Prevalence of orofacial alterations in sickle cell disease: a review of literature

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Abstract

Aim: To evaluate the manifestations of sickle cell disease on the orofacial complex through a review of current literature concerning prevalence of dental caries, periodontal disease, temporomandibular joint disorders and radiographic alterations of maxillofacial bones. **Methods:** Full-text papers retrieved from MEDLINE and LILACS electronic databases were critically reviewed. **Results:** Alterations of maxillofacial bones are well documented in the literature, but studies reporting caries, periodontal condition and temporomandibular joint alterations in are scarce and inconclusive. **Conclusion:** Further well-designed epidemiological studies are needed to indicate the real impact of this disease on the stomatognathic health, collaborating to improve public health policies.

Keywords: sickle cell anemia, hemoglobin C disease, dental caries, periodontal diseases, temporomandibular joint, diagnostic X-ray.

Introduction

Sickle cell disease (SCD) includes genetic blood disorders in which morphologic alterations of erythrocytes are caused by presence of the sickle hemoglobin (HbS). HbS is characterized by a mutation in the sixth position of $\hat{a}$ globulin chain, replacing the glutamic acid by valine[1-3]. Sickle cell anemia (SCA) is the most common and severe form of SCD, resulting from genetic inheritance of HbS genes from both progenitors (SS genotype)[1]. The SC disease is the most second common manifestation of SCD, presenting less severe symptoms[4], and is characterized by heterozygosis of two mutant hemoglobins, HbS and HbC (SC genotype). In sickle cell trace, the heterozygosis for genes of normal (HbA) and mutant (HbS) hemoglobins (AS genotype) does not exhibit clinical symptoms of the disease under physiological conditions[3,5].

SCD can be found in several countries affecting people all over the world, but primarily affects African descendents[5] . In Brazil, it's estimated the existence of more than 2 million carriers of the gene for HbS, with 700 to 1000 new cases of SCD every year, turning such disorder into a public health problem[6].

The sickle erythrocyte presents reduced flexibility and becomes more adherent to vascular endothelium, developing vaso-occlusion of microvasculature and subsequent local hypoxia[1,7]. Premature destruction of sickle red blood cells leads to hemolytic anemia. These mechanisms are the mean hallmarks of SCD and are responsible for its clinical manifestations[1,8].

Algic crises is the most common and important clinical symptom of this disease[9]. Several other complications have been described, including: stroke, pulmonary infarct with decreased lung function, priapism, chronic renal failure, splenic and hepatic dysfunctions, jaundice, retinal ischemia causing transient or permanent blindness, chronic leg ulceration, apathy, cardiac alterations, convulsion and osseous alterations like osteonecrosis, osteomyelitis, osteopenia and osteoporosis[4,10,11]. It is noted a wide interindividual variety of disease severity that has been suggested as result of polymorphisms in several genes[12], mainly of fetal hemoglobin which has been pointed as a target for promising treatments[13].

Little research has been done on the possible impact of this disease in the stomatognathic health. The aim of this paper was to review the literature regarding the actual knowledge concerning orofacial conditions in patients with SCD.

Dental Caries

There are few studies in the literature concerning prevalence of caries lesions in SCD patients and even those presented controversial results.

In 1986, Okafor et al.[14] found a reduced caries prevalence (35.13%) among 37 SCD adult patients (14-33 years old) when compared to 20 control subjects (54%) paired by age and gender. This finding was attributed to a reduced ingestion of sweets but its methodology was not specified in details, neither statistic comparisons were presented.

In a retrospective study, no statistically significant difference was observed in the prevalence of dental caries determined by DMFS index between 35 HbSS subjects and 140 control volunteers, both under treatment at a dental school and frequency matched on enrollment period and age. However, the great age variability among volunteers (5-92 years old) in this study may have influenced its results[15].

The controversial results can be related to socioeconomic factors that may influence caries risk rather than the hematologic disorder itself [16,17]. Comparing DMFS index of 102 sickle subjects (82 HbSS, 15 HbSC and 5 HbS beta-thalassemic) and 103 control volunteers between 18 and 70 years old, the statistical analysis, adjusted for SCD severity, age, gender, risk factors for caries and socioeconomic data, demonstrated that for low-income African Americans, those with SCD presented significantly more decayed and fewer filled surfaces[18]. Since control volunteers were selected at dental colleges, these findings should be considered with regards.

Reduced prevalence of decayed teeth was also reported among 60 HbSS children when compared to a control group paired by age and race. Prolonged use of penicillin by falcemic children prevents acquisition of *Streptococcus mutans*, reflecting the significant reduction in dental caries in these individuals[19].

In the SCD patients, risk factors for caries seem to be similar to that observed in healthy subjects. Passos *et al.*[20] (2012) investigated the prevalence of dental caries and periodontal condition in 99 subjects with SCD and a control group comprising 91 without disease, analyzing some associations with disease severity. Their findings suggested that the sickle condition or the disease's clinical severity were not the main risk factors for the development of caries and periodontal disease. In this study, older age, female gender and daily smoking proved to be more important risk factors for higher Decayed, Missing and Filled Teeth index (DMFT). Their data suggested that risk factors known to affect the occurrence of dental caries were more important than SCD on the dental condition of subjects with SCD.

Periodontal Conditions

It has been reported that hygiene and oral care are important factors that influence the severity of periodontal disease and can prevent complications and infections in patients with SCA[17,21]

A case report of a 14-year-old boy, during his ninth episode of sickle cell crisis, described an unusual complication, characterized by swelling on the right side of the face without any infection related. Gingival enlargement, firm to palpation, was found in the lower arch on both sides. Biopsies suggested that gingival edema was a result from repeated hemorrhage episodes followed by fibrous tissue repair formation[22].

Crawford[23] (1988), evaluating clinical and radiographically 78 African patients with SCA, SC disease or thalassemia, did not observe significant association between SCD and gingivitis or periodontitis when compared to control group. The authors believe that in a larger population, in which more severe cases of SCD could be reached, periodontal disease might be affected by SCD.

Arowojolu *et al.*[24] (1997), through a prospective comparative study over 6 months, analyzed gingival and plaque indexes and probing depths in 50 SCA patients and 50 normal ones (11-19 years). No significant differences were found when groups were compared, suggesting that SCA did not lead to increased periodontal disease. Additionally, statistical significant difference was observed in probing depths only when female patients were considered (2.71 and 2.06 mm, for SCA and controls, respectively). Even though probing depths until 3 mm are accepted as normal, it was suggested that these findings might be of clinical importance with advancing age[21].

The same results were observed by Guzeldemir *et al.*[25] (2011). They evaluated 55 SCD patients and observed that there was no difference regarding the periodontal disease between SCD patients and healthy subjects. The authors were unable to assert that the disease could be a risk factor for periodontal disease.

According to most of literature available, SCD does not appear to predispose to periodontal complications. Passos *et al.*[20] (2012) did not observe association between SCA and periodontal disease in SCD patients. Their study showed that

higher risk for periodontal pockets was associated with older age and the absence of daily use of dental floss, which are recognized as risk factors for periodontal disease. Nevertheless, new investigations should be performed in order to assess the role of periodontal infection in the worsening of SCD picture, initiating or exacerbating vaso-occlusive episodes.

Temporomandibular joint (TMJ) disorders

SCD patients are commonly affected by bone and joint complications. The most common area of bone destruction is the femoral head, but other regions have been described: humeral head, thoracic and lumbar spine and temporomandibular joint (TMJ)[26].

There are few papers in the literature about TMJ disorders in SCD, all reporting clinical cases. It was reported a clinical case of a 23 years old Saudi female with SCA that early demonstrated signs of bony infarction of humeral head and avascular necrosis of TMJ and head femur, all in the left side, diagnosed by clinical examination and computed tomography. The authors suggested that despite the protective mechanisms of TMJ, it was not absolutely immune against vaso-occlusive episodes of SCA nature[27].

Another case of TMJ disorder was reported in a 23–year-old woman with SCA, who presented no trauma history or orthognathic surgery. During clinical examination, it was observed limited mouth opening, central line deviation to the right side and a slight facial asymmetry because of the short right ramus height. A flattened condyle and avascular necrosis of glenoid fossa were demonstrated on the right joint through radiological examination and computed tomography. Authors suggested that subtle onset of TMD symptoms should been taken seriously, especially in SCA adolescents (11 to 15 years), when bone changes become more obviously. Prevention of overloading and conservative approaches can prevent the development of irreversible deformities of TMJ[28].

Caracas et al.[29] (2013) reported a rare case of aseptic arthritis in the TMJ of a 22-year-old woman with SCA. The patient experienced pain in the left preauricular region, hyperalgesia of the left masseter muscle, mouth opening limitation and mild edema. Aseptic arthritis in the left condylar head secondary to a sickle cell crisis was diagnosed after the evaluation of the laboratory tests and images. The treatment consisted parenteral opioid analgesia and nonsteroidal anti-inflammatory drugs for manage of intense pain and blood transfusion because of severe anemia. Health professionals should be aware that aseptic arthritis may also be provoked by SCD. Laboratory tests and diagnostic imaging are important for differential diagnosis.

Radiographic Alterations

SCD patients usually present common radiographic features due to lesions in the cortical bone and bone marrow, often affecting the maxillofacial area[30]. Maxillary bone alterations in SCD are classified as: (1) lesions with osteoporotic appearance due to bone marrow hyperplasia,

(2) radiopaque images associated to vaso-occlusive phenomena and (3) osteomyelitis lesions due to infections. All these maxillofacial features are similar to the ones found in the rest of the skeleton[31].

Hemolytic anemia in SCD patients promotes a compensatory marrow hyperplasia resulting in trabecular bone changes associated with expansion of the jaws[28]. Enlarged bone marrow spaces usually appear as radiolucent areas between the root apices of posterior teeth and in the inferior border of the mandible, creating in some cases a horizontal trabecular pattern described as "step-ladder"[9].

Demirbas et al.[32] (2004) reported decreased trabecular bone density and enlarged bone marrow spaces in 67% of 36 SCA patients. However, "stepladder trabecular" pattern was observed in only 28% of these patients. Faber et al.[33] (2002) evaluated intertrabecular spacing in periapical digital radiographs from 18 SCA patients and control volunteers (mean age 20.8 years). Significant increase of intertrabecular spacing in both jaws and reduction of trabecular complexity were noted in SCA individuals. Demirbas et al.[34] (2008) investigated trabecular bone complexity of posterior mandible in 35 SCA patients (age ranged 11 to 40 years) and 26 control individuals using fractal dimension analysis from panoramic radiographs. SCA patients under age 20 showed significant lower fractal dimension values, pointing to scarcity of trabecular bone, when compared to control individuals.

Neves et al.[35] (2011) used panoramic radiograph to evaluate the radiographic features in the oral and maxillofacial region in Brazilian patients with SCD and healthy subjects. The healthy group showed a significantly smaller number of radiographic alterations when compared to the SCD patients. Increased intertrabecular distance, decreased trabecular complexity and the absence of mandibular canal corticalization were observed in subjects with HbSS. These findings were statistically significant when compared to the control group. The alterations of the trabecular pattern may be related to presence of hemolytic anemia in subjects with SC. Theses alterations may be found in healthy patients, but the occurrence of increased spacing of bone trabecular is more common between patients with SCD. These data provide important information for identifying the disease.

Bone marrow expansion promotes maxilla overgrowth, which can increase the distance between upper and lower incisors teeth, resulting in altered interlabial distance with an untoward physical appearance and occlusion problems[36]. Brown et al.[37] (1986), analyzing lateral skull radiographs of 50 SCA patients and 25 control volunteers matched by age and gender, observed in the first group a significant difference in maxillary protrusion due to increase in palate-alveolar-ridge angle. Licciardello et al.[36] (2007) evaluated cephalometric radiographs from 36 patients with and 36 control volunteers (18.5-51 years). Patients with SCD presented a significantly maxillary incisor proclination and protrusion of the lower and upper lip. However the most severe craniofacial changes occurred in SS patients when compared to thalassemic ones.

A less frequently radiographic finding is the expansion

of bone marrow in the calvarium, which is more often observed in very young patients. The widening of the diploe narrows the outer table, while perpendicular orientation of trabeculae to inner table gives a "hair-on-end" or "bristle-like" appearance[30,31].

Radiopaque lesions presented by SCD patients are commonly associated to bone infarction and osteonecrosis[30-31]. In the first situation, long bones are affected more often, yet osteonecrosis usually takes place in articular surfaces[38]. It is suggested that the mandibular posterior region is the most affected by these lesions, coinciding with severe facial pain during sickle cell crisis. The affected area is ischemic and aseptic. Initially the decalcification is surrounded by reactive sclerosis and later it is separated from cortex by a thinning radiolucent area, characterizing a "bone-within-bone" appearance[31].

Kavadia-Tsatala et al.[31] (2004), evaluating panoramic and cephalometric radiographs, found radiopaque lesions associated to bone infarct in 6 of 42 SCD patients (20-65 years old). Lesions were related to vaso-occlusive phenomena, since it was followed by a painful crises episode and without any dental pathology associated. Podlesh et al.[39] (1995) reported a case of an 21 years-old man, hospitalized during a sickle cell crisis, who presented a profound anesthesia of the right mental nerve, fever, acute pain and tenderness to palpation on the right mandible. Laboratory data showed no evidence of infection, however scans revealed cortical bone and bone marrow infarction of the right mandible. Hamdoun et al.[40] (2012) reported a case of an 15-year-old boy who showed no sensation to pain or touch of the entire lower lip and chin. The finding by magnetic resonance imaging were consistent with bone infartion. This case is considered unique because the patient was a child and had bilateral mental neuropathy. Moreover, patients with SCD are more likely to report pain than a lack of sensitivity. It is possible that frequency of complications such mental nerve neuropathy in patients with SCA be high. Mendes et al.[41] (2011), comparing the prevalence of oral manifestations in 330 patients comprising subjects with SCA and clinically normal patients, observed that the prevalence of previous mental nerve neuropathy in patients with SCA was 2.2 times greater than observed in individuals without the disease, particularly in the female.

Osteomyelitis occurs up to 200 times more frequently in SCD subjects than in the rest of population[38,42]. It is suggested that bone infarcts are the initial incident. The infarcted area is a propitious environment for bacteria growth, especially Salmonella and Staphylococcus aureus that migrate from several sources[38,43]. Mandibular osteomyelitis seems to develop from direct extension of periapical abscess[38] or pericoronitis[43] and displays the same signs of bone infarcts like pain, soft tissue swelling, fever and leukocytosis[39]. Differential diagnosis between infarction and osteomyelitis can be very difficult, however this distinction is important as these two bone lesions are treated differently[44,]. Magnetic resonance imaging was suggested to be useful to investigate these lesions. However, only techniques able to identify the infectious organism are reliable to establish a correct verdict[42].

Final Considerations

Considering the currently available literature, radiographic alterations of orofacial bones are better documented, while there is no precise knowledge concerning the prevalence and impact of caries, periodontal condition and TMD in the SCD.

It seems like orofacial complications depends not only on the presence of sickle disease, but also on factors related to the subject such as oral hygiene, diet habits and social conditions. Although there is no direct association between SCD and orofacial problems, limitations from systemic complications of this disease can reduce the patient's availability for dental care. A poor buccal condition can act as an infectious focus for vaso-occlusive crisis precipitation, compromising even more health and social life of these individuals.

Further well-designed epidemiological studies are needed to understand and recognize oral manifestations related with SCD, indicating the real impact of this disease on stomatognathic health and collaborating to improve public health policies.

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