

THALASSEMIA - PAEDIATRIC DENTISTRY PERSPECTIVE - AN OVERVIEW**¹Dr. SVSG. Nirmala M.D.S., ²Dr. M.S. Minor Babu M.D.S. and ³Dr. Saikrishna Degala M.D.S.**¹Professor, Department of Paedodontics & Preventive Dentistry, Narayana Dental College & Hospital Nellore.²Professor, Department of Paedodontics & Preventive Dentistry, Lenora Dental College & Hospital, Rajahmundry, Andhra Pradesh, India.³Professor & HOD, Department of Oral and Maxillofacial Surgery, JSS Dental College & Hospital, Mysore Karnataka, India.***Corresponding Author: Dr. SVSG. Nirmala M.D.S.**

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ABSTRACT

Thalassemia is a blood disorder, characterised by defective haemoglobin production which is associated with splenomegaly and bone changes and effects early in life. Therefore, it is also known as Cooley's anaemia. Clinical manifestations are mucosa is pale, atrophic glossitis, chipmunk face appearance, nasal bridge is depressed, maxillary sinus is small, teeth are discoloured, spiky shaped short crowns and roots, macroglossia due to flared incisors, increased overjet and multiple spacing between the teeth causing malocclusion, taurodontism, absence of inferior alveolar canal, cortex of the mandible is thin, obliterated, sinus obliterated. Dental care should given as a team approach. Prophylactic antibiotics should be given prophylactically especially post-splenectomy. Avoid aspirin, prefer acetaminophen, oral chelators commonly causes hepatitis, neutropenia and agranulocytosis. Orthodontic treatment should be considered early to reduce the effects on a craniofacial skeleton and apply low forces due to thin cortices and follow short interval between the appointments. Avoid treatment during a crisis and only if the emergency occurs treatment should attempt. Avoid treatment under general anaesthesia. However, if necessary it should be carried out with the haematologist. Oral surgical procedures, periodontal procedures, pericoronitis and abscess, are to be undertaken under antibiotic prophylaxis. Apart from above this article discuss etiology clinical features and management of Children with Thalassemia.

KEYWORDS: children, dental care, oral health, Thalassemia facies.**INTRODUCTION**

Thalassemia is defined as hereditary hemolytic anaemia with various degrees of severity characterised by no or less globin chain synthesis due to the abnormal genetic globin chain quantitative synthesis that commonly found in the whole world. Cooley and Lee first discovered Thalassemia in 1925. It is an autosomal, recessive disease and characterised by reduced integration of one or more of the alpha or beta globin chains leading to decreased haemoglobin production and hypochromic microcytic anaemia. Thalassemia is associated with splenomegaly and bone changes and affects early in life hence it is also known as 'Cooley's anaemia. This disease may be caused by marriage between two thalassemia carriers and often found among children because the patients of this type of thalassemia rarely reach adulthood.^[1,2]

PREVALENCE

Thalassemia is the typical genetic disease of the tropical population such as Sardinia, Italy, Cyprus, Mediterranean, and all Asian country to Papua New Guinea. This difference shows an evident relationship

between the genetic factors and thalassemia. Worldwide approximately 15 million people are expected to suffer from thalassaemic disorders. In India, nearly 12,000 infants are born every year with a hemoglobinopathy. On an average one in every 25 Indian is a carrier of thalassemia.^[1,3-6]

While the typical thalassemia patients have a particularly face called as facies rodent because of the protrusive anterior teeth and disturbed maxilla growth that may cause malocclusion. Beta thalassemia is caused by chromosome 11 mutations that may affect all beta chain production such as transcription, translation and beta globin chain production stability.^[7,8]

In general, this disease shows severe chronic anaemia that is characterised by paleness, weakness, fatigue and malaise. The most severe symptoms are found in beta mayor thalassemia.^[9]

Double heterozygous forms cause a primary clinical syndrome with severe anaemia and extramedullary hematopoiesis. As a result of chronic transfusion, which

is necessary for these patients, excessive iron load and hemochromatosis develop, and many organ systems, especially cardiovascular and endocrine systems, will be affected. Extramedullary hematopoiesis also results in bony deformities. In the face, enlargement of a jaw and its alveolar process produce various and serious malocclusion stages. Prevalence and severity of periodontal diseases increased in some chronic diseases. However, in patients with major beta thalassemia, this association has not been proven.^[9]

Classification

Thalassemia can classify according to the chain involved. There are two types as Beta thalassemia and alpha Thalassemia. In beta thalassemia, there is the deficient synthesis of beta globin, whereas in alpha thalassemia there is the inadequate synthesis of alpha globin. Reduced integration of one of the two globin polypeptides leads to deficient haemoglobin accumulation, resulting in hypochromic and microcytic red cells.^[10]

THALASSEMIA TRAIT^[11-13]

Beta thalassemia occurs when one or both of the two genes that make beta-globin don't work or only partly work. It is also known as thalassemia minor, Beta Thalassemia Major and Thalassemia intermedia.

Beta-thalassemia minor, in which there may be mild anaemia but generally no need for treatment, is the heterozygous condition (i.e., one normal gene and one beta-thalassemia gene). **Beta-thalassemia major**, in which there are severe anaemia and need for lifelong treatment, is the homozygous condition (i.e., two β thal genes). **Beta-thalassemia intermedia**, in which there is moderate to severe anaemia that may require blood transfusions, is intermediate in clinical presentation between the minor and major forms of beta-thalassemia; children with this form of thalassemia start to develop symptoms later in life than those with beta-thalassemia major and features have been given in Table 1.

Table 1: Showing description of Thalassemia Trait.

1.	Thalassemia Minor	<ul style="list-style-type: none"> • Seen in heterozygous individuals with impaired alpha and beta chain production • Does not generate clinical signs, and splenomegaly is rare • -- In beta thalassemia, there is a lack of normal beta chain production. • -- Causes a relative excess of alpha chains, the latter is insoluble and tend to precipitate, forming intracellular inclusions that deform the structure of erythrocytes and lead to premature destruction within the bone marrow and spleen.
2.	Thalassemia Major	<ul style="list-style-type: none"> • Historically called Cooley's anaemia, occurs when both genes necessary for beta globin production are affected. • Beta thalassemia presents at six months of age when adult haemoglobin has replaced fetal haemoglobin. • Peripheral anaemia, caused by the disease, sends signals to the bone marrow to increase production of erythrocytes (via erythropoietin). However, erythrocyte production is abnormal. • The process is called 'ineffective erythropoiesis'. With time, the marrow cavities (skull bones, facial bones and ribs) expand (erythroid hyperplasia), leads to standard facial features and radiographic findings. • Massive erythropoiesis within the bones invades bony cortex, impairs bone growth and produces other skeletal abnormalities. • Erythrocytes are abnormal by the reticulo-endothelial system and are taken up by these organs resulting in enormous hepatosplenomegaly. • In untreated patients, death usually occurs by the end of the second decade of life from anaemia and congestive heart failure. • Patients need regular transfusions to survive (every two to four weeks).
3.	Thalassemia Intermedia	<ul style="list-style-type: none"> • Another form of severe beta-thalassemia. • Patients need a blood transfusion but not regularly. • Prognosis of such cases is much better than in patients with thalassemia major. • Dental treatment is comparatively less problematic. • Diagnostic criteria for the significant verses the intermedia syndrome are rather ill-defined and largely based on the haemoglobin level without transfusion.^[3]

Clinical features can be divided into four different Categories represented (Table: 2)

1. No signs and symptoms	No symptoms are seen in patients with Alpha thalassemia, silent/ carriers.
2. Mild sign and symptoms	Having alpha, beta thalassemia trait may show symptoms like mild anaemia.
3. Mild to moderate symptoms	<ul style="list-style-type: none"> • Seen in patients with beta thalassemia intermedia, symptoms are mild to moderate anaemia, • growth retardation • delayed puberty as a result of anaemia • hepatosplenomegaly • expansion of bone marrow, wider bones, bones are brittle • sunray appearance
4. severe signs and symptoms	Seen early in life the features include <ul style="list-style-type: none"> • severe anaemia • retardation of growth • poor apatite • urine is dark • enlarged spleen, liver, heart • presence of deformities especially facial bones

The clinical symptoms of beta major thalassemia seen when HbF usually replaced by HbA, i.e. in the age of 3-6 months after birth and is characterised by severe anaemia due to the absence of HbA synthesis.^[14,15] Babies with beta major thalassemia will look pale with extended abdominal area due to the splenomegaly and failures in growth and development.^[16-19] The child's weight is usually lower than the average weight for his/her age. Fever, diarrhoea and various gastrointestinal disorders traditionally found during the first year of life. The skin looks pale and yellowish and will become dark due to the iron sedimentation caused by repeated transfusion.^[20]

While the bone abnormalities happen mostly due to the erythroid marrow hypertrophy and expansion that leads to widening bone marrow, thin cortex and osteoporosis.^[18,20] The bone abnormalities are found initially in the metatarsal and metacarpal bones in the shape of the rectangular convex site caused by increased erythropoiesis leading to bone marrow widening.^[20-23] Older patients commonly show a typical face called facies Colley with abnormal facial and cranial bone growth. The nose looks flat without a nasal bridge, the distance between eyes is extensive, and the forehead bone is full too. There is a thickening of cheek bones and deep nose bridge that leads to the typical features of facies Cooley. The teeth look protrusive, and the disturbed maxillary growth will create malocclusion.^[25]

Moreover, medullar tubercle gives a mosaic feature of the bone. Osteoporosis and cortical thinning may lead to a pathological fracture in long bones and shortened arms due to the irregular fusion of the proximal humerus area. The ribs are widened especially in the area where the vertebrae meet that leads to increased Para vertebrae mass and pressure to the cord (cord compression). The characteristic and the severity of the bone abnormalities increase with age. In older patients, the bony changes

more commonly found in the distal areas such as legs and arms.^[26,27]

Other than clinical symptoms have mentioned above; there is a heart abnormality that is often found and included in one of the death causes. Myocardial hemosiderosis or heart disorder caused by hemochromatosis is one of the death causes in patients who receive a routine transfusion. Hemocytosis evokes arrhythmia that also causes sudden death. The abnormality that is caused by severe anaemia heart enlargement that can be accompanied by congestive heart failure. Pericarditis may happen due to the severe iron sedimentation in the pericardium as well as the bacterial infection.^[28]

Beta major thalassemia patient growth and development are commonly disturbed even though the relative intelligence level development not affected — this obstructed growth caused by the severe anaemia and low Hb level leading to tissue hypoxia. The secondary sexual growth is disturbed by the endocrine disorders that puberty reached later and the growth acceleration is delayed or even does not occur. Menstruation in girls and secondary sexual signs in boys delayed.^[15]

The kidney usually enlarged as a result of extra medullar hematopoiesis with dark brown urine caused by heme catabolism product excretion.^[14,20]

Growth and development of oral cavity in beta major thalassemia patients show several differences compared to normal children especially regarding facial bone structures, dental arrangement and gingival colour.^[29,30]

Beta major thalassemia craniofacial growth and development characteristics

The face and head of beta major thalassemia patients show a typical form known as facies Cooley or facies

thalassemia. The cranial bone is thickened resulting in frontal bone protrusion with widened diploe space and thin external and internal plate. The excessive malar bone grows due to the erythroid marrow expansion creates prominent cheeks and deep nasal base. According to Meredith and Higley, there is a relationship between the transversal growth of the head and face with the dental arch. The excessive maxillary bone grows dental malocclusion. The pneumatization of the maxillary sinus commonly delayed in beta mayor thalassemia patients.^[31-33]

RADIOGRAPHIC FEATURES

The changes in beta major thalassemia patient bones that are caused by bone marrow hyperplasia can observed in the radiographic images. Diploe in the cranial bones experiences expansion that the interplate space becomes widened while the external and internal part of the plate becomes thinner. The frontal bone creates a vertical tubercle that is parallel with the dipole plate outer plate and, due to erythroid hyperplasia, the parietal bone has a porous part in the diploe plate external part that creates hair on end or sun ray appearance. The tubercle on the jaw bone can be seen in the panoramic image and gives a Honeycomb appearance.^[34,35]

Oral manifestations are summarised in table 3 & 4^[31,36-38]

- Characteristic facial findings in beta-thalassemia major result from malformation of the facial bones due to marrow expansion and faster rate of growth of the jaw. These manifestations include prominent cheekbones; depression of the nasal bridge; prominent premaxilla and enlargement of the upper jaw (“chipmunk face”); protrusion, flaring, or migration of and spacing between the maxillary anterior teeth (particularly rotation or forward drift of the maxillary incisors); and varying degrees of malocclusion (overbite, open bite, overjet).
- Development of dentition may delayed, as may be air cavity development of the maxillary sinuses.
- Teeth may be discoloured, with short crowns and roots as well as taurodontism (large pulp cavities with reduced roots) and attenuated lamina dura.
- Dental caries is a common finding, for a variety of reasons, and decay is often advanced by the time of presentation to the dentist. There is a tendency toward higher rates of plaque, gingivitis, and periodontitis.
- Mucosal pallor and jaundice (particularly yellow discolouration of the gingiva) may arise from the hemolytic anaemia associated with thalassemia.
- Macroglossia (enlarged tongue) found in some thalassaemic patients/clients. Sore or burning the tongue may result from chronic anaemia and folate deficiency.
- Painful swelling of the salivary glands occasionally results from iron deposition, and xerostomia (due to iron deposition) may be present. Reduced salivary protection results from reduced IgA and phosphorous production.
- Oral ulceration occurs occasionally, and necrotising gingivostomatitis (possibly linked to reduced white blood cell count due to iron chelation agents) very rarely.
- Osteonecrosis of the jaw can result from the taking of bisphosphonates (e.g., alendronate) by patients/clients with beta-thalassemia major to combat weakened bones.
- Radiographs show reduced trabeculation of the maxilla and mandible, with the prominence of some trabeculae and a blurring and disappearance of others (“salt and pepper” effect).
- The tooth-bearing bone may have a "chicken wire" radiological appearance. Thinning of the lamina dura and radiolucencies in the alveolar bone may also be seen. Thickened frontal bone, the thinned cortex of the mandible and faint inferior dental canal may be seen.
- The increased chance of infection should consider during the dental treatment.
- Thalassemia patients undergoing splenectomy are at a massive risk of infection
- followed by bacteremia.
- Antibiotic prophylaxis must be given before performing invasive dental procedures
- Furthermore, these patients are also at high risk of having AIDS or viral hepatitis due to repeated blood transfusion, and therefore, screening tests should be carried out at regular intervals.
- Teeth extraction should be carried out at the time of admission for blood transfusion when the haemoglobin level is at its highest.
- Moreover, regular fluoride and prophylaxis applications are also recommended

Table 3: Showing Facial Features.

S.No	Type	causes
1.	Class II malocclusion	The maxillary protrusion, mandibular atrophy
2.	Lateral displacement of orbits	Marrow overgrowth in maxillary bone
3.	The maxillary protrusion	Early fusion of occipital sutures, hyperplasia of anterior maxillofacial structures
4.	Chipmunk facies	Malar prominence, saddle nose, frontal bossing
5	Brodie syndrome	Mandibular arch telescoped within the maxillary arch
6.	Pneumatisation of paranasal sinuses	Hyperplasia of marrow in frontal, temporal and facial bones

Table 4: Showing Oral Manifestations.

S.No	Oral manifestations	causes
1.	Malocclusion	The maxillary protrusion, increased overjet, anterior open bite
2.	Mucosal pallor, atrophic glossitis	Decreased haemoglobin levels
3.	Severe gingivitis	a constant finding especially when haemoglobin drops below 8mg/dl
4.	High caries index	Poor oral hygiene, less phosphorous and IgA in saliva
5.	Inflammation of salivary glands	Iron deposits
6.	Dark coloured gingiva	High ferritin levels in the blood
7.	Thin mandibular cortex	Marrow proliferation, expansion of medulla
8.	Multiple diastemas	
9.	Roots-short and spike-shaped, taurodontism	

Diagnosis of Thalassemia involves a three-tier approach represented in Table 5.

Table 5: Showing diagnosis tests.

S.No	Name of the Test	Description
1	Complete blood count	This test gives a general idea of the cells in the blood stream. If Mean Corpuscular Volume and Mean Corpuscular Haemoglobin are low and iron deficiency has been ruled out, thalassemia should be considered. In thalassemia RBCs may show anisocytosis, poikilocytosis, be nucleated and have uneven haemoglobin distribution (producing target cells that look like bull's eye under the microscope)
2.	Thalassemia screen test or haemoglobinopathy test.	This test measures the type and relative amounts of haemoglobin(Hb) present in the RBCs. This test is done once a haemoglobinopathy is suspected based on family history or full blood count. Hb A ($\alpha_2 \beta_2$) is the usual type of Hb found in adults. A raised Hb A2 ($\alpha_2 \delta_2$) is the key parameter indicating the presence of beta-thalassemia. Hb F($\alpha_2 \gamma_2$) also raised in beta thalassemia. Hb H inclusions (β_4 tetramer) is a definitive test to confirm alpha thalassemia in adults. Bart haemoglobin (γ_4 tetramer) seen in new borns with α thalassemia.
3.	DNA mutation analysis-	This test is used to investigate deletions and mutations in alpha and beta globin producing genes.

Dental Treatment of Thalassemia

The treatment for beta major thalassemia is performed routinely especially when patients experience decreasing haemoglobin level. Therefore, the dental treatment should be performed by paying attention to these following considerations: Factors that may influence Dental Care are as follows.

Chronic anaemia

No correlation between the skeletal, dental and chronological age observed in β -thalassemia major patients. The skeletal retardation increases with age due to endocrine hypofunction (secondary to iron deposition), hypoxia (from severe anaemia) or toxic actions of iron enzyme systems, leading to tissue injury. The enamel and dentin are the best indicators of iron deposition. Moreover, the deciduous and permanent teeth of thalassemia patients contain up to five times more iron concentration compared to that in normal individuals. High iron concentration explains teeth discolouration in patients with β -thalassemia major. Besides the orofacial appearances associated with chronic anaemia, patients may appear to be exhausted, lazy and poorly interested in physical activities. Dental care should be modified

according to their tolerance level on the day of treatment.^[26,38]

Dental caries

Thalassaemic children also experience frequent tooth decay problems due to the median salivary concentrations of IgA and phosphorous. In cases of severe dental caries, the risk of infections in the roots (or abscess) increases. At times, the infections spread to the tissues of face and neck that leads to extraction of the affected teeth resulting in loose gums and teeth structure.^[36]

Dental Infections

The increased chance of infection should be considered during the dental treatment. Thalassemia patients undergoing splenectomy are at a massive risk of infection followed by bacteremia. Antibiotic prophylaxis must be given before performing invasive dental procedures.^[30] Furthermore, these patients are also at high risk of having AIDS or viral hepatitis due to repeated blood transfusion, and therefore, screening tests should be carried out at regular intervals. Teeth extraction should be carried out at the time of admission for blood transfusion when the haemoglobin level is at its highest. Moreover, regular

fluoride and prophylaxis applications are also recommended.^[39]

Iron overload and deposition

Iron overload, also known as hemochromatosis, is one of the common complications of thalassaemia. This hereditary disorder of metabolism can lead to organ damage and mortality.^[40,41] if left undiagnosed and untreated. Iron deposition in the parenchymal tissues of thalassemia patients can observe within a year of the onset of regular blood transfusions.^[33] Studies have shown that iron gets accumulated in the cardiac, endocrine, hepatic tissues and gingivae of major thalassemia patients.^[42,43] While the impact of iron deposits on periodontal health is unidentified, more studies investigating the use of gingival biopsies for the diagnosis of iron overload are required. It is, thus, advised that dentists should be extra-attentive in case of dental problems in thalassemia patients. The oral ailments may worsen with an increase in the iron load.^[36]

Transfusion-transmitted infections

Individuals with thalassemia are at high risk of carriage of HIV and Hepatitis B, C, and G viruses. Invasive dental care in thalassemia patients receiving regular exchange transfusion should be scheduled within a week of the planned transfusion, as the patient's blood counts would be optimal.^[26]

Cardiomyopathy

Chronic anaemia can result in a cardiomyopathy and get further exacerbated by cardiac iron overload. Although patients may be asymptomatic with their cardiac dysfunction when experiencing a stressful dental procedure and being anxious, they may rapid their cardiac symptoms.^[27,28] Studies have also revealed that the bacteria causing periodontal problems can move into the bloodstream and result in vasculitis, thereby, contributing to heart disease and stroke.

During the dental procedures of patients with cardiac problems, the dentists should be decisive of using anaesthesia. Epinephrine content in anaesthesia may result in cardiovascular problems in patients with heart ailments, which involves high blood pressure, angina (chest pain), heart attack and arrhythmias. An orthodontist needs to be aware of the degree of cardiac involvement and should use appropriate precautions accordingly.

Dental Considerations^[44]

Utmost attention should be focused on the obtainment of as much information as possible on thalassaemic patients for proper distinction before subjecting to a guaranteed safe dental management. Therefore, the type of thalassemia must be recognised, accompanied by the treatments received, the degree of iron accumulation-related organ involvement, and consequently, the patient's prognosis and life expectancy.

The medical diagnosis is of great aid in the planning of dental treatment as it varies according to the type of thalassemia involved. Thalassemia trait patients can be considered for more complex treatment modules. A simple case history documented by the dental expert is, therefore, important for dental treatment, which can be suitable as per the patient's oral health and quality of life.

As in any patient with chronic anaemia, poor healing may ensue after surgical, dental procedures. The possibility of exacerbated symptoms of cerebral or cardiac hypoxia persists in an anaemic patient in the case of substantial bleeding; hence, surgery is the best possible option for successful treatment of the facial deformities.

All the dental procedures of thalassaemic patients should be conducted under the guidance of a haematologist and should not bump with the patient's blood transfusion schedules. The patients with low haemoglobin level are mostly not suggested with oral surgical procedures, and the side-effects of the prescribed medications to the thalassemia patients should be considered beforehand.^[44] (Table 6).

Before beginning the treatment, the following factors should be ascertained: (Table 6)

1.	Type of Thalassemia
2.	Present haemoglobin level of the patient
3.	A degree of iron overload in the body
4.	Relative organ involvement with iron
5.	Chelators administered to the patient
6.	Presence or absence of splenomegaly
7.	History of splenectomy
8.	Overall patient prognosis and life expectancy.

Dental management^[44]

- The treatment for beta major thalassemia is performed routinely especially when patients experience decreasing haemoglobin level. Therefore, the dental treatment should complete by paying attention to these following considerations:
- Consult all dental treatments planned with the haematologist.
- The dental treatment should be performed in a short time as possible and should do after the patient receives a blood transfusion.
- Do not do dental treatment when the haemoglobin level is less than 100 g/l. Provide antibiotics prophylaxis especially for children who have undergone splenectomy.
- Excess iron in the body increases the risk of fibrosis, cirrhosis and liver cancer.
- The liver function and coagulation tests should be performed before dental procedures are carried out. This is to rule out any liver disorder that may have been caused by excess iron. Diminished coagulation factors could also be due to intense vitamin K absorption deficiencies due to prolonged antibiotic

coverage or previously progressing hepatitis. Caution should be exercised by the dentist in employing the commonly administered hepatotoxic drugs.

- Tetracycline, metronidazole and erythromycin estolate should avoided entirely. Paracetamol is a safe alternative to NSAIDs and Aspirin.
- If orthodontic treatment is needed, the dental movement should be watched closely because there may be faster movement compared to the normal situation. The retention phase is also more difficult in these patients.
- The anaemic condition in beta major thalassemia patients makes patients lazy to clean their teeth that oral hygiene becomes poor and a high caries index found.
- The dentist, especially the pediatric dentist, should be careful in giving dental treatment. The cooperation with the haematology expert should established in each treatment action.
- Collaboration with haematologist has to make in every dental treatment.

CONCLUSION

Preventive dental care is a prime necessity for thalassemia patients, and the treatment procedure should be modified according to the patient's need to minimize any physical damage and for better treatment outcomes. Dentists should have an in-depth understanding of the proper management of the dental problems of thalassaemic patients. Multidisciplinary approaches should implemented by dental experts in association with haematologists for safe dental treatment of this patient. Current reports show a significant improvement in thalassaemia major patients' survival rates. With increased life expectancy, the need for improved oral healthcare is very important to ensure a high quality of life for this patient population

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