Literature Review

Sickle Cell Anemia: A Review for the Pediatric Dentist

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Abstract: *Sickle cell anemia is an inherited defect that affects the structure and synthesis of hemoglobin. In sickle cell trait, the affected individuals carry one gene for the abnormal hemoglobin (HbS). Sickle cell disease, however, is the homozygous state in which the abnormal hemoglobin is predominant in red blood cells, leading to devastating multisystem problems. Complications of the disease in children include: painful crises, stroke, pulmonary disease, delayed growth, osteomyelitis, organ damage and psychosocial dysfunction. Oral and dental manifestations include: orofacial pain, paresthesia of the mental nerve, stepladder appearance of the alveolar bone on radiographs, pulpal necrosis and enamel hypomineralization. The purpose of this manuscript was to review: (1) the pathophysiology of the disease; (2) its manifestations in the craniofacial complex; (3) contemporary medical therapy; and (4) recommendations for dental care. (Pediatr Dent 2007;29:159-69)*

KEYWORDS: SICKLE CELL, DENTAL MANAGEMENT, REVIEW, PEDIATRIC DENTISTRY

Normal adult red blood cells (RBCs) contain 3 types of hemoglobin (Hb):

1. HbA is composed of 2 α and 2 β globin chains ($\alpha_2\beta_2$), comprising 96% to 98% of total Hb.
2. HbA_2 is formed by 2 α and 2 δ chains ($\alpha_2\delta_2$) and accounts for 1.5%-3.2% of the total.
3. Fetal Hb (HbF) is made up of 2 α and 2 γ chains ($\alpha_2\gamma_2$) and comprises 0.5%-0.8%.[1]

For the first 10 weeks of life, HbF makes up approximately 90% of the total Hb.[1] Production of the α chains is coded by 4 alleles paired on chromosome 16, whereas non-alpha chains are synthesized under the control of 2 alleles located in the β-gene cluster on chromosome 11.[2] The term hemoglobinopathy describes a group of autosomal recessive disorders that affect the structure and synthesis of Hb, resulting in hemolytic anemia. Alpha and β thalassemia and sickle cell anemia (SCA) are the most common types of hemoglobinopathies worldwide.

SCA is the most common genetic disorder of the blood and is most frequently observed in persons of African, Mediterranean, Middle Eastern, Indian, Caribbean, Central American, and South American ancestry.[3-6] SCA comprises sickle cell trait and sickle cell disease (SCD). SCD is a group of complex, chronic disorders characterized by: hemolysis, chronic organ damage and unpredictable acute complications that may become life-threatening.[3] It is caused by a variant of the β-globin gene called sickle hemoglobin (HbS), which makes up at least half of the Hb present.[6-8] The gene is involved, like other globin genes, in oxygen transportation.[6] For SCD expression, either 2 copies of HbS or 1 copy of HbS plus another β-globin variant are required.[6]

Therefore, there is a variety of sickle cell genotypes, including homozygosity for HbS (HbSS), the most common, and several symptomatic heterozygous states (Table 1). The molecular nature of the disease is a substitution of valine for glutamic acid at the sixth amino acid position in the β-globin gene, allowing HbS to polymerize when deoxygenated.[1,5,8] In a newborn infant with SCD, HbF represents 60% to 80% of the total Hb, with no HbA. By 3 to 6 months of age, HbF levels drop to 10% to 20% and HbS predominates.[1] Between 0.3% and 1.3% of the American black population (1/600) have SCD.[1,7]

The trait form is benign; the affected individuals do not present anemia and need no treatment nor occupational restrictions.[1,4,7] They present approximately 40% of HbS, which is a low concentration for polymerization to occur under most circumstances. Thus, the cellular injury that leads to the clinical manifestations of SCD is not seen.[7] Eight percent of African Americans and 10% to 30% of equatorial Africans carry the trait.[1,4,7]

In the US, SCD is the most prevalent disorder identi-

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Table 1. MOST COMMON SICKLE CELL DISEASE (SCD) GENOTYPES[3,4,8]

GENOTYPE	US SCD PATIENTS (%)	PHENOTYPE (SEVERITY)
HbSS disease (sickle cell anemia)	65	Severe / moderate
HbSC disease	25	Intermediate
HbS/ β^+ thalassemia	8	Mild to moderate
HbS/ β^0 thalassemia	2	Almost indistinguishable from sickle cell anemia

fied by neonatal screening, which is done on blood from the umbilical cord or from a heel prick.[3,4,6] The District of Columbia and 49 states have mandatory universal programs for newborn screening for Hb disorders.[9] Any high risk infant (i.e, those who come from or are descendants of families from areas where the disease is prevalent) not screened at birth should have the test done prior to 2 months of age so that comprehensive care and family education can be initiated.[3,4] Tests commonly used to detect SCD include: cellulose acetate/citrate agar electrophoresis, isoelectric focusing and high performance liquid chromatography.[6] Interestingly, HbS carriers are protected from malaria infection, which probably led to the high frequency of HbS in individuals of African and Mediterranean descent.[1,6] RBCs infected with the parasite Plasmodium falciparum appear to sickle more easily and are subsequently destroyed by the reticuloendothelial system.[1]

Pathophysiology of SCD

The polymerization of deoxygenated HbS ("gellation") is the primary indispensable event in the molecular pathogenesis of SCD.[8] This process is dependent on: intra-RBC HbS concentration, degree of cell deoxygenation, pH and intracellular concentration of HbF.[8] Gellation does not happen instantaneously upon deoxygenation. Therefore, sickling occurs after a period of time necessary for sufficient intracellular polymerization to deform the cell. This time interval is greater than the circulation time required for most cells to return to the pulmonary capillaries and reoxygenate.[2] The polymer is a rope-like fiber that aligns with others, forming a bundle and distorting the RBC into a crescent or sickle shape which interferes with one of its most critical features—its deformability.[8] Some cells sickle but return to normal if reoxygenation occurs before significant polymerization has happened. The mean lifespan of sickle RBCs is 12 to 17 days (normal lifespan is 120 days).[1]

It was originally thought that impaired RBC deformability caused microcirculatory obstruction during capillary transit, leading to a vaso-occlusive crisis (VOC).[8] The actual mechanism is much more complex, however. The polymer-containing sickled cells are trapped predominantly in the slow-flowing venular side of the microcirculation. Adhesion of RBCs to the endothelium is enhanced, and a heterocellular aggregate is formed. This results in: local hypoxia increased HbS polymer formation and spread of the occlusion to the adjacent vasculature.[8] Neutrophil migration adds to the increased inflammation in the microvasculature.[8] An abnormal cation homeostasis leads to the formation of dehydrated dense sickle cells and short-lived cells that do not return to their normal shape even when oxygenated because of irreversible membrane damage.[8] The abnormal vasomotor tone favors vasoconstriction, the pH falls, and there is low concentration of protective Hb types such as HbF and HbA2.[8] Platelets do not seem to be critical to the pathophysiology of vaso-occlusion, but their quality may be affected and their number may be reduced due to functional asplenia.[8]

In summary, HbS produces a problem of erythrocyte "sticking" rather than simply "sickling."[2] Adhesion, hemolysis, and deformation are interconnected causing profound vascular dysfunction. SCD symptoms arise mostly from chronic endothelial damage instead of acute erythrocyte deformation. Thus, the clinical picture is that of a chronic inflammatory vascular disease.[1,2,8]

Systemic manifestations of SCD

Symptoms usually start appearing within the first 6 months of life, with anemia and vasculopathy being the hallmarks of the disease.[5,6] The remarkably varied clinical picture (Table 2) is one of evolving organ damage punctuated by intermittent periods of severe pain and pulmonary complications.[2,7] Genotype is the most important risk factor for disease severity; HbSS individuals are the most severely compromised.[6] Patients usually present Hb levels of 6 to 9 g/dl (normal=12-18 g/dl) and reticulocyte counts of 5% to 15% (normal: 0.5 – 1.5%).[1] Hemolytic or aplastic crises are caused mainly by human parvovirus B19 and result in accelerated RBC destruction, leading to massive suppression of normal erythropoiesis. This can be corrected with transfusion, although most individuals recover spontaneously within a few days.[1,3,5,8]

Painful crises or VOC manifest in early childhood as dactylitis (hand-foot syndrome), becoming less common after 5 years of age but often continuing throughout life in an unpredictable manner.[1,8,10] Although many episodes have no identifiable cause, triggering factors include: infection, dehydration, extreme temperatures, hypoxia, physical or emotional stress and menstruation.[1,7] Premature epiphyseal

fusion and permanently shortened, deformed small bones may occur as a consequence of dactylitis. After age 2, pain remains the most common manifestation of SCD, involving most frequently the articulations of long bones such as: hips, knees, elbows, shoulders, spine, sternum, pelvis and ribs.[1,8] Bone pain is often excruciating, symmetrical, and present in multiple areas, lasting from a few minutes to several days.[7,8] Young children complain mainly of limb pain, whereas adolescents are afflicted most frequently with abdominal discomfort.[1,7,8] Although only 1% of patients have more than 6 VOC episodes a year, 39% have none.[2]

Splenic sequestration crises, most common in the first 5 years of life, are caused by RBCs being sequestered in great numbers in the spleen, producing a precipitous drop in the Hb concentration.[1,8] It is considered a major event when the Hb levels are less than 6 g/dl or when there is a drop of at least 2 g/dl below the patient's baseline, requiring fluid resuscitation and blood transfusion.[1,8] Acute sequestration presents with rapid, often painful, splenic enlargement associated with sudden and severe anemia, thrombocytopenia and reticulocytosis, and can be fatal without prompt treatment.[5,11] Chronic sequestration (hypersplenism) shows a mean RBC lifespan of 2 to 4 days and Hb levels of 3 to 4 g/dl.[1] Chronic transfusion and splenectomy (partial, total, splenic embolisation or irradiation) may resolve the problem if it does not correct itself spontaneously.[1,11] The main objection to performing splenectomy in young children is the increased risk of infection, which is also seen in cases of autoinfarction (hyposplenism).[1,6,11] Life-threatening postsplenectomy sepsis is primarily caused by polysaccharide encapsulated bacteria, particularly Streptococcus pneumoniae.[12] Acute sequestration is also seen in the liver, albeit less frequently than in the spleen.[5]

The majority of SCD patients present abnormalities in the cardiovascular system.[1] Chronic anemia can lead to cardiomegaly, systolic murmurs are very common, and some children may even develop congestive heart failure.[1,8] Bone problems are a common manifestation in SCD. Because of a diminished immune system, osteomyelitis occurs 200 times more frequently in affected patients than in the normal population, usually caused by salmonella.[1] It normally presents with: fever, pain, swelling and tenderness over the affected area.[13] These signs and symptoms are similar to those seen in VOC, thus a confident diagnosis of osteomyelitis in SCD relies more on clinical assessment together with positive cultures from blood or bone than any single imaging modality.[13] Osteonecrosis or avascular necrosis occurs when vaso-occlusion results in the infarction of the articular surfaces and heads of the long bones. Marrow hyperplasia can produce osteopenia and osteoporosis.[13] Growth disturbance is a well-recognized complication of SCD.[13]

Acute chest syndrome (ACS), the leading cause of death and hospitalization among SCD patients, is the radiological appearance of a new pulmonary infiltrate of at least one complete lung segment, accompanied by fever and respiratory symptoms.[1,2,8] Potential triggers include: a variety of infectious pathogens, fat embolism after bone marrow infarction, pulmonary

Table 2. CLINICAL MANIFESTATIONS OF SICKLE CELL DISEASE[2,4,7,8,16]

Neurological	**Pulmonary**
Pain crisis	Acute chest syndrome
Stroke	Airway hyper-reactivity
Proliferative retinopathy	Restrictive lung disease
Peripheral neuropathy	
Chronic pain syndrome	
Genitourinary	**Gastrointestinal**
Hyposthenuria	Cholelithiasis
Chronic renal insufficiency	Liver disease
Urinary tract infection	Dyspepsia
Priapism	
Hematological	**Orthopedic**
Hemolytic anemia	Osteonecrosis
Acute aplastic anemia	Osteomyelitis
Splenic enlargement/fibrosis	Dactylitis
	Osteopenia/osteoporosis
	Impaired growth
Immunological	**Cardiovascular**
Immune dysfunction	Leg ulcers
Hemolytic transfusion reactions	Cardiomegaly
	Systolic murmurs
RBC auto/alloimmunization	Congestive heart failure
	Vaso-occlusive crisis
	Pulmonary hypertension
Psychosocial issues	
Depression	
Anxiety	
Disturbed or altered sexuality	
Emotional and behavioral problems	
Poor peer relationships	
Poor body image and self-concept	

infarction and surgical procedures.[2] ACS leads to chronic progressive lung damage—which, in turn, triggers more hypoxemia and sickling events.[2,7,14]

Overt or silent cerebrovascular accidents (CVA) are a major complication of the disease and may lead to motor and intellectual impairment.[1,9] There is a 200-fold increase in the stroke risk in the SCD population, and mortality is as high as 26% in patients with hemorrhagic strokes.[9,14,15] Intracerebral hemorrhage is the second most frequent cerebrovascular complication in SCD.[1] The kidneys are very vulnerable to sickle vaso-occlusion, thus SCD patients may present impaired tubular function, limiting the concentration of urine and becoming prone to dehydration.[1] Progressive glomerular fibrosis may lead to chronic renal failure, typically in the third or fourth decade of life.[1,2] Priapism is probably caused by the stagnation of blood within the sinusoids of the corpora cavernosa during a physiological erection. This reduces RBC deformability, causing prolongation of the erection and pain.[1] It can lead to impotence in the long-term.[8]

SCD is better conceptualized as a disease with psychosocial and physiological complications. Long-term consequences of all the hospitalizations and pain these patients endure are: impaired psychosocial functioning, altered intra- and interpersonal relationships and reduced quality of life.[16] Indicators of poor psychological adjustment in SCD children include: emotional and behavioral pro-blems, disturbed or altered sexuality, poor body image and self-concept, poor social and interpersonal functioning, social withdrawal and poor academic performance.[16] The parent-child relationships are usually not affected negatively, but marital relationships between an adult patient and a spouse or the patient's parents tend to suffer due to the disease's chronicity.[16]

Prevention and treatment of SCD complications

Elevated HbF is associated with fewer sickling episodes and fewer long-term sequelae because it prevents the formation of HbS polymers. When initially used as an antineoplastic agent, hydroxyurea (HU) caused inhibition of DNA synthesis and was associated with increased levels of HbF.[9] Although its mechanism of action is not well understood, HU-induced marrow suppression results in stress erythropoiesis that favors proliferation of precursors containing HbF.[9] It also improves sickle RBC hydration and RBC adherence to endothelial cells, reducing the: frequency of painful episodes, hospitalization rate and length of stay for vaso-occlusive pain.[8,9] It is licensed in the United States for patients who are older than 18 months and who have at least 3 crises a year.[8,14] Ten to 25% of adult patients do not respond to the drug.[7,8] HU toxicities are mild and transient and include: anemia, liver enzyme elevation, nausea, neutropenia and thrombocytopenia. This required monitoring of cell count.[9] Long-term safety and efficacy have shown a reduced mortality rate in adults and no adverse effects in school-aged children on: height, weight or pubertal development.[9] Potential for teratogenicity, carcinogenicity and impaired cognitive development for young children diminish the enthusiasm for the drug.[14] HU remains unlicensed in most countries not because its clinical efficacy is in doubt, but because the long-term adverse effects are still unknown.[14]

The search for new agents for the treatment of SCD complications has been intense. Decitabine is a potent demethylating agent that can reactivate HbF production.[9] Its toxicities include local skin reactions and neutropenia, and concerns regarding its carcinogenicity are unresolved.[9] Butyrate is a short fatty chain acid that induces HbF production.[8,9] Although these 2 agents have shown promise in early clinical studies, they lack the convenience of oral administration.[14] Omega-3 polyunsaturated fatty acids, which occur naturally in fish oil, are vital to the structural integrity of RBC membranes, conferring resistance to hemolysis.[14] Although thrombosis is part of several clinical manifestations of SCD, trials of antiplatelet or anticoagulant therapy drugs have provided mixed results.[9] Heparin and warfarin were shown to reduce rates of pain episodes but were associated with significant bleeding.[9] Agents that interfere with other disease mechanisms—such as reducing adhesion of sickle cells to endothelial cells or counteracting inflammation or leukocyte activation—are under investigation.[9,14]

Currently being studied are the roles of:

1. vascular lubricants (Poloxamer 188);
2. xanthine oxidase inhibitors (allopurinol);
3. nitric oxide enhancers (L-arginine);
4. Gardos channel inhibitors (the antifungal drug clotrimazole and its analogs);
5. monoclonal antibodies; and
6. statins in controlling acute and chronic manifestations of the disease.[7-9,14]

The only available curative therapy for the disease is hematopoietic stem cell transplantation (HSCT), which should be done before organ dysfunction develops.[4,8,9] Gene therapy also shows promise, and clinical trials are being considered.[8]

Currently accepted practices of acute sickle cell pain management are widely variable, and no studies have addressed chronic pain strategies.[10,17] No single or combination of pharmacological analgesic interventions completely abolish acute sickle cell pain.[17] Most vaso-occlusive crises are managed at home with anti-inflammatory agents and opioid and nonopioid analgesics.[8,10]

Severe pain requiring hospital care is treated with intravenous opioids at full therapeutic dose (morphine is the drug of choice) as well as additional opioids for breakthrough pain and hydration.[8] During episodes of severe pain, life-threatening complications may arise and accompany abrupt clinical changes.[10] Sedatives and anxiolytics can also be given to

reduce anxiety associated with SCD pain while antidepressants, anticonvulsants, and clonidine can be used for neuropathic pain.[4]

Although various nonpharmacological strategies are available for pain management in conjunction with medications, there is little empirical evidence for one strategy over another.[10] New interventions include using: heating pads, deep tissue/deep pressure massage therapy, neuromuscular trigger points acupressure/acupuncture and transcutaneous electrical nerve stimulation.[10] Behavioral and cognitive interventions include: deep breathing, progressive muscle relaxation, guided imagery, activity rest cycling, pain-coping skills training, increased social support, reinforcement strategies and self-hypnosis.[10,16] Since infection and VOC may co-exist, empiric antibiotic therapy is initiated until culture results become available.[8] ACS is managed with exchange transfusion in severe cases and simple transfusions in simple cases, together with a macrolide antibiotic.[8]

The immediate treatment of splenic sequestration includes correction of hypovolemia with transfusion. Because the rate of recurrence is high, follow-up management is crucial. Splenectomy shortly after the acute episode is recommended for children older than 2 to 3 years.[4,8] Infants younger than 2 years who have a severe episode of acute splenic sequestration should be placed in a chronic transfusion program to keep HbS levels at no more than 30% until splenectomy can be done after age 2.[4] Older patients with chronic hypersplenism should be also considered for splenectomy.[4,8] The most important intervention in the routine management of SCD is penicillin prophylaxis to prevent pneumococcal infection. It is recommended that children with HbSS be given penicillin V potassium 125 mg orally, twice daily, starting at 2 months old. For children older than 3 years, the dose should be doubled and continued up to at least 5 years of age and at least for the first 2 years postsplenectomy.[3,12,18] The age at which the prophylaxis is discontinued is often an empiric decision and very controversial.[12] Family compliance with administration of prophylactic penicillin to their SCD children is a problem.[19] Affected patients must also receive the 7-valent pneumococcal conjugate, 23-valent pneumococcal polysaccharide, and quadrivalent meningococcal polysaccharide vaccines.[3]

Identification of SCD children at risk for CVA is done by measuring blood flow velocity in major intracranial vessels using transcranial doppler ultrasonography. Thus, it is recommended that all patients between 2 and 16 years old have an annual screening.[9] Increased velocity is associated with a higher risk of stroke.[9] Regular blood transfusions reduce the incidence of clinically overt stroke in patients who have a velocity of at least 200 cm/second in the middle cerebral or terminal part of the carotid artery. The optimal duration of transfusion therapy, however, has not been established.[5,14] No intervention is currently recommended for prevention of silent infarcts.[8]

Blood transfusion can be life-saving and can ameliorate some of the complications of SCD. The goals are to:

1. increase oxygen-carrying capacity lowered by anemia; and
2. improve end-organ perfusion by decreasing the pro portion of circulating HbS cells.[5]

Indications for acute transfusion are:

1. severe symptomatic anemia;
2. acute splenic sequestration;
3. ACS;
4. acute organ damage (such as CVA); and
5. major surgery requiring general anesthesia (orthopedic procedures, cholecystectomies, splenectomies, etc).

Chronic transfusion is useful for: primary and secondary stroke prevention, amelioration of chronic organ damage and pulmonary hypertension.[5] Clinical situations not requiring transfusion include:

1. stable compensated anemia;
2. infections without aplastic crisis;
3. nonsurgically managed aseptic necrosis;
4. minor surgeries that do not require prolonged general anesthesia; and
5. uncomplicated acute painful crisis.[4,5]

Transfusion complications include: alloimmunization, hemolytic reactions, viral infection (hepatitis, HIV, HTLV, and parvovirus B19), hyperviscosity, hypertension and iron overload.[4,5] Oral administration of iron chelators has been desired for many years by patients and physicians alike because of the challenges and inconveniences associated with long-term infusions of desferrioxamine, the main chelating drug.[5,14] Deferasirox (ICL670 or Exjade) is a newly approved oral iron chelator which, unlike the first one (deferiprone), does not seem to affect granulocyte count.[14]

Many SCD deaths are not attributable to overt chronic organ failure but occur during: an acute episode of pain, respiratory compromise, stroke or a combination of events.[2] Pneumococcal sepsis is a leading cause of mortality among infants because a damaged spleen cannot clear pneumococci from the blood.[7,20] SC and $S\beta^+$ subjects clearly have a lower risk of death and stroke than those with SS and $S\beta^0$.[20] Mortality has decreased, the mean age at death has increased, and fewer patients die of infection.[20] In the United States, the mean age at death is approximately 42 years for men and 48 years for women homozygous for HbS.[2]

SCD and general anesthesia

Dental restorations and simple extractions can be done as outpatient surgery for low-risk patients, whereas moderate- and high-risk individuals should be admitted pre- and post-operatively and treated in a fully equipped operating room

facility. SCD patients have a high incidence of both perioperative and postoperative problems. These can be specific to the disease (pain crisis, ACS, and transfusion reactions) or nonspecific (fever, infections, bleeding, thrombosis, etc).[2,8] The risk of complications is based on several variables, such as:

1. type of surgical procedure planned;
2. disease activity (recent complications, hospitaliza tions within the past year, pre-existing infections, etc);
3. organ dysfunction and damage (especially the lungs, kidneys and brain);
4. age (the older the patient, the more complications are seen due to disease progression);
5. haplotype (African haplotypes present more severe disease than Asian or Arab ones); and
6. pregnancy.[1,2]

Early loss of splenic function in children may be also prognostically important.[1] Evaluation of pulmonary damage, a useful marker of disease progression, is essential to establish lung function and to predict perioperative risk of sickle events.[2] Therefore, a preoperative consultation with an experienced anesthesiologist, together with the patient's hematologist, is of paramount importance.

The broad clinical spectrum of the disease, however, makes it difficult to establish definitive protocols for the management of these patients, leaving many unanswered questions.[2,4] For instance, the use of prophylactic perioperative blood transfusions is controversial.[2,4,5] A general Hb concentration at which transfusion should be initiated cannot be specified, due to the wide clinical variation of SCD. Firth and Head[2] proposed that transfusion should not be used for patients at low risk for complications. For moderate- and high-risk individuals, however, they suggested that transfusion should aim for a hematocrit of 30% rather than aim to achieve a target dilution of HbS.

The National Institutes of Health recommend simple transfusion to achieve an Hb concentration of 10 g/dL and an HbS level of no more than 60% before all but the lowest risk procedures, such as: dental/oral surgery, herniorrhaphy, ophthalmogical procedures and tympanostomy tube placement.[1,4] The scientific evidence is scant in other areas as well. There are no published data demonstrating that hypoxia leads to perioperative sickle events, which still occur at a high frequency even when adequate oxygenation is provided.[2] Although dehydration is assumed to cause complications, there is no scientific proof that it actually does.[2] Evidence for prophylactic modification of standard fluid management to prevent perioperative sickle events does not exist either.[2] In summary, the fundamental goal of management remains meticulous attention to the basic principles of safe anesthesia, mainly maintenance of hydration, oxygenation, vascular stability, and normal temperature, with avoidance of acidosis and infection.[1,2,4,8]

Oral, dental, and craniofacial manifestations of SCD

The oral manifestations of sickle cell disease (Table 3) are nonspecific and may be present in healthy individuals as well as in other systemic disorders, such as: thalassemia, spherocytosis and metabolic bone disease. The mucous membranes tend to show jaundice due to hemolysis and pallor caused by the low hematocrit in these patients. Glossitis may also be observed.[21,22] Delayed tooth eruption is seen, although dental shape and size are not affected.[22] Radiographic findings include a decreased radiodensity of bone and formation of a coarse trabecular pattern caused by erythroblastic hyperplasia and medullary hypertrophy with consequent loss of trabeculae and increased marrow spaces.[21,23] When found close to tooth roots, the pattern is described as "stepladder" due to the trabecular lines' horizontal arrangements. The increased radiolucency of bone is more commonly observed in the area between the teeth's apices and the inferior border of the mandible; however, it is not specific to SCD.[21,23]

Other abnormalities include: thinning of the inferior border of the mandible, loss of alveolar bone height, pronounced lamina dura, hypomineralization of the dentin,

Table 3. ORAL, DENTAL, AND CRANIOFACIAL MANIFESTATIONS OF SICKLE CELL DISEASE[21-31]

Craniofacial bones	Oral mucosa
Decreased radiodensity	Pallor
Coarse trabecular pattern ("stepladder" appearance)	Jaundice
Prominent zygomatic and parietal bones	Glossitis
Widening of diploic space	Gingival enlargement
Vertical trabeculations ("hair on end")	Spontaneous hematoma
Thin border of the mandible	**Teeth**
Granular appearance of the skull	Delayed eruption
Calvarial lesions ("doughnut lesions")	Dentin hypomineralization
Mandibular radiopaque lesions	Pulp calcifications
Osteomyelitis	Pulpal necrosis without dental pathology
Osteopenia/osteoporosis	Interglobular dentin in the periapical area
Avascular necrosis	**Other**
	Facial and dental pain
	Neuropathy
	Malocclusion

interglobular dentin in the periapical area, inclusion in the peripulpal dentinal tubules, abrupt interruption of dentinogenesis, denticle-like calcified bodies in the pulp chamber and hypercementosis.[23,24] Craniofacial abnormalities, such as bimaxillary protrusion with flared incisors, are produced by a combination of: cellular hyperplasia, circulatory factors, muscular imbalance and absence of labial seal.[21,22,25] Affected patients have been described as having a "tower skull" because of their prominent zygomatic and parietal bones.[21] Lateral skull radiographs often show widening of diploic space, with thinning of the outer table of the calvarium and vertical trabeculations (the "hair-on-end" appearance).[21,25] The latter is seen in about 5% of the patients, which confirms the rarity and nonspecificity of this finding.[25] The skull's granular appearance, which is usually misinterpreted as osteoporosis, results from increased red marrow volume rather than loss of minerals.[25] "Doughnut lesions" are calvarial lesions with a ring-like appearance and are presumed to be areas of fibrosis.[25]

Vaso-occlusive involvement should be considered when assessing painful episodes or neurological symptoms in the maxillofacial region.[26] It is suggested that SCD patients suffer orofacial pain in the absence of odontogenic pathology because of sickling crises within the microcirculation of the facial bones and dental pulps and small areas of necrosis in the bone marrow, which may lead to pulpal necrosis.[26-28] Mental nerve neuropathy, caused by a vaso-occlusive episode at or near the mental foramen, may result in persistent anesthesia of the lower lip that can last for months and may affect the result of pulp vitality tests.[28] Radiopaque lesions of vaso-occlusive involvement are seen distal to the mandibular premolars.[26] Once dental pathology has been excluded, differentiation of mandibular infarction from osteomyelitis must be made using clinical and laboratory evidence such as bone and blood cultures.[26]

A patient with osteomyelitis usually has signs of infection (pain, swelling, fever, and leukocytosis), whereas in a vaso-occlusive crisis there is pain of variable severity in the area without marked swelling or erythema.[26] The mandible is the most affected area of the face because the blood supply is relatively low.[22] Olaitan et al[29] showed an incidence of 5% of osteomyelitis of the jaws, with a striking predominance among men. The mean age at presentation was 23 years, and most lesions were in the mandible's posterior region and had predominantly mixed organisms and *Staphylococcus aureus*, without isolation of any salmonella strain. This contrasts with osteonecrosis in other parts of the body in which salmonella is the predominant microorganism. Pericoronitis was responsible for 75% of the infections. A case of avascular necrosis of the mandibular condyle causing ankylosis was described by Baykul et al,[30] showing that the temporomandibular joint is not immune against the vaso-occlusive nature of SCD. Spontaneous hematomas may also occur. Scipio et al[31] reported the case of a 14-year-old SCD boy who presented with acute facial swelling mimicking cellulitis of odontogenic origin, which was caused by sickle-cell related hemorrhage. The patient also exhibited gingival enlargement, an outcome of repeated hemorrhagic episodes and fibrous repair.

SCD patients are not more prone to periodontal disease than nonaffected individuals, leading to the speculation of the role of antibiotics in the prevention of the disease.[32] Cases of crises precipitated by periodontal infection, however, have been described.[33] In relation to dental caries experience, Fukuda et al[34] showed that long-term penicillin prophylaxis in SCD patients likely prevented the acquisition of mutans streptococci (MS), resulting in a significantly lower caries rate. SCD children under 6 years of age who were on a prophylactic daily antibiotic: had no detectable MS levels, were free of interproximal lesions and only rarely (13%) had occlusal lesions. In contrast, 70% of the control patients had detectable MS and 47 % had caries. This benefit, though, occurred during active administration of the drug, only delaying the acquisition of the microorganism because the number of caries-free patients decreased after age 6. By age 8, there was no significant difference between the 2 groups regarding to dental caries. Laurence and coworkers[35] showed that adult African American SCD patients were significantly more likely to have more decayed teeth than healthy controls.

Dental management

The first step in providing safe dental care is to obtain a detailed patient history (Table 4). In the case of the SCD individual, it is important to gather information about the patient's:

1. SCD-related complications (particularly organ damage—spleen, liver, heart, ACS, CVA, etc) and other medical problems since birth;
2. characteristics of pain episodes (frequency, duration, average number and duration of hospitalizations, date of last crisis, treatment received, etc);
3. past and current medical treatment (surgeries, trans fusions, immunizations, medications, allergies);
4. presence of venous access catheters and orthopedic prostheses;
5. carriage of blood-borne viruses due to transfusions; and
6. growth and development issues.

A brief social and psychological profile is also important to help the pediatric dentist understand how the patient and the family are coping with the disease and how likely they are to comply with the dental recommendations as well as to anticipate behavioral problems in the dental office. Questions should be asked about: school performance, compliance with medical treatment and appointments, coping strategies, stressors and family support.[4] The name and contact number of the patient's physician must be noted. The dental history

should be reviewed next, including: frequency of preventive visits, past dental needs and treatment, history of trauma, dental caries experience, odontogenic infections, facial pain, oral habits, diet, use of fluorides and oral hygiene frequency.

Considerations for dental treatment are summarized in Table 5. Family education is a pivotal step to enhance the child's potential for a successful outcome, and the importance of preventive dental care must be reviewed at every visit. A thorough oral and dental examination must be done with the appropriate radiographs. Infection is the most common precipitating event in a sickle cell crisis. Therefore, any potential sources of oral infection must be removed (pericoronitis, symptomatic impacted teeth, nonrestorable teeth, etc).

Although SCD patients are not prone to developing periodontal disease, its prevention is of utmost importance because periodontal infections can lead to a crisis.[33] Complaints of pain in healthy teeth should be taken seriously because of the possibility of pulpal infarction and necrosis, which are part of the disease process. No conclusions have been drawn regarding the best pulp therapy approach in these situations. A careful assessment of the prognosis of teeth with pulpal involvement must be done. Although restorations are preferable to extraction, the latter should be considered if there is any doubt about a possible failure of the planned therapy.[21,36] All oral infections must be treated vigorously with appropriate antimicrobial agents (antibiotics, rinses, etc). The causative agent must also be removed as soon as the patient is ready to undergo invasive procedures. Facial cellulitis may warrant hospitalization for: intravenous antibiotics, hydration, pain management and close monitoring of the patient.

Osteomyelitis is treated with antibiotics alone or combined with surgery; a consultation with or referral to an oral surgeon is appropriate.[29] Extractions should be done as atraumatically as possible, and extreme care should be exercised because of the risk of jaw fractures since osteopenia and osteoporosis as well as a thin border of the mandible may be present. If the patient is using or has used bisphosphonates for treatment of osteoporosis or osteopenia, the pediatric dentist must inform the family about the risk of jaw osteonecrosis (ON) following invasive procedures.[37,38]

Dental procedures can be done in the dentist's office, as with any other patient, and should be rendered during noncrisis periods.[4,21] Individuals carrying the trait present no problems for routine dental treatment. Patients who have orthopedic prostheses and/or implanted venous access catheters require bacterial endocarditis prophylaxis in addition to the daily penicillin dose they may already be taking.[4,12] A complete blood count should be ordered before any invasive dental procedure if the patient is taking HU, which can trigger neutropenia and thrombocytopenia, or if there is liver involvement, which can lead to prolonged bleeding. If therapy with bisphosphonates is

Table 4. REVIEWING THE SICKLE CELL DISEASE PATIENT'S HISTORY AT INITIAL AND RECALL VISITS

MEDICAL HISTORY	Past and current medical treatment (medications, allergies, surgeries, immunizations) Disease-related complications Transfusion-related complications Blood-borne viruses (HIV, hepatitis, etc) Frequency of pain episodes and hospitalizations Pain management Presence of venous central catheter and orthopedic prostheses Physician's contact phone number
FAMILY AND PATIENT'S SOCIAL AND PSYCHOLOGICAL PROFILE	Compliance with medical appointments and treatment Behavioral issues Stressors Coping strategies Social support
DENTAL HISTORY	Frequency of preventive dental visits Trauma history and prevention Caries experience Oral and odontogenic infections Facial and oral pain Oral habits Oral hygiene habits Diet Use of oral liquid and topical medications Fluoride exposure

Table 5. DENTAL TREATMENT CONSIDERATIONS FOR SICKLE CELL PATIENTS

CRANIOFACIAL, ORAL AND DENTAL EXAM	Note craniofacial, oral, and radiographic manifestations Use radiographs judiciously Identify present and potential sources of infection Assess: • Diet and oral hygiene status • Need for fluoride supplementation • Periodontal status
FAMILY AND PATIENT EDUCATION	Review: • Clinical and radiographic findings • Risk of jaw osteonecrosis with invasive procedures in bisphosphonate patients • Risk of osteomyelitis with dental infections • Diet counseling and oral hygiene instruction • Potential cariogenicity of sugar-containing medications • Importance of preventive dental care
PLANNING DENTAL TREATMENT	Goal: Eliminate existing and potential sources of infections Consider family compliance, behavioral issues, medical therapies, blood counts, medical complications, office care vs general anesthesia Discuss the need for antibiotic prophylaxis with medical doctor * Consider patient's spleen function, presence of central venous catheter or orthopedic prostheses, infection history, type of procedures (invasive vs noninvasive) Complete all treatment before bisphosphonate therapy or HSCT conditioning starts Avoid: • Invasive dental procedures for patients who are using or have used bisphosphonates • Elective surgeries • Dental procedures during crises Obtain complete blood count for patients at risk for thrombocytopenia, neutropenia, or prolonged bleeding Treat odontogenic infections and pain vigorously Discuss care under sedation and general anesthesia with hematologist and anesthesiologist before proceeding Carefully assess orthodontic treatment plan Carefully assess pain in healthy teeth
DENTAL PROCEDURES	In general, restorations are preferable to extractions Crowns or veneer restorations for teeth with extensive decalcification or hypomineralized areas Carefully assess teeth with pulpal involvement • Consider risk of infection post-pulp therapy • Extract if successful outcome not foreseeable and no history of bisphosphonate use No contraindication for local anesthetic with vasoconstrictor Avoid hypoxia when using nitrous oxide or sedative agents Stress reduction protocol during dental appointments
AFTER DENTAL TREATMENT	Establish recall schedule according to patient's caries risk Close follow-up of patients at risk for osteonecrosis or osteomyelitis

going to be started, all dental treatment must be completed before therapy initiation.[37,38] Routine dental care of patients taking bisphosphonates is a challenge. There are no prospective studies to support specific recommendations regarding whether providing dental treatment for these patients places them at risk for the development of bone ON.[38] Close follow-up of these patients is mandatory. ON in children using bisphosphonates has not been reported to date.

There is no evidence to support the use of local anesthetics without vasoconstrictors for SCD patients because they do not impair local circulation, even though hypovascularization and circulatory impairment may be evident.[21,36] Teeth with enamel hypomineralization or extensive decalfication may benefit from the use of stainless steel crowns or veneer restorations instead of intracoronal restorations due to their longevity.[21,36] Minimizing physical and emotional stress reduces the risk of a crisis thus, the use of adjuvant therapies during dental treatment may be considered. It is also important to remember that SCD patients present more psychosocial issues than their nonaffected peers, including emotional and behavioral problems.[16]

Nitrous oxide is safe, but care should be taken to avoid hypoxia at all times. Using at least 50% of oxygen during the procedure and 100% for a few minutes afterwards is suggested. Oral sedation can be considered after the physician's approval and careful consideration of the drugs to be used in order to avoid respiratory depression. A consultation with an experienced anesthesiologist is required before proceeding with general anesthesia in order to determine the patient's risk and the best approach to prevent perioperative complications. Mild to moderate pain in children can be managed with nonsteroidal anti-inflammatory drugs or acetaminophen. It is best to avoid aspirin due to the risk of: Reye's syndrome, acidosis and prolonged bleeding.[4,23]

The need for antibiotic prophylaxis before dental procedures for SCD patients remains a controversial issue. There is no consensus in both the medical and dental literature regarding which patients and dental procedures require antibiotic supplementation and which one should be prescribed, for how long and for what reasons. A recent survey of pediatric dentistry residency program directors and pediatric hematologists validated the need for more research in the area.[39] An interesting finding in that study was that the hematologists used prophylaxis with the intention of preventing endocarditis, whereas program directors were aiming for prevention of systemic infection. Because of the lack of consensus, it is recommended that an individual assessment—including risks, benefits, costs, and patient compliance—be performed together with the hematologist.

Elective surgeries, such as extraction of asymptomatic teeth or for orthodontic purposes, should be avoided.[22] No contraindications for orthodontic treatment exist in these patients, but it is purely elective. Orthodontic planning should take into consideration bony architecture and physiology as well as the restoration of the regional microcirculation by increasing the resting intervals and reducing the tooth movements and the forces applied to them.[21,22] More careful management is necessary in cases of intense orthodontic/orthopedic forces such as extraoral anchorage or maxillary disjunction.[22]

In summary, sickle cell disease is a chronic and complex multisystem entity in which the pediatric dentist plays an important role in the prevention of complications and in the amelioration of the patient's quality of life. Due to the wide variation in the clinical presentation of the disease, every patient should be approached on an individual basis and the physician should be consulted before any dental care is started.

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