites. The mean patient age was 30.5 years. Most patients (61.8%) reported up to three crises per year, with a predominance of high-intensity pain (65.5%). Radiographic alterations were present in 80% patients. A total of 140 lesions were identified, most which were located in the spine, femur, and shoulders. Most lesions were osteonecrosis and osteoarthritis and were statistically associated with the non-use of hydroxyurea.

Conclusions: There was a high prevalence of chronic osteoarticular alterations, which was statistically associated only with the non-regular use of hydroxyurea.

Keywords: Osteonecrosis, Osteoarthritis, Osteopenia, Sickle cell disease, Hydroxyurea

Introduction

Hemoglobinopathies are a group of diseases of genetic origin in which mutations in the genes encoding hemoglobin (Hb) can result in changes in their synthesis. Most of them comprise qualitative defects that result in the production of different Hb molecules with abnormal structure, resulting in sickle cell disease (SCD), and quantitative defects that affect the synthesis of globin chains, resulting thalassemias [1].

Hemoglobin S (HbS) is caused by a mutation in the β-chain gene due to the replacement of the amino acids glutamate with valine at position 6 of chromosome 11. Hemoglobinopathies in which at least one of the mutant hemoglobin is HbS are known as SCD. Hemoglobin S in homozygosis (HbSS), is called sickle cell anemia (SCA), which is the most severe form of SCD. HbS may also be associated with other abnormal hemoglobins, such as HbC, HbD, and β-thalassemia, leading to hemoglobinopathies SC, SD, $S\beta^0$, and $S\beta^+$, while the combination of HbS and HbA is called sickle cell trait, in which the carrier does not develop the disease [2]. The most severe SCD phenotypes are associated with the SS and $S\beta^0$ genotypes, with similar clinical manifestations [3].

Since 1998 in Minas Gerais, Brazil, SCD is diagnosed at birth using the "little foot test," and children diagnosed with SCD are referred early for specialized follow-up.

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The clinical manifestations of SCD are due to two main phenomena—hemolysis and consequent chronic anemia as well as vaso-occlusion by red blood cells, followed by infarction in various organs and tissues. The vaso-occlusive phenomenon manifest acutely with severe pain crisis and chronically with lesions in various organs and tissues such as the lungs, heart, kidneys, liver, retina, skin, joints, and bones [4].

Osteoarticular manifestations occur in different forms of SCD and are more severe in SCA [5]. Acute lesions include hand-foot syndrome (sickle cell dactylitis), pain crises, osteomyelitis, infectious and inflammatory arthritis, stress fractures, bone infarctions, vertebral collapse secondary to osteonecrosis (ON) with a typical "fish mouth" appearance, dental changes, and orbital compression [6]. Chronic changes include avascular necrosis or ON, vertebral collapse due to low bone mass (fragility fractures), inflammatory chronic arthritis, osteoarthritis (OA), bone marrow hyperplasia triggering morphological changes and growth disorders, osteopenia, and osteoporosis [7].

Acute osteoarticular changes determine a severe clinical picture with generally intense events such as sickle cell dactylitis. In contrast, chronic changes can develop silently or after an acute event, determining functional limitations and symptoms of varying degrees of intensity. They are often underdiagnosed, although with an important impact on the morbidity and mortality of these patients, requiring accurate knowledge of the different manifestations to provide correct diagnosis and appropriate treatment.

Therapeutic approaches capable of modifying the natural history of SCD include hypertransfusion, use of hydroxyurea (HU), and hematopoietic stem cell transplantation (HSCT). Currently, HU is the only drug capable of altering the natural history of SCD. Its use in Brazil is guided by hematological clinical indications according to the Clinical Protocol and Therapeutic Guidelines of the Ministry of Health [8].

In addition to increasing the fetal hemoglobin (HbF) concentration, HU increases the total concentration of Hb and causes a reduction in the number of neutrophils, monocytes, and reticulocytes. Furthermore, HU affects the red blood-endothelium interaction and acts as a nitric oxide donor. Although HU treatment is effective, there is variability in patients' response to HU. In 10–25% cases, treatment with HU is not effective, perhaps due to genetic variation, bone marrow exhaustion, variation in drug metabolism, and possibly lack of adherence to treatment [9].

Objective

This study aimed to verify chronic osteoarticular alterations and their association with clinical and laboratory characteristic of patients with SCD of the more severe phenotype (SS and $S\beta^0$) who were followed up at Regional Blood Center of Uberaba (RBCU) and Clinical Hospital of Federal University of Triângulo Mineiro (CH-FUTM) on a steady-state fasis.

Methods

A cross-sectional study was conducted from May 2017 to January 2018 at RBCU. The sample size was maximized. All eligible patients who attended routine consultations were invited to participate and were included in the study according to their consent and compliance with the evaluation protocols. Of the 67 eligible patients (SS and $S\beta^0$, 14 years or older, non-pregnant women), 12 did not accept participation or did not complete the evaluation protocol, resulting in 55 participants (non-probabilistic sampling).

After signing the free and informed consent term and/or the informed consent form, the patients were referred for medical consultation with a rheumatologist, consisting of a clinical interview and physical examination with specialized assessment of the locomotor system, followed by laboratory and radiographic examinations. Data on patient's past history were collected from the medical records provided by the Medical File Service of RBCU and CH-FUTM.

Regarding age, the participants were divided into two groups according to the United Nations (UN) classification [10], with individuals aged 14–24 years being considered young patients and individuals aged > 25 years being considered adult patients. The skin color was classified as white, brown, or black based on self-reported data. However, for analysis, white and brown patients were included in the same subgroup since all non-black patients reported no black ancestry.

Prolonged use of HU was defined as use for at least 1 year without interruption.

The participants were asked about the average number of painful crises presented per year and classified into mild, moderate, or high groups according to the Pain Analog Scale scores [11].

The laboratory tests included those for ferritin, reticulocytes, C-reactive protein (CRP), and lactic dehydrogenase (LDH). We retrieved the values of fetal hemoglobin and basal hemoglobin (BHb) from the medical records.

For radiographic screening, the following were examined: the hand and wrist, shoulders, cervical, thoracic and lumbar spine, pelvis, and skull. When changes in physical examination were observed, the knees, ankle, feet, and long bones were examined.

The data were arranged in an Excel spreadsheet, from which descriptive statistical analysis and association were performed using the chi-square test. Statistical Package for Social Science for Windows (SPSS) version 22.1.1.1

was used for statistical analysis. The level of statistical significance set at 5% ($p < 0.05$).

Results

Among the 55 individuals, 41 (74.5%) had SS hemoglobinopathy, 14 (25.5%) had $S\beta^0$ hemoglobinopathy, 37 (67.3%) were female, 27 (49.1%) were black, and 28 (50.9%) were non-black. The mean (± standard deviation [SD]) patient age was 30.5 (± 11.5) years (range: 15–54 years). In total, 21 patients were categorized as young patients (age: 14–24 years; 38.2%), and 34 patients were categorized as adult patients (age: ≥25 years; 61,8%). Thirty-five (63.6%) participants used HU for at least 1 year uninterruptedly.

The mean (± SD) values of the various laboratory parameters evaluated were as follows: FHb, 11.3 (± 6.7) g/dL; BHb, 7.9 (± 1.2) g/dL; ferritin, 743.2 (± 1159.7) ng/mL; reticulocytes, 6.6% (± 2.9%); CRP, 0.7 (± 0.9) mg/L; and LDH, 472.9 (± 166.8) U/L.

The distribution of participants according to the frequency and intensity of pain crises is shown in Table 1. We observed that most participants reported up to three attacks per year (61.8%), and the pain was high in 65.8% painful episodes.

Regarding radiographic alterations, 140 lesions were identified, most of which occurred in the spine (62.1%), followed by the femur (16.4%) and the shoulders (7.1%). The most frequent alteration was ON (55%), followed by OA (21.4%) (Table 2). ON was identified in 29.1% patients, OA was identified in 25.4% patients. Most patients had several lesions simultaneously (Table 2).

Regarding the number of radiographic lesions per patient, most patients had 1–4 lesions (63.6%), with a variation of zero (20.0%) to nine (1.8%), with mean and SD of 2.61 and ± 2.22, respectively.

The association between laboratory and clinical parameters and the number of radiographic lesions was not statistically significant, except for the use of HU ($p = 0.0038$) (Table 3).

Among people with ≥5 injuries, most were women (21.6%), non-black (17.9%), adults (20.6%), with ≥4 attacks in 1 year (19.9%) and with high pain intensity (16.7%); however, the difference was not statistically significant (Table 3).

Of the 35 individuals who used HU regularly for > 1 year, only 8.6% had ≥5 injuries, while of the 20 individuals who did not use it regularly, 30.0% had ≥5 injuries ($p = 0.0038$) (Table 3).

Table 1 Distribution of the participants according to the frequency and intensity of painful crises

Variables	N	%
Number of crises per year		
0–3	34	61.8
≥ 4	21	38.2
Intensity of pain in crises		
Mild and moderate	19	34.5
High	36	65.5

Table 2 Distribution of radiographic lesions according to location and type of alteration

Radiographic Changes	N	%
Location of lesions		
Spine	74	52.8
Proximal femur/hip	23	16.4
Shoulders/humerus	10	7.1
Skull	7	5.0
Hands and wrists	4	2.8
Other[a]	22	15.7
Total	140	100.0
Types of alterations		
Osteonecrosis	77	55.0
Osteoarthritis	30	21.4
Other SCD-related changes[b]	17	12.2
Non-specific changes[c]	16	11.4
Total	140	100.0

Other[a]: tibia, fibula, knees, distal femur, ulna, ankle, and feet
Other changes related to SCD [b]: thickening of the diploe, sequelae of osteomyelitis, pyogenic arthritis, dactylitis, and discitis, consolidated fractures
Non-specific changes [c]: Non-specific lytic lesions, flexion deformity, clinodactyly, tendinopathy, kyphosis, scoliosis, transition vertebra, omovertebral bone, trigone bone, and equine foot

Discussion

The patients' profiles in this study are compatible with those described in the literature, with a predominance of homozygous disease (SS), female sex, non-white individuals, and young individuals [9, 12, 13]. However, most patients in this study reported a low frequency of pain crises, which is different from that reported in previous studies [9, 14, 15].

Platt and colleagues has suggested that people with SCD with HbF values > 8% have a higher survival rate [11], which may indicate a better prognosis for our patients, but with cumulative damage to the osteoarticular system.

The bone is the second most affected organ by SCD after the spleen [16]. We found 140 osteoarticular lesions in our cohort (mean: 2.61/participant). However, 20% participants did not present any radiographic lesions.

Previous studies have evaluated osteoarticular involvement in patients with SCD in the acute phase. However, our study evaluated lesions in patients on a steady-state fasis, which explains the low incidence of infectious and inflammatory changes, which were highly prevalent in past studies [17–19], and a high incidence of OA and ON.

Table 3 Evaluation of the number of lesions according to epidemiological and clinical characteristics

Number of injuries									
Clinical data	**0**		**1–4**		**≥5**		**Total**		***p* value***
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Sex									
Male	6	33.3	11	61.1	1	5.6	18	100	0.1156
Female	5	13.6	24	64.8	8	21.6	37	100	
Total	11	20.0	35	63.6	9	16.4	55	100	
Skin color									
Black	4	14.8	19	70.4	4	14.8	27	100	0.5575
Non-black	7	25.0	16	57.1	5	17.9	28	100	
Total	11	20.0	35	63.6	9	16.4	55	100	
Age									
Young	7	33.3	12	57.1	2	9.6	21	100	0.1215
Adults	4	11.7	23	67.6	7	20.6	34	100	
Total	11	20.0	35	63.6	9	16.4	55	100	
Number of crises per year									
0–3	5	14.7	24	70.6	5	14.7	34	100	0.3546
≥ 4	6	28.6	11	52.4	4	19.0	21	100	
Total	11	20.0	35	63.6	9	16.4	55	100	
Intensity of crises									
Mild and moderate	4	21.1	12	63.2	3	15.8	19	100	0.9886
High	7	19.4	23	63.9	6	16.7	36	100	
Total	11	20.0	35	63.6	9	16.4	55	100	
HU use ≥ 1 years									
Yes	4	11.4	28	72.8	3	8.6	35	100	0.0038**
No	7	35.0	7	35.0	6	30.0	20	100	
Total	11	20.0	35	63.6	9	16.4	55	100	

* X^2 test; ** statistically significant

The main sites of bone involvement were the spine, followed by the femur and the shoulders and the most frequent changes were ON, followed by OA, as classically described [6].

The prevalence of ON in people with SCA ranges from 3.2 to 26.7% [19–22]. In our study, this complication affected approximately one-third of the patients. However, like other studies, we observed that the prevalence of ON increases with age, which may be a consequence of recurrent episodes of bone infarctions. Globally, SCD is probably the most common cause of avascular necrosis that most commonly affecting the femoral and humeral heads [23].

Patients with SCD may develop OA, usually secondary to ON, which progresses to OA in 86% patients when not properly treated [24, 25]. These data justify the high prevalence of this type of lesion verified in the evaluation of patients in an outpatient setting on a steady-state basis.

The occurrence of radiographic alterations did not present a statistically significant association with sex, skin, age, number, and intensity of pain attacks; however, we observed that despite the higher percentage of individuals without radiographic lesions in the young group, painful crises were of high intensity in this group. In the group of people with ≥5 injuries, the majority were adults and females. Radiographic changes are secondary to injuries suffered by patients throughout their lives, which may explain the higher incidence of young patients among those without identifiable radiographic injuries and adults with a higher incidence of radiographic damage.

Individuals who regularly used HU had a lower incidence of multiple lesions than those who did not use it, statistically significant result.

Treatment with HU is associated with a significant reduction in the incidence of hospitalization, acute chest crisis, stroke, and vaso-occlusive crises, however, the impact of the use of this drug on the prevention and treatment of chronic osteoarticular lesions needs further investigation.

There is only one study published thus far regarding the osteoarticular alterations of SCD, which has cited high-dose HU significantly reduced the incidence of ON in white and non-white patients aged > 18 years with ßS/ßS and ßS/ß $^{+}$ treated for 10 years [26].

A review article on the role of HU in SCD describes the importance of this medication in reducing the morbidity and mortality in these individuals [27]. Because of the effects of HU in reducing the sickling of red blood cells, elevating HbF, reducing oxidative stress and vaso-occlusive crisis consequently, we infer that HU also has a positive impact on osteoarticular lesions, as reinforced by the findings of the present study.

SCD is a disease that has a great impact on the osteoarticular system of affected patients, which can lead to functional limitations and low quality of life, requiring special care by a health team. Until new drugs are available, HU should always be considered an important therapeutic option in patients with SCD.

The main limitations of the study were the small sample size, its heterogeneity, the limitation in the recording of data in medical records, and the difficulty in performing some tests in our hospital.

Future studies with a larger sample, including other hemoglobinopathies, control group and nuclear magnetic resonance exams may bring further clarifications on this topic.

Conclusions

In patients whith SCD SS e $S\beta^0$ followed at RBCU and CH-FUTM, we observed a high prevalence of chronic osteoarticular alterations, being statistically associated, as a protective measure, only with regular use of HU.

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Authors' contributions
Calculations and nutritional assessments: Alexandra Silva Leal; Conducting and reporting the imaging exams: Ana Paula Teixeira dos Santos; Conception and design of the research: Taciana Fernandes Araújo Ferreira, Gilberto de Araújo Pereira, Sheila Soares Silva, Helio Moraes-Souza. The author(s) read and approved the final manuscript.

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Availability of data and materials
The datasets generated and/or analyzed during the current study are not publicly available due due to the confidentiality of participants' data but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The work was approved by the Institutional Research Ethics Committee. Participants signed the Informed Consent Form to participate in the research.

Consent for publication
All authors give consent for publication of this work.

Competing interests
None of the authors have conflicts of interest in relation to the topics covered in this article.

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