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Review Article

DENTAL MANAGEMENT OF BETA THALASSEMIA MAJOR PATIENTS: A REVIEW.

Fayçal Labrini[1], Hanan Oubenyahya[2]
[1]Médical analysis laboratory, Military Hospital Agadir , Morocco.
[2]Dental Service, Military Hospital Agadir, Morocco.

Correspondence should be addressed to **Fayçal Labrini**

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ABSTRACT

Beta Thalassemia Major is a hereditary hemoglobinopathy that can take on different clinical expressions, with intense and multiple orofacial manifestations.

It's a major public health problem and a challenging condition that requires a multidisciplinary approach involving health practitioners from different paths (hematologist, dentist, orthodontist, cardiologist etc).

The changes to the maxillofacial region stemming from this genetic form of anemia, makes it an obligation for dental practitioners to have in depth knowledge towards the nature of this disorder, its effects on oral health, and better understanding of the proper management of beta thalassemic patients.

The purpose of this paper is to provide the dentist with a simplified understanding of the physiopathology of the disease, its various systemic and orofacial manifestations, and the keys to a better dental approach. Until medical research is able to provide a definitive solution to these diseases, through gene therapy or otherwise, it is necessary to welcome these patients into the cycle of dental care and offer them the most possibly complete dental experience through coordinated team work.

KEYWORDS: Dental patients Beta Thalassemia.

INTRODUCTION

Thalassemia is an autosomal recessive genetic disorder characterized by a reduced rate of production of alpha or beta globulin chains in hemoglobin molecules, thus resulting in the production of faulty hemoglobin.

Depending on the globin chain affected, thalassemia can be divided into two major groups: Alpha thalassemia and Beta thalassemia.

Beta thalassemias result from a large lack of normal beta chain production and lead to diverse clinical presentations due to the relative excess of alpha chains. Homozygous, heterozygous or compound heterozygous forms can be differentiated.

The heterozygous form is called minor thalassemia or thalassemia trait; it comes with limited clinical signs and may be confused with iron deficiency anemia.

In the homozygous form, two groups can be distinguished based on whether or not regular blood transfusions are required: beta thalassemia intermedia and beta thalassemia major.

Patients with Thalassemia Intermedia have moderate anemia. Due to the presence of a higher amount of healthy hemoglobin, these patients do not need blood transfusion on the regular. Their prognosis therefore is much better.

Patients with B thalassemia major (also called Cooley's anemia or Mediterranean Anemia) need regular blood transfusions (every 2 to 4 weeks) to keep their hemoglobin levels at 90-100g/l and thus to survive. With a better understanding of this condition the prognosis has greatly improved over the years.

A BREAKDOWN OF THE PHYSIOPATHOLOGY AND SYSTEMIC MANIFESTATIONS OF BETA THALASSEMIA MAJOR.

In this particular genetic condition, the beta globin chain production is altered leading to an accumulation of alpha chains within erythroid cells. The degradation of these alpha chains causes damage to cell membranes which in turn leads to ineffective erythropoiesis within the bone marrow and premature hemolysis of red cells in the circulation and spleen. This translates to severe anemia. The latter further accentuates hypoxia and increased erythropoietin synthesis which leads to expansion of the bone marrow spaces, skeletal deformities, thin cortex and osteopenia. The substances from degenerated red cells increase iron absorption leading to iron overload. This excess of iron in different tissues is responsible for secondary hemochromatosis and multi organ damages (liver, heart, endocrine glands).

Beta thalassemia major usually appears during infancy (between 3 to 6 months old) when the transition from fetal hemoglobin to adult hemoglobin occurs. The physiopathology of the condition as described above can lead to the systemic manifestations resumed in Table 1.

Table 1: Systemic manifestations of Beta Thalassemia Major Patients.

Hematological: - Severe anemia - Thromboembolism - Iron overload - Secondary hemochromatosis	**Cardiovascular:** - Arrhythmias - Reversible myocyte failure, myocyte scarring - Congestive heart failure - Arterial changes, vascular stiffness - Thrombosis - Pulmonary hypertension
Liver: - Fibrosis - Cirrhosis - Hepatocellular carcinoma - Hepatic iron overload	**Endocrine:** - Growth alteration and short stature - Hypogonadism and delayed puberty - Diabetes Mellitus - Impaired glucose tolerance - Hypothyroidism - Hypoparathyroidism - Growth hormone deficiency
Immune system - Susceptibility to infections - Infections related to transfusions - Splenectomy	**Orthopedic:** - Skeletal deformations - Osteopenia/Osteoporosis - Cortical thinning - Fractures
Psychosocial issues: - Vulnerability to psychiatric problems - Passiveness, tiredness - Depression - Anxiety - Reduced physical activity - Parent overprotection	**Skin and mucosa:** - Pallor - Slight jaundice -

The earlier transfusion therapy is initiated, the less apparent these manifestations are. Over the last decade, the life expectancy of transfusion dependent thalassemia major patients has greatly improved. While they would rarely make it to the second decade of life before, serial blood transfusions have currently allowed far better life quality well into middle age and beyond. (

IMPACT OF THE CLINICAL MANIFESTATIONS OF BETA THALASSEMIA MAJOR ON THE OROFACIAL SPHERE AND ON DENTAL APPROACH.

Skeletal changes: one of the most common orofacial manifestations that should call out the dental practitioner. Commonly referred to as the Cooley facies, Thalassemia major patients can develop the following orofacial deformities to varying degrees, depending on how early transfusion therapies have been initiated, up to 50% of patients might either not present them or do so mildly if blood transfusions have been carried out since birth.

i. Skeletal class II malocclusion due to the protrusion of the maxillary and general resistance of the mandible to expansion
ii. Major mandibular transverse defects (Brodie syndrome)
iii. Increased overjet
iv. Anterior open bite
v. Malar prominence, saddle nose, frontal bossing (Chipmunk facies)

vi. Orbital hypertelorism
vii. Migration and spacing of upper teeth
viii. X ray findings include rarefaction of the alveolar bone, thinning of the mandibular cortex, obliteration of paranasal sinuses, short roots, taurodontism, thinning of the lamina dura.

Dental parameters to take into consideration: Possibility of orthodontic and/or orthopedic treatments? Maxillary osteotomies are not indicated for beta thalassemia major patients particularly if blood transfusion and chelator therapy has been shown to be barely effective It is recommended to initiate preventive and interceptive orthodontics as early as possible to correct anterior maxillary teeth drifting and the excessive overjet and to reduce the susceptibility of trauma. Forces used in thalassemic patients should be low since there is an increased risk of fracture due to the thin corticals These patients should be followed more closely with shorter intervals between appointments. The retention phase usually proves more difficult.

Anemia and hemoglobin levels: Associated with the distinctive orofacial appearance, anemia is also responsible for patients appearing tired and having little interest in oral hygiene. Beta thalassemia major patients' physical growth is commonly disturbed due to severe anemia and tissue hypoxia, intellectual development is however not affected Low hemoglobin is responsible for mucosal paleness and atrophic glossitis High ferritin levels may lead to a dark colored gingiva

Dental parameters: Keep the visits short, adapt to patient's tolerance level, take into consideration poor healing especially during invasive procedures, patients should be medically cleared before invasive procedures, their hemoglobin level should not be lower than 110g/l

Iron overload and iron chelation: If left untreated, iron overload can lead to organ damage and be fatal. Iron gets accumulated in the cardiac, endocrine, hepatic tissues as well the gingiva of thalassemia major patients. Iron deposits can diminish saliva flow (xerostomia) and cause painful swelling and inflammation of salivary glands Their impact on periodontal tissues is still unkown. While blood transfusions have improved the prognosis of thalassemia major, it has also led to increased levels of iron accumulation. Thus why it is necessary to introduce chelation therapy to remove the excess iron.

Dental parameters: Dentists should always be aware of iron overload (mild, moderate or heavy) through biological tests, as it impacts the prognosis. Dentists need to take additional precautions to compensate for potential complications such as impaired liver function and diabetes. Oral chelators' side effects can include hepatitis, neutropenia, kidney dysfunction, cytopenia, agranulocytosis and gastrointestinal bleeding Caution should be exercised while prescribing any medication. The possible involvement of the immune system as a side effect of oral chelators is one more argument towards the use of antibiotic coverage.

Cardiac involvement: Beta thalassemia major patients suffer from a load of cardiac complications due to chronic anemia paired with accumulation of iron in the myocardium. These iron related cardiac abnormalities were once the leading cause of mortality by heart failure. With the introduction of iron chelators, life expectancy has significantly improved but some cardiac abnormalities still persist and should be taken in consideration when dealing with these patients.

Dental parameters: Even asymptomatic cardiac dysfunctions can get complicated under situations of stress. Dentists should enquire about any underlying heart ailments or medication. Anesthetics with vasoconstrictors should be carefully used with the presence of arrhythmias especially if they're treated with beta blockers Epinephrine may raise blood pressure and complicate arrhythmias and chest pain.Risk of pericarditis and sepsis should be kept in mind in case of invasive procedures and periodontal disease.

Hepatic manifestations: Patients with severe beta thalassemia suffer from increased liver iron concentration. HVC and HVB of transfusional origin is also a major concern.

Dental parameters: Presence or not of HVC/HVB should be known. In the case of associated hepatic disease, caution must be used when prescribing medication, as to avoid hepatotoxic drugs.

Splenectomy: the main rationale for splenectomy in beta thalassemia major patients is to control iron overload and space transfusions Better transfusion regimens have rendered this therapeutic option less probable. The major risk after splenectomy is sepsis, this great risk of infection puts such patients on a daily chemoprophylaxis schedule.

Dental parameters: Always check for a history of splenectomy as the presence or absence of this organ changes the dental approach. Due to risks of bacteremia and sepsis, antibiotic prophylaxis is obligatory, As splenectomised patients are usually under regular penicillin chemoprophylaxis, a change in antibiotic is recommended during dental treatment to avoid bacterial resistance. Thromboembolic complications are more frequent in splenectomised patients, which may lead to being radical in dental treatments to prevent infection spread In consultation with the treating hematologist, it is possible to resort to administration of anti-platelet drugs to reduce the risk of thrombosis.

Diabetes: Beta thalassemia major patients are at risk of developing diabetes as an expression of secondary hemochromatosis.

Dental parameters: Periodontal and gingivitis foci are potential sources of infection that should alert the dentist to adopt strict preventive measures.

Infections: The increase in infections in beta thalassemia major patients stems from both disease related and therapy related factors. These patients suffer from severe anemia, hemolysis and ineffective erythropoiesis and possible diabetes, treatments including transfusions, splenectomy, iron chelation therapy, central venous catheters and stem cell transplantation further contribute to a greater risk of infection. These infections can be bacterial, viral or fungal Infection related mortality has jumped on the forefront in modern times and became the leading cause of mortality of thalassemia patients.

Dental parameters: Guidelines regarding antibiotic prophylaxis vary with some recommending prophylaxis similar to that used for the prevention of bacterial endocarditis. Dental infections or abscesses should are an emergency and should not be left untreated.

Transfusion therapy schedule: Invasive procedures should be done in the week after transfusion following antibiotic prophylaxis and the study of the coagulation profile Hemoglobin level should be more than 110g/l before any clinical procedure.

Bisphosphonate therapy: Bisphosphonates are commonly used in thalassemia patients to inhibit bone resorption Comprehensive health and dental assessments should be carried out before the start of the treatment. Due to the high risks of bisphosphonate related necrosis of the jaw, it is important to reduce mucosal trauma and avoid dental extractions. In case of bone exposure or surgical extractions, the practitioner should refer the patient to an oral surgery specialist All patients should be advised of the risk pre-operatively and closely monitored post-operatively.

SUGGESTION OF DENTAL CARE PLANNING FOR BETA THALASSEMIA MAJOR PATIENTS.

The key to optimal dental care for thalassemia patients in general and beta thalassemia major patients in particular, is multi-disciplinary team work. Close liaison should be maintained with the hematologist and/or cardiologist during each step of the dental treatment planning. The more informed the dental practitioner is about this complex condition and its systemic implications, the better level of care he can provide to his patients. (Table 2)

Table 2: Dental Care Planning for Beta Thalassemia Major Patients.

DENTAL AND OROFACIAL EXAM	1) Record craniofacial manifestations 2) Note tooth decay and periodontal status 3) Identify all sources of infection, present and potential 4) Take radiographs 5) Assess oral hygiene status
PSYCHOLOGICAL APPROACH	1) Due to lifelong adherence to frequent hospitalizations, thalassemia major patients often appear fatigued, noticeably passive and poorly motivated for dental care. Their willingness to accept dental procedure could be further impacted by potential depression. 2) The dentist should understand how likely the patient and the family are to comply with preventive measures and dental recommendations.
DENTAL TREATMENT PLANNING	1) First step in safe dental care is to obtain a detailed patient history: 2) type of thalassemia 3) present hemoglobin and coagulation levels 4) treatments provided 5) degree of iron overload 6) chelators administered 7) organ involvement (heart, liver, endocrine glands),possible medications 8) presence or absence of splenomegaly 9) splenectomy 10) transfusion schedule 11) presence of transfusion transmitted infections (Hepatitis C, B, HIV) 12) potential use of bisphosphonates 13) patient prognosis 14) future patient therapies 15) Establish treatment plan and differentiate the type of procedures: invasive, non-invasive, and urgent or not. Plan dental interventions according to transfusion schedule. 16) Eliminate existing or potential sources of infection. If there is need for invasive procedures, the dentist should be able to assess the potential risks by looking at the biological levels, presence of systemic co-morbidities, transfusion schedule, existence of bisphosphonates therapy, spleen function etc, and keep close contact with the hematologist in charge to discuss the feasibility in dental office and the need for antibiotic prophylaxis. 17) Anesthesia: 18) Most patients can receive local anesthesia without problems. For short interventions, anesthesia without vasoconstrictor could be used with 2% Lidocaine and 1/100,000 epinephrine used for longer procedures requiring more profound anesthesia. Beware of epinephrine and vasoconstrictors in case of cardiac complications. 19) Sedation should be used with caution because of anemia and the risk of respiratory depression 20) General anesthesia should be avoided. If absolutely necessary, it should be done under the care of a hematologist team as an in-patient procedure

	21) Discuss care under sedation or general anesthesia with hematologist or anesthesiologist before proceeding. 22) Pulpal involvement: 23) Carefully assess the risk of infection post pulp therapy as these patients are immunologically fragile 24) If there is no successful outcome possible, it is better to be on the safe side and extract 25) Excess confidence is not advised 26) Deciduous teeth with infected pulps should be removed without attempt at pulpal therapy 27) Dental extractions: 28) Antibiotic prophylaxis should be discussed with the patient's doctor 29) Check hemoglobin levels 30) Avulsions should be done in a gentle manner 31) Avoid if patient under bisphosphonates therapy 32) Beware of hemorrhagic risk 33) Orthodontic treatment: Discuss the possibility with the patient's physician, low forces should be used and closer monitoring mandatory. 34) Emphasis on preventive measures to minimize the need for invasive procedures: 35) Oral hygiene instructions 36) Dietary advice 37) Fluoride application, fissure sealants 38) Early diagnosis of orofacial manifestations to assess the need for orthodontic interceptive therapeutics.
FOLLOW UP	1) Establish a schedule according to the patient's caries risk 2) Establish a preventive program

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