Review Article

Orthodontic Treatment of Patients with Sickle-cell Anemia

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ABSTRACT

Sickle-cell anemia is a genetic blood disease characterized by a hemoglobin gene mutation. The genetic failure is basically constituted by replacement of the hemoglobin beta chain in the sixth position so that the amino acid valine is encoded instead of glutamic acid. As a result, the erythrocytes have their normal biconcave discoid shape distorted, generally presenting a sicklelike shape, which reduces both their plasticity and lifetime. Because a complete blood supply is so important during application of both intraoral and extraoral forces, this article addresses the general and oral aspects associated with sickle-cell anemia. This will guide the clinician regarding such patients who seek orthodontic treatment by making references to literature on multidisciplinary management. (*Angle Orthod* 2006;76:269–273.)

INTRODUCTION

When a patient with sickle-cell anemia needs orthodontic treatment, the practitioner involved should know about the disease and the respective treatment because of the importance of a complete blood supply after application of intraoral and extraoral forces. In the face of such a necessity, this article addresses the aspects related to sickle-cell anemia according to the current literature. This will guide both the diagnosis of clinical manifestations and therapeutic planning regarding such patients who seek orthodontic treatment.

Sickle-cell disease is a commonly used term for designating a family of various blood disorders characterized by the presence of hemoglobin S (Hb-SS). Herick, in 1910 *apud* Santos[1] was the first one to use the term sickle-cell anemia for a type of hemolytic anemia characterized by morphologically changed red blood cells (erythrocytes) and increased blood viscosity.[1]

Many years later, sickle-cell anemia was defined as a hereditary type of chronic hemolytic anemia caused by genetic mutation of the hemoglobin molecule. Stability and physical-chemical properties of the hemoglobin molecules (Hb-AA) are modified and hemoglobin S (Hb-SS: derivation of ''sickle''), results from the amino acid switch (glutamic acid replaced by valine) in the beta chain of hemoglobin present in chromosome 11. Sickle-cell syndromes are caused by different inheritance patterns involving the sickling gene, which is autosomal recessive. Therefore, homozygous individuals have nearly S-type hemoglobin only (Hb-SS), and sickle-cell anemia develops as a result. Nevertheless, heterozygous individuals (Hb-SA) have approximately 40% of S-type hemoglobin (Hb-SS) and the remaining red blood cells are normal (Hb-AA), which define a trace of sickle cell and milder characteristics concerning the disease. In this case, the parents are asymptomatic carriers, and consequently, the mutated gene is transmitted to their offspring.[2–4]

In situations where the oxygen concentration is low, the Hb-SS molecules are deoxygenated, and the presence of the valine results in hydrophobic interaction with other hemoglobin molecules, thus unleashing an aggregation of great polymers. The blood consequently becomes viscous instead of liquid. Polymerization of S-type hemoglobin is the primary event underlying the molecular pathogenesis of the sickle-cell disease. As

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a result, the red blood cells have their biconcave discoid shape changed into a sickle form, which reduces their plasticity. Although the sickling process initially is reversed as the oxygen level increases, in terms of microcirculation, these constant morphological changes cause lesions in the red blood cell membrane by affecting its cytoskeleton. Therefore, even in situations of adequate oxygenation the red blood cells cannot become normal again and die prematurely. For that reason, they are also called irreversibly sickled erythrocytes.[5]

The sickling process causes the red blood cells to loose their ability of carrying oxygen properly to the tissues and also reduces their life span from 120 to approximately 20 days. Such a phenomenon involving the red blood cells is responsible for the physiopathological picture presented by the patients. The early destruction of the red blood cells results in gradual tissue degradation, interference with organic functions, recurrent painful crisis, frequent bacterial infections, and chronic hemolytic anemia, which requires the constant production of erythrocytes.[6,7]

According to the World Health Organization, the life expectancy of Brazilian patients having sickle-cell anemia is 42 years for men and 48 years for women; 85% of all such patients have a low school education and, consequently, the labor market reserves only nonspecialized work involving physical effort for them, which is not compatible in the face of such a disease. Epidemiological studies have revealed that the mean prevalence of sickle-cell disease carriers in the Brazilian population is 2.1%. In the United States, 8–10% of all Afro-Americans have sickle-cell traces. In Brazil, the sickle-cell anemia has a frequency of about one in 1500 people and is considered the most frequent hemoglobinopathy.[3,8–12]

The diagnosis is usually based on clinical findings, and the observation of cellular aspect by scrubbing the peripheral blood reveals not only the morphological changes but also the various phases of erythroblast maturation and the presence of large red blood cells.[4]

The positive sickling test (solubility test) indicates the presence of Hb-SS, but no distinction is made between sickle-cell anemia, sickle-cell trace (asymptomatic form), and composite heterozygote (thalassemia). Hemoglobin electrophoresis is the method used for establishing the differential diagnosis for selecting homozygous and sickle-cell trace individuals who need, respectively, treatment and genetic counseling.[3]

Nowadays, the development of studies into recombinant DNA allows a prenatal diagnosis of either heterozygote or homozygote sickle-cell disease using amniocentesis. On the other hand, the postnatal diagnosis for detecting the sickle-cell disease is performed during the first or second year of life when the level of fetal hemoglobin (Hb-FF) is significantly decreased, despite being predominantly high in the newborn. In addition, there is no interaction between Hb-FF and the changed hemoglobin (Hb-SS).[13,14]

The sickle-cell anemia may have periods of acuteness better known as vasoocclusive crises or recurrent painful crises, originally denominated ''sickled crises.'' The occurrence of such crises is due to ischemic injury to the tissues after the obstruction of small blood vessels by the sickled red blood cells. This prevents the local blood from circulating and leads to local oxygen depletion, acidosis (which enhances the sickling process), necrosis, and severe pain. Each sickle-cell episode usually lasts 3–10 days, and several precipitating events have been described, such as infection, cold, dehydration, acidosis, hypothermia, emotional stress, menstruation, consumption of alcohol, and rigorous physical exercises. During these crises, the blood count generally reveals normochromic and normocytic anemia. Indirect signs of hemolysis characterized by indirect hyperbilirubinemia and reticulocytosis are also diagnosed. Leukocytosis with moderate neutrophilia, not necessarily related to infections, and thrombosis complete the hematological findings.[15–17]

Although all the patients with sickle-cell anemia have the same genetic mutation, one can observe a great diversity of clinical manifestations. It is possible to find asymptomatic individuals presenting the most severe form of the disease (sickle-cell trace).[18]

The evolution of the disease may result in complications involving any part of the organism, mainly those areas seriously affected by hypoxia and infarct. In addition, infants may have their development and growth impaired and also greater risk of contracting severe infections.[6]

Among the clinical systemic manifestations, the following are frequently observed: paleness of both the skin and the mucous membrane, icteric sclera, apathy, cardiac alterations by myocardial hypoxia, cephalangia, convulsion, osseous alterations (eg, osteonecrosis), chronic hemolytic anemia, impaired growth, low body weight, decreased production of testosterone, delay in skeletal and sexual maturation; learning difficulties, cerebral hemorrhage, and propensity to infections, which are all important causes of either morbidity or mortality.[19–21]

The diagnosis of enamel hypoplasia is suggested by the presence of white spots on the tooth surface, delayed tooth eruption, impaired mineralization of the dentine, paleness of the lip tissues and the oral mucous membrane, and changes in the cells on the tongue surface (glossitis). Osteoporosis on the alveolar crest has been identified by radiographic examination.[3,22–26]

In radiological terms, the changes involving maxil-

lofacial and dental tissues are similar to those observed in cases of rickets, fluorosis, and after thyroidectomy.[20] Authors have reported that the dura-lamina remains intact, although areas of osteoporosis may be found. In addition, trabecula with a parallel pattern among the teeth, an aspect called ''step ladder,'' was not found to involve the edentulous area.[27–30]

Dental shape and size are not affected. The cusps of the teeth may exhibit evidence of intrinsic opacity. Hypocalcification of the teeth occurs as a result of insufficient absorption of calcium caused by intestinal problems, inadequate absorption of proteins, metabolic disorders involving vitamin D and calcium, calcitonin, or parathyroid hormone.[31]

The increased number of malocclusions in patients with sickle-cell disease can be related to muscular imbalance, absence of labial sealing, or changes in the osseous base, thus leading to orthodontic intervention.[32]

Such clinical manifestations show great individual variability, worsen over time, and are related to health care quality, health service access, and early diagnosis. When the sickle-cell disease or its trace is detected in the new born, both parents and siblings should be examined to increase the life expectancy, improve the treatment, and give them genetic counseling.[16,33–35]

DISCUSSION

Although oral changes are not pathognomonic of sickle-cell anemia, they may be suggestive of such a condition to the orthodontist. Such changes may include those related to the color of oral mucous membrane and osseous density. In some cases, malocclusion can be observed because of maxillary protrusion and retrusion of anterior teeth. The former can be associated with the increased medullar activity and marked maxillary growth. In addition, lip pressure caused by overjet results in retrusion of the incisor teeth. Similar to what happens to the maxilla, the medullar hyperplasia leads to an increase in the diploic space, thus thickening the frontal bones as well as the flattened ones.[36]

Both increased medullar space of the mandible and calcifications of the pulpal tissue can be radiographically identified. Areas of radioluminescence are created by the osseous modifications because both cortical thinning and trabecular increase, whereas radiopaque areas are the result of repaired osseous infarcts. The skull radiographs can show projections similar to ''hair threads,'' also known as ''brushed skull'' images, which correspond to secondary osseous formation after bone absorption occurred during bone marrow expansion.[24,37–40] In addition to oral changes, the orthodontist should know the previous medical history as well as the particular aspects involving the clinical management of the patients with sickle-cell anemia. Information concerning the disease favors the multidisciplinary management. Consequently, the orthodontist, as a health provider, is responsible for supervising the patient, intervening in the treatment, and referring the patient to other professionals. For example, complaints of ache in the mandible because of vasoocclusive crisis may be mistakenly diagnosed as pulp changes. The decision about whether the treatment is local or systemic should be jointly taken by the patient's physician and endodontist.[41]

Because of the complications faced by the patients with sickle-cell anemia, they are commonly submitted to yearly blood reposition. On average, however, such procedure exposes them to the risk of contamination by blood diseases. Although the orthodontic treatment is not contraindicated for such a condition, necessary care should be taken to prevent other infections from contaminating the clinical setting.[34,35,42,43]

During orthodontic treatment, emotional stress should be avoided, and care should be taken to have both adequate levels of oxygenation and bodily temperature, as well as the use of biologically compatible mechanical forces. The clinical appointments should be arranged during the chronic phase of the disease because orthodontic procedures are not performed during periods of crisis or acuteness. In cases where painful symptoms appear during acute crises, the use of acetylsalicylic acid should be avoided because this drug changes the platelet's adhesion capacity, induces intestinal and gastric ulceration, and causes frequent hepatic lesions in such patients.[26,43,44]

Elective surgeries, such as the extraction of asymptomatic teeth for orthodontic indication, are contraindicated. Nevertheless, some authors recommend that such patients should be referred to a maxillofacial surgeon, who will ask for a complete blood count and evaluate the possibilities for treatment. Preoperative blood reposition will be indicated whenever the hemoglobin level is less than seven g/dL and the hematocrit level is less than 20%. Coagulability should be analyzed for probable hepatic lesion.[40,45] Susceptibility to infections justifies the use of antibiotic coverage instead of invasive procedures, thus avoiding both bleeding and bacteremia.[41]

Local anesthesia can be used for patients with sickle-cell anemia without restrictions; however, the use of a vasoconstrictor is still unclear because such a drug may damage the local blood circulation and begin an infarct or keep the tissue oxygenation intact after its use. The decision of prescribing such medication as well as other anticoagulant drugs should be taken together with the medical team involved in the patient's

treatment, but the possible systemic impairment and the type of intervention should also be considered.[15,39]

Mandibular osteomyelitis is an oral complication commonly observed in patients with sickle-cell anemia and is rarely manifested with other complications, which make easy both its diagnosis and treatment. The mandible is the most affected part of the face because the blood supply is relatively insufficient. Aches in the mandible can be preceded by widespread painful crises and be accompanied by neuropathy involving the inferior alveolar nerve and paresthesia of the lower lip. Intravascular impairment can result in both ischemic infarct and osteonecrosis, thus allowing bacterial proliferation by *Streptococcus* or *Salmonella*.[40,46]

CONCLUSIONS

- Several advancements have been achieved not only in cytogenetics and diagnosis regarding sickle-cell anemia but also in the treatment of the complications resulting from such a disease.
- In the near future, patients with sickle-cell disease will have a better quality of life as well as a higher life expectancy.[47]
- Routine medical assistance should be regularly performed to control the blood conditions, the use of medications during clinical exacerbation, and prevent complications.
- Sickle-cell anemia carriers should be encouraged to have their oral health under control by practicing preventive procedures.
- The orthodontist should pay attention to the possible pulpal necrosis involving healthy teeth, the changes in the bone turnover during orthodontic movements, the mandibular painful episodes, and the greater susceptibility to infections.
- Orthodontic planning should be adjusted to restore the regional microcirculation by increasing the rest intervals as well as to reduce the movements of the teeth and the forces applied on them.
- Intense orthodontic or orthopedic forces such as extraoral anchorage or maxillary disjunction require more careful management.

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