Sickle-cell disease: a review of oral manifestation and presentation of a case with an uncommon complication of the disease

Ozgur Erdogan[1*], Halil Ibrahim Kisa[2], and Sureeporn Charudilaka[3]

[1]Faculty of Dentistry, Rangsit University, Patumthani, Thailand
E-mail: ozgerdogan@yahoo.com
[2]Faculty of Dentistry, Cukurova University, Adana, Turkey
E-mail: hikisa@cu.edu.tr
[3]Private Practice, Bangkok, Thailand
E-mail: sureeporn_aim@hotmail.com

*Corresponding author

Submitted 11 January 2013; accepted in final form 18 October 2013

Abstract

Sickle-cell disease (SCD) is a genetic hematological disease, in which polymerization of abnormal hemoglobin leads to morphologic alteration in erythrocytes. It is characterized with several systemic and local manifestations. An unusual complication of SCD is the mental nerve paraesthesia, which is associated with acute phase of the disease. The aim of this article is to review the general clinical and radiographic findings of the disease and to present a SCD patient with bilateral mental nerve paraesthesia.

Keywords: *sickle-cell disease, oral complications, paraesthesia, case report*

1. Introduction

Sickle-cell disease (SCD) is a genetic hematological disease, in which polymerization of abnormal hemoglobin leads to morphologic alteration in erythrocytes (Neves, Passos, Oliveira-Santos, Cangussu, Campos, Nascimento, et al., 2012). This disease is caused by a homozygous point mutation in the beta chain of the hemoglobin gene. Oral and maxillofacial tissues are affected by SCD as the other parts of the body. Symptoms of SCD may manifest in soft tissues as well as in bony structures of maxillofacial region. The frequent oral manifestations of SCD include paleness of the oral mucosa, delay in tooth eruption, atrophy of the tongue papillae, impaired dentine mineralization, mandibular osteomyelitis, orofacial pain, craniofacial skeletal alterations such as exaggerated growth/protrusion of the midface, maxillary expansion, a predominance of vertical growth, mandibular retrusion, a convex profile, and maxillary protrusion (Maia, dos Santos, Coletta, Mendes, Bonan, Maia, & Junior, 2011; Mendes, Fonseca, Martelli, Bonan, de Almeida, de Melo, & Martelli, 2011) Radiographic features of SCD are increased radiolucency of the jaws due to the decreased number of trabeculae, coarse trabeculae pattern, thin inferior border of mandible, distinct areas of radiopacity, stepladder appearance created in the interdental alveolar bone by horizontal rows of trabeculation (da Fonseca, Oueis, & Casamassimo, 2007; Neves et al., 2012) A list of oral manifestations of SCD is given in Table 1.

The mental nerve neuropathy is one of the uncommon oral complications of SCD. Mental nerve paraesthesia is usually associated with oral surgery, metastatic malignancies, local infection, bone injury, and cysts or tumors in the mandibular bone. Few cases have been reported in patients with sickle-cell anemia during/after a sickle-cell crisis (de Fonseca et al., 2007). In this report, we describe a 23-year-old male patient, who developed bilateral mental nerve paraesthesia during a sickle-cell crisis. This case differs from the previous cases since the paraesthesia developed bilaterally and the patient had both thalassemia and sickle-cell anemia.

2. Case report

A 23-year old male patient, who was known to have thalassemia and sickle-cell anemia, admitted to the Department of Oral and Maxillofacial Surgery at the Faculty of Dentistry, Cukurova University, Adana, Turkey in November, 2011. His major complaint was numbness of chin and lower lip in both sides. Clinical touch tests conducted on both sides confirmed altered or no sensation on lips. Clinical examination showed no sensation to pain or

DOI : 10.14456/rjas.2013.5
Copyright © 2011, Rangsit University. All rights reserved

touch of the mucous membrane and cutaneous portion of the entire lower lip. Sensation of the upper lip, gingiva and teeth appeared to be intact. The neurologic examination of other parts was normal. Oral examination revealed normal soft tissue and salivary glands. There was a full range of mandibular motion, and occlusion was acceptable (Figure 1). No cervical lymphanedopathy was detected. Oral hygiene was almost optimal, with no significant caries. The patient stated that he had experienced pain at the right and left lower lip and chin at the same time with present generalized pain crisis. Computer tomography (CT) did not show any evidence of cortical bone destruction or bone pathology (Figure 3). His laboratory studies were consistent with sickle-cell disease with a blood hemoglobin content of 9.1 g/dL and a hematocrit of 26.9%. The white blood cell count was 26.6 x 10^3 cells/µL. Elevation in white blood cell count may occur in severe sickle cell anemia cases due to increased leukocyte adherence to its endothelium (Okpala, 2004). He was transfused 1 unit of packed red blood cell while at hospital. An informed consent form signed by the patient and his parents was obtained for using his data and clinical information for publication.

No specific treatment was applied but the patient was followed closely. Over the next few months, he reported resolution of numbness of the chin and lower lip. Follow-up revealed total resolution of the paraesthesia within 6 months.

Table 1 Possible oral manifestations of sickle-cell disease

Clinical	**Radiographic**	**Craniofacial Growth Abnormality***
Orofacial pain	Overall increased radiolucency	Exaggerated growth/protrusion of the midface
Pale oral mucosa	Decreased number of trabeculae,	Maxillary expansion
Delay in tooth eruption	Coarse trabeculae pattern	Predominance of vertical growth,
Atrophy of tongue papillae and glossitis	Thin inferior border of mandible	Mandibular retrusion
Impaired dentin mineralization	Distinct areas of radiopacity	A convex profile
Mandibular osteomyletis	Stepladder appearance created in the interdental alveolar bone	Malocclusion
Mental nerve neuropathy	Tooth intrinsic opacity	
Gingival enlargement		

*Craniofacial growth abnormality may vary according to racial background of the individual

Table 2 Previous reports documenting sickle-cell anemia patients with mental nerve paraesthesia

Investigators	Publication Year	Patient's age and sex	Prognosis
Konotey-Ahulu	1972	23 year-old male 33 year-old male 23 year-old female 31 year-old female 37 year-old female	Recovery is slow, took 18 months in 1 patient
Kirson & Tomaro	1979	18 year-old male 29 year-old male	Recovered in 9 months Recovered in 1 month
Friedlender et al.	1980	40 year-old male	Recovered in 18 months
Seeler & Royal	1982	11 year-old female	Recovered in 4 months
Hamdoun et al.	2012	15 year-old female	Recovered in 2 months

Figure 1 Clinical intraoral view of the patient. Note the normal interocclusal relation and healthy periodontal tissue.

Figure 2 Clinical photograph showing needle touch test. Patient does not have sensation to needle touch test.

Figure 3 Computed tomography images at coronal sections. Note increased trabecular space without intraosseous or extraosseous pathology.

3. Discussion

The hemoglobinopathies represent a hereditary group of diseases, in which a qualitative abnormality occurs in globin, or protein portion of the hemoglobin molecule. Thalassemia, while not demonstrating qualitatively abnormal hemoglobin, is also regarded as a hemoglobinopaty. In this hereditary disease, there exists a subnormal rate of synthesis of one of the substructures of the protein portion of hemoglobin molecule (Beutler, 1998). There are several forms of SCD. The principal genotypes include homozygous sickle-cell anaemia, sickle-cell haemoglobin C disease, and sickle-cell β-thalassaemia (Licciardello, Bertuna, & Samperi, 2007). The alteration in hemoglobin results in formation of a gelatinous network of fibrous polymers called tactoids, that stiffen and distort the cell producing rigid, misshapen erythrocytes that transverse small vessels with great difficulty or not at all (Beutler, 1998). The obstruction of small vessels by sickle cells results in repeated infarctions, leading to gradual involvement of all organ systems. The clinical manifestations of sickle cell disease are signs and symptoms of chronic anemia with pallor of mucous membranes, fatigue, and decrease exercise tolerance. Other general symptoms include leg ulcers, repeated episodes of pulmonary infarction causing several pulmonary complications, heart failure, ocular damage, renal papillary necrosis, spleen atrophy, osteomyelitis, priapism and cerebrovascular accidents (Beutler, 1998; Rees, Williams, & Gladwin, 2010). Although SCD is a chronic systemic disease it may manifest acute exacerbations. Three types of acute episodes termed crises may occur, which are Infarctive or painful crisis, Sequestration crisis, and Hemolytic crisis. The most commonly seen type is infarctive crisis, which takes several days or weeks and associated with severe skeletal pain (Beutler, 1998; Rees et al., 2010) The diagnosis of SCD is made based on the presence of sickle-cell hemoglobin, which can be established by sickling/solubility tests, electrophoreses, or DNA polymorphisms prenatally (Platt, Brambilla, Rosse, Milner, Castro, Steinberg, & Klug, 1994; Boehm, Antonarakis, Phillips 3rd, Stetten, & Kazazian, 1983) The Management of

SDC is mainly based on avoidance of complications and their symptomatic treatments if occurred. The patients should avoid high altitudes, maintain an adequate fluid intake and they should be given supplementary folic acid (Beutler, 1998). Management of acute crises poses more difficult challenges for the clinicians dealing with the patient. Painful situations is solved by prescription of analgesics including narcotic analgesics. Blood transfusion may be required in more severe instances.

The majority of the normal adult's hemoglobin is hemoglobin A (HbA), which constitute approximately 97% of all hemoglobins. The globin portion of HbA is comprised of two pairs of polypeptide chains; two α chains, each formed of 141 amino acids, and two β chains, formed of 146 amino acids (HbA = $\alpha_2\beta_2$). The remaining 3% of the normal adult hemoglobin is mostly hemoglobin A_2 (HbA_2). In HbA_2 the two α chains are identical with that of HbA; however, the β_2 chains are replaced by different polypeptide chains which are designated as δ chains (HbA2 = ($\alpha_2\delta_2$). At birth, the predominant hemoglobin is fetal type (HbF), and is composed of two α chains, identical to those of HbA, and two γ chains, which have the identical number of amino acids as do the β chains of HbA but differ in the amino acid sequence (HbF = $\delta_2\gamma_2$). Over the first 6 months of life, the concentration of HbF slowly decreases and is replaced by the adult hemoglobins (Cooper & Bunn, 1977). It is at this stage that the adverse effects from abnormal adult hemoglobin begin to manifest themselves (Cooper & Bunn, 1977). The majority of the clinical problems associated with sickle-cell disease are related to the vascular occlusive processes that occur. As sickling of the red blood cells develops, the cells are unable to pass freely through the microcirculation. As the blood flow stagnates, waste products are poorly cleared, resulting in an acidosis and increased sickling. Oxygen and waste product clearance suffers in an ever-increasing area. Painful crises appear at irregular intervals and normally manifest themselves in the abdomen, chest, and joints. Patients may go several months without problems and then incur several pain crises in quick succession. Precipitating factors include infection, dehydration, over exercise, cold in some patient, and heat in others. Often no precipitating factor is evident (McFarlane, 1977).

SCD manifests itself with variety of symptoms in the oral and maxillofacial region. Clinical symptoms can be detected by direct examination, while several radiographic features are deterministic for the existence of SCD. The most significant problem for clinicians, who deal with diseases of oral cavity, is tendency to stubborn infections and osteomyelitis. Other manifestations are only significant for the diagnosis of the disease which does not need any treatment or can be solved by relatively simpler treatments. A summary of the oral manifestation is given in Table 1.

Mental nerve paraesthesia developed in our patient is relatively uncommon finding of SCD. There are few cases documenting mental nerve paraesthesia in patients with sickle-cell anemia. A list of the previous reports is given in Table 2. Although, limited numbers of case reports are available, Mendes et al. (2011) reported that 27.5% patients with SCD have a history of mental nerve paraesthesia in a Brazilian population (Mendes et al., 2011). This finding shows that despite the low number of cases reporting mental nerve paraesthesia associated with SCD, it is actually a usual but overlooked manifestation of sickle cell crisis. The reason may be that patients suffer from so much pain in the other parts of their skeleton and do not recognize or report this symptom to their physician. The mental nerve is one of the two terminal branches of the inferior alveolar nerve. The inferior alveolar nerve, the largest branch of the mandibular nerve, descends with the inferior alveolar artery between the sphenomandibular ligament and the ramus of the mandible to the mandibular foramen. It then passes forward in the mandibular canal, beneath the lower teeth, as far as the mental foramen, where it divides into two terminal branches. Just before it enters the mandibular foramen it gives off the mylohyoid nerve, which supplies the mylohyoid and the anterior belly of the digastric muscles. While the inferior alveolar nerve is passing in the mandibular canal, it gives off the dental branches to supply sensation to the molar and premolar teeth. The incisive branch, the other terminal branch of the inferior alveolar nerve, continued onward within the mandibular bone to supply the canine and incisor teeth. The mental nerve exists through the mental foramen with its artery. It divides beneath the triangularis muscle into three branches: one branch is distributed to the skin of the chin and two branches are distributed to the skin and mucous membrane of the lower lip. Nontheless, variations in the anatomic and topographic patterns of the inferior alveolar nerve have been reported. For example, Anil et al. (2003)

reported that the mental nerve continues to the terminal incisive branch that supplies sensation to the lower canine and incisor teeth (Anil, Peker, Turgut, Gülekon, & Liman, 2003). These variations have contributed to the complexity of the signs and symptoms of the patients.

The mental nerve neuropathy most commonly occurs in accidental or iatrogenic injury to the mandible. It is also caused by metastatic malignancies, lymphoproliferative disorders, local infections, and cysts in the mandibular bone. The neuropathy is also associated with a number of systemic disorders such as HIV, Lyme diseases, sarcoidosis, diabetes (McFarlane, 1977). The etiology of the mental nerve paraesthesia in sickle-cell crisis is considered by infarction of the inferior alveolar nerve at or near the mental foramen where the mental nerve has an unusual bending course exiting the canal (Hamdoun, Davis, McCrary, Eklund, & Evans, 2012). A case report by Hamdoun et al. (2012) presents Magnetic Resonance Imaging (MRI) findings of a SCD patient with an acute bilateral mental nerve paraesthesia. The MRI abnormalities included increased T2 signal in both mandibular rami with small subperiosteal fluid collection abutting the medial aspects of the rami that did not enhance on T1 images with contrast (Hamdoun et al., 2012).

In conclusion, sickle-cell disease has several oral and maxillofacial manifestations. Although mental nerve paraesthesia is known to be unusual complication of the disease it should be considered one of the etiologic factors of mental nerve paraesthesia. Complete recovery of the paraesthesia is expected lasting as long as 6 months.

4. References

Anil, A., Peker, T., Turgut, H. B., Gülekon, I. N., & Liman, F. (2003). Variations in the anatomy of the inferior alveolar nerve. *Br J Oral Maxillofac Surg, 41*(4), 236-239.

Beutler, E. (1998). Hemoglobinopathies. In T.R.Harrison & A. S. Fauci (Eds), *Harrison's principles of internal medicine*, 14th ed., (pp. 645-652). New York, USA: The McGraw-Hill Companies, Inc.

Boehm, C. D., Antonarakis, S. E., Phillips, J. A. 3rd, Stetten, G., & Kazazian, H. H. Jr. (1983). Prenatal diagnosis using DNA polymorphisms. Report on 95 pregnancies at risk for sickle-cell disease or beta-thalassemia. *N Engl J Med, 308*(18), 1054-1058.

Cooper, R. A., & Bunn, H. F. (1977). Hemolytic anemias and hemoglobinopathies In G. W. Thorn, R. D. Adams, E. Braunwald, K. J. Isselbacher, & R. G. Petersdorf (Eds), *Harrison's principles of internal medicine*, 8th ed., (pp1674-1688). New York, USA: The McGraw-Hill Companies, Inc.

da Fonseca, M., Oueis, H. S., & Casamassimo, P. S. (2007). Sickle cell anemia: a review for the pediatric dentist. *Pediatr Dent, 29*(2), 159-169.

Friedlander, A. H., Genser, L., & Swerdloff, M. (1980). Mental nerve neuropathy: a complication of sickle-cell crisis. *Oral Surg Oral Med Oral Pathol, 49*, 15-17.

Hamdoun, E., Davis, L., McCrary, J. S., Eklund, N. V., & Evans, O. B. (2012). Bilateral mental nerve neuropaty in an adolescent during sickle cell crises. *J Child Neurol, 27*(8), 1038-1041.

Kirson, L. E., & Tomaro, A. J. (1979). Mental nerve paresthesia secondary to sickle cell crisis. *Oral Surg Oral Med Oral Pathol, 48*(6), 509-512.

Konotey-Ahulu, F. I. (1972). Mental-nerve neuropathy: a complication of sickle cell crisis. *Lancet, 2*(7773), 388.

Laurencet, F. M., Anchisi, S., Tullen, E., & Dietrich, P. Y. (2000). Report of five cases and rewiew of the literature. *Crit Rev Oncol Hematol, 34*(1), 71-79.

Licciardello, V., Bertuna, G., & Samperi, P. (2007). Craniofacial morphology in patients with sickle cell disease: a cephalometric analysis. *Eur J Orthod., 29*(3), 238-242.

Maia, N. G., dos Santos, L. A., Coletta, R. D., Mendes, P. H., Bonan, P. R., Maia, L .B., & Junior, M. H. (2011). Facial features of patients with sickle cell anemia. *Angle Orthod., 81*(1), 115-120. **doi:** http://dx.doi.org/10.2319/012910-61.1

McFarlane, J. (1977). Sickle Cell Disorders. *Am J Nurs, 77*(12), 1948-1954. PMID: 244260 [PubMed - indexed for MEDLINE]

Mendes, P. H. C., Fonseca, N. G., Martelli, D. R. B., Bonan, P. R. F., de Almeida, L. K. Y., de Melo, L. A., & Junior, H. M. (2011). Orofacial manifestations in patients with sickle cell anemia. *Quintessence Int, 42*(8), 701-709.

Neves, F. S., Passos, C. P., Oliveira-Santos, C., Cangussu, M. C., Campos, P. S., Nascimento, R. J., Crusoé-Rebello, I., & Campos, M. I.

(2012). Correlation between maxillofacial radiographic features and systemic severity as sickle cell disease severity predictor. *Clin Oral Investig*, *16*(3), 827-833. DOI: 10.1007/s00784-011-0577-0

Okpala, I. (2004). The intriguing contribution of white blood cells to sickle cell disease - a red cell disorder. *Blood Rev*, *18*(1), 65-73.

Platt, O. S., Brambilla, D. J., Rosse, W. F., Milner, P. F., Castro, O., Steinberg, M. H., & Klug, P. P. (1994). Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med*, *330*(23), 1639-1644.

Rees, D. C., Williams, T., N., & Gladwin, M. T. (2010). Sickle-cell disease. *Lancet*, *376*(9757), 2018-2031.

Seeler, R. A., & Royal, J. E. (1982). Mental nerve neuropathy in a child with sickle cell anemia. *The American Journal of Pediatric Hematology/Oncology*, *4*, 213-213.