

## Oral Changes in Patients with Sickle Cell Anemia of Dentistry Interest

### Alterações Bucais em Pacientes com Anemia Falciforme de Interesse para o Cirurgião-Dentista

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Received: January 07, 2018

Approved: March 20, 2018

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#### Abstract

Sickle cell anemia is determined by the presence of S hemoglobin in homozygous, autosomal recessive and characterized by the presence of red cells with abnormal shape (sickle shape). The clinical manifestations may vary from one individual to another, and it may appear in the first year of the patient's life, which emphasizes the importance of early diagnosis as the main measure of positive effect in the care of people with the disease. The aim of this study was to conduct a review of the literature on oral alterations of dental surgeon's interest in patients with sickle cell anemia. The search for the key words "sickle cell anemia" and "oral manifestations" was carried out in the Scientific Electronic Library Online database (SciELO), linked to the Virtual Health Library (VHL). The oral manifestations described in the literature were: paleness of the oral mucosa, smooth, bleached and despalpated tongue or jaundice, delays in dental eruption, periodontal disease, hypo mineralization of the enamel, pulp calcifications, hypercementose, aseptic pulp necrosis, mandibular nerve neuropathy, osteomyelitis and orofacial pain. People with the disease may also exhibit mouth ulcers, particularly in the gums. Anemia causes a high degree of suffering for patients, who deserve special attention from all the multiprofessional team that attends them. Therefore, it is important that the dental surgeon understands and knows the symptoms of the disease, as well as its implications for oral health, as well as the best treatment. The adoption of constant care, with prevention measures in oral care and health, is important to inhibit the occurrence of dental infections.

**Keywords:** Anemia, Sickle Cell. Dental Care. Oral Manifestations.

#### Resumo

A anemia falciforme é determinada pela presença da hemoglobina S em homocigose, de caráter autossômico recessivo e caracterizada pela presença de células vermelhas com formato anormal (forma de foice). As manifestações clínicas variam de acordo com o indivíduo e ao longo do percurso da doença, pois pode surgir no primeiro ano de vida do paciente, o que enfatiza a importância do diagnóstico precoce como principal medida de efeito positivo na assistência às pessoas com a doença. O objetivo deste trabalho foi realizar uma revisão de literatura sobre as alterações bucais de interesse do cirurgião-dentista em pacientes com anemia falciforme. A busca pelas palavras chaves "anemia falciforme" e "manifestações bucais" foi realizada na base de dados Científic Electronic Library Online - SciELO, vinculada à Biblioteca Virtual em Saúde - BVS. As manifestações bucais descritas na literatura foram: palidez da mucosa oral, língua lisa, descorada e despapilada ou icterícia, atrasos na erupção dentária, doença periodontal, hipomineralização do esmalte, calcificações pulpares, hiper cementose, necrose pulpar asséptica, neuropatia do nervo mandibular, osteomielite e dor orofacial. Os portadores também podem exibir úlceras bucais, particularmente na gengiva. A anemia provoca alto grau de sofrimento aos pacientes que merecem atenção especial de toda a equipe multiprofissional que os assiste. Desta forma, é importante que o cirurgião-dentista conheça a doença, assim como suas implicações para a saúde bucal e a condução do melhor tratamento. A adoção de cuidados, com medidas de promoção e prevenção em saúde bucal, é importante para evitar a ocorrência de infecções dentárias.

**Palavras-chave:** Anemia Falciforme. Assistência Odontológica. Manifestações Bucais.

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#### 1 Introduction

The sickle cell anemia - AF is the most common disease among the hemoglobinopathies in Brazil and in the world. Its cause is a mutation in the gene that produces hemoglobin A originating another mutant, the hemoglobin S (or HbS), which causes sickling (sickle shape) of the blood cells.<sup>1-3</sup> It is characterized clinically by algic crises that start in general in early childhood and extend throughout the life. People with sickle cell anemia have chronic hemolytic anemia and

episodes of severe pain resulting from obstruction of the blood vessels caused by the way that the sickle erythrocytes assume, preventing the oxygen circulate properly, infarction and necrosis in various organs, bones and joints.<sup>4,5</sup> Other complications include the vulnerability to infections and acute chest syndrome.<sup>2-4</sup>

It presents high incidences in Africa, Saudi Arabia and India and is part of the group of diseases and disorders that affect mainly the black population<sup>3,4</sup>. It affects several organs and

systems, being the oral findings the most common: paleness of the oral mucosa, smooth, bleached and despalpated tongue or jaundice, delays in dental eruption, periodontal disease, hypo mineralization of the enamel, pulp calcifications, hypercementose, aseptic pulp necrosis, mandibular nerve neuropathy, osteomyelitis and orofacial pain<sup>5-7</sup>.

The sickle cell anemia is a chronic incurable disease which, although treatable, causes a high degree of suffering to its patients, thus deserving special attention from a medical, dental, genetic and psychosocial point of view<sup>8,9</sup>.

Therefore, to the patients' appropriate dental treatment, the surgeon dentist must understand the most important aspects related to the disease, as well as their implications for oral health. Thus, the present study aims to review the scientific literature about changes of interest of the dental surgeon in patients with sickle cell anemia.

## 2 Development

### 2.1 Methodology

Bibliographic survey was carried out on the basis of *Scientific Electronic Library Online* (SciELO), linked to the Virtual Health Library - VHL. The selection of the key words used in the search process was carried out through consultation with the Subject Descriptors in Health Science - DeCS. The terms used were: "*anemia falciforme*," "*manifestações bucais*" their counterparts in the English language: "*sickle cell anemia*", "*oral manifestations*" and "dental care".

The inclusion criteria were: Date of publication in the period from 1992 to 2016 and to be written in English or Portuguese language.

### 2.2 Sickle cell Anemia

The sickle cell anemia is a genetic hemoglobinopathy, characterized by the change in the hemoglobin molecule. Hemoglobin (Hb) is the respiratory protein present in the interior of the erythrocytes, which has as main function the transport of oxygen. It is composed of four polypeptide chains held together by non-covalent connections. Each of them contains a heme group and one central connection to oxygen. Hemoglobin A, the principal of adults, is structurally composed of chains of type  $\alpha$  (alpha) and two of the type  $\beta$  (beta). The sickle cell anemia stems from the mutation in the gene that produces hemoglobin, causing another mutant, called hemoglobin S (HbS). There are other mutant hemoglobins as, for example, C, D, E, etc. Pairing up with the S, integrate the group called DF. The most well known is the SS, which is called sickle cell anemia (SS), in which individuals are homozygous for HbS (HbSS). There are also the S/Beta thalassemia (S/B.), the diseases SC, SD, and other more rare. Among the sickle cell diseases, sickle cell anemia is the one that presents greater clinical and hematologic severity, besides being the most prevalent<sup>10-12</sup>.

It is an autosomal recessive disease not related to sex,

which is common among individuals of African descent. Individuals who have an affected gene (HbS) and a gene for normal hemoglobin (HbA), configure a standard in heterozygosis and are called carriers of the sickle cell trait (HbAS), which produces no manifestations of the disease<sup>12</sup>.

The mutation in the gene of the HbS occurs through the substitution of a nitrogenous base, adenine (A), on the other, the thymine (T), in the sixth codon of the gene beta. Thus, from GAG it passes to GTG, resulting in the substitution of glutamic acid by valine in the beta chain. The substitution of a single amino acid in the beta chain leads to hemoglobin S assume a different setting, amending the discoid shape of red blood cells, and makes them to have the scythe shape<sup>13,14</sup>. The clinical manifestations are highly variable among individuals with the disease and in the same person, throughout his or her life. Symptoms may begin to appear in the first year of life, showing the importance of early diagnosis as the primary measure of positive impact on the quality assistance to persons with the disease<sup>12-15</sup>.

The HbS, in the deoxygenated form, loses its complex quaternary structure and acquires a primary structure (hemoglobinic polymerization). From its polymerization, HbS becomes insoluble, changing the erythrocyte form (which is typically a hard biconcave) for a structure that resembles a scythe: phenomenon of sickle cell formation.<sup>16</sup> Initially it is reversible, but the constant changes affect the cell membrane, making it permanently changed<sup>16</sup>. The erythrocytes sickle formation, reduces its useful life, which goes from 120 to approximately 20 days and reduces its capacity carrier of oxygen to the tissues. Therefore the patients become more susceptible to infection and their healing process is hindered; they also suffer intravascular hemolysis causing chronic hemolytic anemia, usually of relevant magnitude<sup>19</sup>. In addition, the passage of the blood cells is hampered in microcirculation, they become more adherent to the vascular endothelium - an additional mechanism for vascular obstruction, preventing blood flow, causing tissue hypoxia, anoxia, necrosis and pain<sup>3,5,13,14</sup>.

Of African origin, during the forced migration of slaves, the sickle cell anemia was brought to the Americas and currently has become widely distributed in all continents, reaching a high prevalence among the black population and their descendants<sup>14,15</sup>.

The recognition that AF is a prevalent disease in Brazil<sup>17</sup> it was decisive in the institution of the National Policy of Integral care to people with Sickle Cell Disease - PNAIPDF of the Ministry of Health<sup>18</sup>. It is estimated that 4% of the Brazilian population has the sickle cell trait (heterozygous) and 0.1 to 0.3% of the black population has the anemia, reaching an increasingly significant portion of the population due to the increased intermingling in the country<sup>17</sup>.

### 2.3 Systemic manifestations

The sickle cell anemia can manifest in different intensities in affected individuals<sup>2</sup>. Among the clinical manifestations of the disease are the vaso occlusive or painful crises (periods of exacerbation). It is the most frequent symptom of sickle cell disease caused by the obstruction of small blood vessels by red blood cells in the form of sickle and consequent vascular insufficiency<sup>3,19</sup>. The pain is more frequent in the bones and joints, but may reach any part of the body like lungs, abdominal and dorsal regions, brain, liver, spleen and penis<sup>2,13</sup>.

Each crisis lasts for around 3 to 10 days and multiple agents triggers were described, highlighting the infections, dehydration, acidosis, hyperthermia, emotional stress and physical exercises stringent<sup>20,21</sup>.

In small children, the crises of pain may occur in small blood vessels of the hands and feet, causing swelling, pain and redness at the site, being called hand-foot Syndrome or Dactylitis<sup>2,22</sup>. Jaundice is the most frequent sign of disease. When the red blood cell breaks, bilirubin is released, causing the sclera of eyes and skin to turn yellow<sup>2,13,16</sup>.

Individuals with this disorder have increased susceptibility to develop infections, mainly children<sup>1,2,16</sup>. It is common the occurrence of ulcers in the lower limbs, more often next to the ankles, from adolescence, which can take years to complete healing if they are well cared for at the beginning of their appearance<sup>23</sup>.

In children with sickle cell anemia, spleen may increase rapidly by sequestering the whole blood (splenic sequestration) and this can quickly lead to death due to lack of blood to the other organs such as the brain and heart.<sup>2</sup> Pallor of the skin and mucous membranes are still described; Organomegaly; cardiac changes as a result of myocardial hypoxia; complications of central nervous system, mainly in the form of headaches, convulsions, hemiplegia and cerebral vascular accidents; bone alterations, hepatomegaly, hematuria and pulmonary and renal insufficiency. Occasionally there are ocular alterations, characterized by retinal infarction, retinitis proliferans and displacement of the retina<sup>22,24</sup>.

### 2.4 Oral manifestations

The sickle cell anemia can also lead to the occurrence of oral alterations. Such manifestations are not pathognomonic of the disease and may vary from patient to patient<sup>19</sup>. Among the oral manifestations are: paleness of the mucosa; yellowish coloration of the tissues, delays in dental eruption, degree of periodontitis considered uncommon, even in children; changes in the cells of surface of the tongue; hypo maturation and Hypo mineralization of tooth enamel and dentin; pulp calcification; hypercementosis; bone changes resulting in maxillary protrusion which ends up leading to malocclusion<sup>4,7,12,25</sup> pulp necrosis aseptic and asymptomatic, mental nerve neuropathy and mandibular osteomyelitis<sup>6,9,19,26</sup>.

People with sickle cell disease have more carious lesions

that healthy individuals<sup>10,12,27,28</sup>. Factors such as changes in the formation and calcification of the enamel and dentin; frequent use and continuous medications containing sucrose; high frequency of complications and hospitalizations may represent risk factors<sup>2,27</sup>. It can also occur due to the smaller amount of IgA and lysozyme in the saliva<sup>28</sup>. Other studies, however, associate this greater prevalence to factors such as negligence to oral health and psychological problems generated by anemia<sup>29</sup>. The adoption of oral care, with prevention measures in oral health, are important to minimize and avoid the occurrence of dental infections.

Disorders may occur even during the early stages of development, and will be responsible for reductions in the quantity or thickness of the enamel (hypoplasia), in contrast, disturbances occurring during the phases of calcification and maturation of the enamel result in changes in the translucency or enamel opacities (hypocalcification). The enamel hypoplasia, as well as mineralization may increase the risk for the development of caries lesions<sup>2,4,7,25</sup>.

The pulp organ is likely to be compromised by micro-thrombi of sickle cell during crises, causing blockage of blood vessels. If the blood supply is interrupted, there may be the aseptic necrosis of the pulp, with posterior possible periapical involvement<sup>32</sup>. Generally the clinical signs are asymptomatic, rarely accompanied by pulp pain and without the knowledge of the patient. Thus, it is recommended that clinical evaluation and conducting of periodic X-rays for the differentiation between periapical radiolucences secondary to pulp necrosis, from the other bone changes<sup>33</sup>.

The paleness of the mucosa and the yellowish coloration of the gums are the result of the deposition of blood pigments, secondary to hyperbilirubinemia caused by the extensive destruction of erythrocytes<sup>34</sup>. The carriers can also have oral ulcers, especially on the gums, representing areas of infarction secondarily infected<sup>25</sup>. There is no systematic record regarding the greater susceptibility of individuals with sickle cell disease for dental caries and periodontal diseases in children<sup>25</sup>.

The sickle cell anemia may lead to changes in bone mineral density, increase of the medullary spaces and the formation of a coarse trabeculate, attributed to erythroblastic hyperplasia and medullary hypertrophy which results in loss of thin bone trabeculate and formation of wide medullary spaces<sup>14,35</sup>. The compensatory hyperplasia of the medullary spaces can cause expansion of maxilla and because this is a bone predominantly medullary, changes are more visible. Patients have maxillary prognathism and accentuated overjet<sup>36-38</sup>.

Osteomyelitis should be considered in the differential diagnosis for people with AF, that exhibit bone pain and edema. It is frequent among patients with sickle cell anemia and in spite of being more common in long bones, can also affect the bones of the face, mainly, the mandible, due to its reduced blood supply<sup>12,39</sup>. The temporomandibular joint is also not immune to the vaso-occlusive episodes of sickle cell anemia<sup>5</sup>. The vascular impairment can lead to ischemia

and osteonecrosis, creating a favorable environment to the bacteremia, with high potential of evolution to septicemia. The signs and symptoms of osteomyelitis are local pain, edema, lymphadenopathy, exudate in the gingival sulcus and may be accompanied by fever and trismus. Pericoronitis of partially-erupted teeth or impacted teeth and/or periodontitis, and also the sickling crises that occur, usually, days before the start of the mandibular complication can be etiological factors<sup>3,12,36-39</sup>. The treatment consists of the combination of support therapies and antibiotic therapy and surgical approach. Hospitalization may be necessary.

Another important finding is the mental nerve neuropathy. This is preceded, in most cases, by pain and mandibular generalized painful crises. Hours or days after, unilateral loss of the lower lip sensitivity is reported, as well as the underlying gum tissue and pre-molar, canine and incisors teeth of the lower affected hermiarcade<sup>6,30,36-40</sup>. Paresthesia in the INVERVAÇÃO MENTONIANA mentalis innervation areas, can also be observed<sup>41</sup>. It is believed that the loss of sensitivity is caused by bone infarctions in the microcirculation of blood supply of the nerve and its branches<sup>41</sup>. In contrast with the other peripheral nerves, the NERVO MENTONIANO is particularly vulnerable and susceptible to this complication, due to being located in very narrow bone canal, similarly to the dental pulp, in the occurrence of local inflammation<sup>42</sup>. The recovery of sensitivity is slow and the numbness may persist for up to two years<sup>41-43</sup>.

## 2.5 dental treatment

With the direct reflection of the greater life expectancy of patients with sickle cell anemia, the number of individuals seeking routine dental treatment increases every day, often by medical recommendation<sup>44</sup>. The professional should be aware of the disease, being able to detect its signs and symptoms, determine if there is a risk for the treatment, or even if treatment does not affect the patient's overall health status. Routine dental treatment in individuals must be carried out in periods without crises, requiring careful planning. The therapy during a crisis, however, should be directed to a palliative treatment<sup>13</sup>. In the event of an urgency service, the anamnesis will be brief and therapy will be to relieve pain and treat acute infections or traumatic injuries<sup>12</sup>.

After completion of the detailed anamnesis and clinical examination, the history of the disease and its complications should be taken into account, as well as the patient's physical and emotional conditions, and still, the tolerance to surgical procedures, with the aim of avoiding or reducing the stress, as this can trigger a sickle cell crisis<sup>6,12,14</sup>. On clinical examination, it is essential that the surgeon dentist evaluate the tissues in the oral cavity, the periodontal structures and dental elements. The periapical and panoramic X-rays are valuable, and often indispensable, because they can help in the diagnosis<sup>12</sup>. The laboratory tests, the consultation with the doctor, as well as the contact with other health professionals who assist the

person with the disease are fundamental, considering that knowing his or her clinical signs is of great usefulness for the treatment<sup>34</sup>.

It is recommended that consultations be the morning, with short duration procedures, in order to avoid stress, emotional tension and maintain appropriate levels of oxygenation and body temperature<sup>40</sup>.

The adequacy of the oral environment is an effective way to reduce and eliminate sites of retention, being the ideal to perform at the first consultation, by supragingival scraping and restorative treatment with sealing of the cavities with glass ionomer cement and coronal polishing. Root remnants and the edges of the remaining coronary polishing need to be rounded so that they do not cause injury to soft tissues<sup>12,40</sup>.

The oral surgeries are invasive procedures of higher risk, therefore they must be carefully planned so that the intervention is safe. A complete blood count and coagulation tests should be requested in the event that there is a need for surgical intervention<sup>14</sup>. Before invasive dental procedures or that involve bleeding and that may cause transient bacteremia, it is indicated antibiotic prophylaxis, since infections can trigger sickle cell anemia crises<sup>3,6,12,40</sup>.

The choice of the type of anesthesia, whether local or general, is according to the conditions of each person. In sickle cell anemia, it is classified as the anesthetic risk ASA III (moderate or severe systemic disease, with some functional limitations). Whenever possible, the preference is through the use of local anesthesia, due to its lower risk and lower potential to reduce the blood oxygenation. Anyway, it is worth mentioning that several consultations should be avoided in a short space of time and/or extensive procedures, because they are stressful. If the stress is too high, reducing the capacity for cooperation of the person in treatment or in the case of other systemic complications, general anesthesia is indicated<sup>12</sup>.

The use of local anesthetics with vasoconstrictors is still controversial. According to the authors, they can prevent the local circulation and cause infarction. For others, it does not bring effects on local circulation, despite the hypo vascularization. Therefore, it is indicated that routine dental procedures be performed with local anesthetic without vasoconstrictor and surgical procedures, however, those with vasoconstrictors should be used<sup>3,6,12,14</sup>. The use of benzodiazepines in small doses is also indicated as pre-anesthetic medication<sup>45</sup>. The nitrous oxide may also be used for analgesia, when applied within the established parameters of oxygenation and ventilation<sup>6,12</sup>.

The surgeon dentist as part of an interdisciplinary and multiprofessional group, plays an important role, since the diagnosis and treatment of sickle cell anemia, until the maintenance of health for the implementation of educational measures to the person with the disease and his or her family, since that the oral health conditions can cause great impact on general health and quality of life of individuals with the disease<sup>34,12</sup>.

### 3 Conclusion

Among the sickle cell diseases, sickle cell anemia is the one with the most clinical significance and greatest prevalence in Brazil, being essential that the surgeon dentist be part of the interdisciplinary team which assists these patients, since that the oral health conditions can cause great impact on general health and quality of life of individuals with the disease.

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