



The Neurological Complications In Beta Thalassemia

¹ Hiranmai Shriram Dharmadhikari, ²Paras Anil Mohare, ³Koustubh Mohanrao Joshi,

⁴Syed Azhad Mushir

Vishweshwar Dharashive.

Shivlingeshwar collage of pharmacy, Almala, Dist.-Latur-413512

Abstract:- Thalassemia, a common monogenic disorder, encompasses a spectrum of conditions from mild to severe. Beta-thalassemia, characterized by reduced or absent beta-globin chain synthesis, leads to ineffective erythropoiesis and anemia. Severe cases require regular blood transfusions, causing iron overload and complications. Endocrine issues are common. Understanding the clinical and hematological aspects is vital for effective management and complication prevention.

Keywords:- Thalassemia, Monogenic Disorder, Beta- Thalassemia, Complications, Anemia.

• Introduction:

Thalassemia was first illustrated by Cooley and Lee in 1925. thalassemia is derived from the Greek word Thalassa meaning 'sea,' and haema meaning 'of blood'(1).Thalassemia is the most common monogenic disorder in the world(2). The thalassemias are the most common single gene disorder in the world(3).

"Beta thalassemia minor" is mild and usually doesn't cause problems. Anemia from "beta thalassemia intermedia" causes slowed growth in children, weak bones, and an enlarged spleen. "Beta thalassemia major" is the most serious type, and it can cause many complications, including slow growth in children, an enlarged spleen, heart and liver problems, and bone damage.

Beta-thalassemia syndromes are a group of hereditary blood disorders characterized by reduced or absent beta globin chain synthesis, resulting in reduced Hb in red blood cells (RBC), decreased RBC production and anemia [5]. In β -thalassemia patients, β -globin chain is either reduced (β^+) or absent (β^0). This will lead to an excessive amount of α -globin chain in the red blood cells which precipitate in the red blood cell precursors within the bone marrow. This will cause mechanical and oxidative damage to the red blood cell precursors in the bone marrow leading to ineffective erythropoiesis. Shortening of the life span of the red blood cells is seen due to associated haemolysis (4).

Individuals that develop severe anaemia due to β -thalassemia need regular blood transfusions for survival and optimal growth. Over time, regular blood transfusions will result in iron overload. Such iron accumulation over a prolonged period may result in iron-toxicity and prompt complications such as heart failure, malocclusion of the teeth, infections, and endocrine abnormalities(4). The clinical and haematological spectrum of β -thalassemia disease ranges from mild to clinically overt conditions including transfusion dependent (TDT) β -thalassemia major (TM) and non-transfusion dependent (NTDT) β -thalassemia intermedia (TI) or thalassaemia minor (TMin)(5).

The clinical spectrum of thalassaemia encompasses the asymptomatic carriers to the severe thalassaemia major patients who require life-long blood transfusions and iron chelation. Thalassaemia is associated with multiple endocrine complications involving the pituitary, thyroid, pancreas, gonads, parathyroid and bone(6). The known common manifestations of the disease are inefficient erythropoiesis, chronic anemia, splenomegaly, cholelithiasis, leg ulcers, osteoporosis, and extramedullary hemopoiesis; patients need frequent blood transfusions and splenectomy, leading respectively, to iron overload and thrombocytosis(7).

The common feature of all thalassaemia syndromes derives from an imbalanced production of either globin chain. When produced in excess, damage to RBC precursors and mature red blood cells leads to anemia. This leads to a compensatory increase in expansion of the ineffective marrow with deleterious effects on bone formation and growth. The need for regular RBC transfusions can be associated with severe iron overload. The major cause of morbidity and mortality is the effect of iron deposition in the endocrine organs, liver, and heart, which results not only from transfusion therapy but from increased intestinal absorption of iron (8).

- **Epidemiology:** Beta thalassaemia is widespread in India, the Middle East, Central Asia, and Mediterranean countries. Southeast Asia and Cyprus have the highest beta thalassaemia carrier frequency reported in the literature. Thalassaemia is the most widespread genetically influenced blood disorder in Pakistan. Milder or carrier form of thalassaemia has a 5-7% prevalence in our country, with around 100,000 individuals affected with thalassaemia major. This number is increasing, with 5-9,000 new cases are seen each year(9). It has estimated that about 3% of the world's populations carry the thalassaemia gene. Due to migration and intermarriage between different ethnic groups, thalassaemia has become a disease of international interest(10).

It has been estimated that about 1.5% of the global population (80 to 90 million people) are carriers of betathalassaemia, with about 60,000 symptomatic individuals born annually, the overwhelming majority in the developing world.

The total annual incidence of symptomatic individuals is estimated at 1 in 100,000 throughout the world and 1 in 10,000 people in the European Union(11).

The highest carrier frequency is reported in Cyprus (14%), Sardinia (10.3%), and Southeast Asia [05]. More recent studies found renal dysfunction in 1.8% of TDT patients, whereas renal problems were classified as the fourth most common cause of morbidity (4%) after endocrine (44.7%), cardiovascular (41.3%) and hepatic (40.5%) disease in the same patient population(12).

- **Types:** Beta-thalassaemias can be classified into: - Beta-thalassaemia • Thalassaemia major •Thalassaemia intermedia •Thalassaemia minor - Beta-thalassaemia with associated Hb anomalies • HbC/Beta-thalassaemia • HbE/Beta-thalassaemia • HbS/Beta-thalassaemia (clinical condition more similar to sickle cell disease than to thalassaemia major or intermedia) - Hereditary persistence of fetal Hb and beta-thalassaemia - Autosomal dominant forms - Beta-thalassaemia associated with other manifestations • Beta-thalassaemia-tricothiodystrophy • X-linked thrombocytopenia with thalassaemia(11).

- **Etiology:** Etiology More than 200 mutations have been so far reported; the large majority are point mutations in functionally important regions of the beta globin gene. Deletions of the beta globin gene are uncommon. The beta globin gene mutations cause a reduced or absent production of beta globin chains(11).

Cross-sectional studies in various thalassemia groups from five thalassemia centers in North America have shown reduced creatinine clearance in 7.8%, and albuminuria in up to 59% of patients. More recent studies found renal dysfunction in 1.8% of TDT patients, whereas renal problems were classified as the fourth most common cause of morbidity (4%) after endocrine (44.7%), cardiovascular (41.3%) and hepatic (40.5%) disease in the same patient population(12).

- **DIAGNOSIS:**

1. **Evoked potentials (VEPs, BAEPs, SSEPs):** Evoked potentials are a valuable noninvasive method for assessing the central nervous system (CNS). While they may lack disease-specific characteristics, they serve as sensitive tools for detecting even subclinical CNS lesions. Several types of evoked potentials, including visual evoked potentials (VEP), brainstem auditory evoked potentials (BAEPs), and somatosensory evoked potentials (SSEPs), have been employed in the evaluation of various conditions, such as thalassemia.
2. In the case of VEP, Gelmi et al. reported that abnormalities in VEPs in patients with beta-thalassemia major (b-TM) were correlated with iron overload. Pathological VEP findings, which were partially reversible, were attributed to the neurotoxic effects of the iron-chelating agent DFO (deferroxamine) in several studies.
3. For BAEPs, a study involving individuals with mild sensorineural hearing loss found abnormal BAEP findings, most of which were reversible and related to DFO neurotoxicity. The use of other iron-chelating agents, such as deferasirox or deferiprone, in the management of iron overload has not been associated with similar abnormalities, although limited research on this topic exists.
4. In the case of SSEPs, increased cortical latencies of median or posterior tibial somatosensory evoked potentials were observed in some cases. These findings collectively indicate that central nervous system lesions are not uncommon in both b-TM patients and thalassemia intermedia individuals. These lesions may remain subclinical and require specialized examinations for detection(13).
5. **Extramedullary hematopoiesis and neurological complications/ Extramedullary hematopoiesis (EMH):**

Extramedullary hematopoiesis (EMH) is a compensatory physiological response that occurs when the bone marrow's function is insufficient to meet the increased demands for blood cell production. This phenomenon is commonly observed in chronic anemias and various hematological diseases. EMH can result in a range of clinical presentations, and when it affects the spine and nervous system, it can lead to neurological complications.

Clinical presentations associated with spinal cord involvement due to EMH include the following symptoms:

- **Back pain:** Patients may experience discomfort or pain in the back, often in the thoracic region, due to the expansion of EMH within the vertebral column.
- **Lower extremity pain:** Pain and discomfort in the legs may occur because of spinal cord compression or nerve compression.
- **Paresthesia:** Abnormal sensations, such as tingling, numbness, or "pins and needles" sensations, may be felt in the lower extremities.
- **Abnormal proprioception:** There can be disturbances in the sense of body position and movement.

- Exaggerated or brisk deep tendon reflexes: Reflexes may become hyperactive due to spinal cord compression.
- Babinski response: This is an abnormal reflex in which the big toe moves upward when the sole of the foot is stimulated, often indicative of neurological pathology.
- Lasegue sign: This sign refers to pain radiating down the leg when the straight leg is raised while the patient is in a supine position, and it can be indicative of nerve compression.

Urgency of urination and bowel incontinence: Neurological involvement can affect bladder and bowel control.

The severity, acuteness, and multiplicity of these signs and symptoms depend on factors such as the size and location of EMH lesions and the extent of spinal cord involvement.

Meara reported a rare case of extramedullary hematopoiesis occurring in the middle ear of a patient with thalassemia intermedia, resulting in conductive hearing loss. This example demonstrates that EMH can manifest in various locations throughout the body.

Treatment options for EMH may include transfusion therapy to manage the underlying anemia, irradiation of the masses to reduce their size, and synovectomy (surgical removal of the synovial membrane surrounding the joints). Early diagnosis and intervention are critical in the management of EMH, as they can help prevent irreversible neurological damage that may occur if EMH remains undiagnosed or untreated.(12,13).

6. **Cerebrovascular disease:** Patients with beta-thalassemia (b-TM) can experience specific complications, including large hemispheric territorial infarcts, which are a form of stroke. In these patients, the etiology of stroke is often attributed to various factors, and one important cause is cardioembolic. Siderotoxic cardiomyopathy, as well as arrhythmias, are believed to contribute to the risk of stroke in b-TM patients.

Hemosiderosis-related diseases, such as cardiomyopathy, liver dysfunction, and diabetes mellitus, are common complications associated with iron overload in thalassemia. Proper chelation therapy is crucial for managing iron overload and preventing these complications. Chelation therapy is also important in reducing the risk of cerebrovascular accidents, including stroke, in thalassemia patients.

In patients with beta-thalassemia major and thalassemia intermedia, the presence of a hypercoagulable state is a significant risk factor for thrombotic stroke. This hypercoagulable state predisposes individuals to the formation of blood clots, which can potentially lead to a stroke. It's worth noting that in cases of beta-thalassemia major, cardioembolism, often associated with underlying cardiomyopathy and arrhythmias, is commonly identified as the primary cause of stroke(14).

7. **Peripheral neuropathy and myopathy:** clinical evidence of a sensory neuropathy (absent or diminished deep tendon reflexes and loss of sensation in a stock-glove distribution) additionally 25 % had decreased sensory conduction velocities, and only 10 % also had decreased motor NCVs. Peripheral neuropathy is a reality that reduces daily activities and hampers the quality of life of a high proportion of thalassemic patients.
8. **Chelation neurotoxicity:** three major iron chelators used in thalassemia namely Desferrioxamine, Deferiprone and Deferasirox. Of the three Desferrioxamine has been extensively studied for neurotoxicity. Porter et al., found a significant correlation between therapeutic index (mean daily DFO dose divided by serum ferritin level) and risk of sensorineural hearing loss in thalassemic patients.

Ocular toxicity - high-dose intravenous DFO.

9. **Sickle cell disease:** a hemolytic anemia caused by the presence of hemoglobin S (Hb S) in homozygous, depends on the associated genotype and other factors that alter the hemoglobin concentration or the blood flow. The mutation for Hb S occurs in the beta globin gene and it is responsible for the hemoglobin

polymerization under conditions of hypoxia, acidosis or dehydration, altering the erythrocytes morphology for a sickling state(14).

10. **Cardiac Complications:** Cardiac disorders and, most notably, left-sided heart failure are responsible. Heart disease may manifest as hemosiderotic cardiomyopathy, heart failure, pulmonary hypertension, arrhythmias, systolic/diastolic dysfunction, pericardial effusion, myocarditis or pericarditis. Thalassaemic cardiomyopathy and arrhythmias caused by myocardial siderosis are the most severe side effect of iron overload in patients with β -thalassaemia contributing to mortality and morbidity; The clinical presentation of cardiac failure varies from affecting ventricular pathology to pulmonary hypertension, to symptomatic supraventricular arrhythmias which will cause sudden death.

β -thalassaemia cardiomyopathy is typically characterised by two different phenotypes, a dilated type, left ventricular dilatation and reduced contractility, and a restrictive type of restrictive left ventricular filling, pulmonary hypertension and right heart failure.

a) **Arrhythmia:** Cardiac pathologies such as an increase in left atrial diameter, interventricular septum diameter, and left ventricular posterior wall diameter seem to contribute to the pathogenesis of arrhythmias, particularly supraventricular arrhythmias. In addition to atrial fibrillation and flutter, the most common thalassaemia-related arrhythmias were premature atrial contractions, premature ventricular contractions, ventricular hypertrophy and atrioventricular, ventricular tachycardia and cardiac arrhythmia.

In terms of electrocardiographic and echocardiographic parameters, thalassaemia major patients displayed increase in the length of P wave, and increased length of QRS relative to normal controls. Additionally, prolonged P wave and dispersion of P wave are seen in patients with thalassaemia major, and that they were related to increased risk of episodes of atrial fibrillation. It has been shown that increased length of QRS, even among normal limits, predicts mortality within the general population(15).

B) Heart failure: heart failure used to be the most common cause of death in thalassaemia major patients undergoing daily transfusions. Magnetic resonance imaging assessment of iron overload using T2* imaging is used to measure iron loading in all organ systems, including the heart, prior to clinical manifestations. A cardiac T2* below 20 ms is indicative of cardiac iron and a T2* below 10 ms carries substantial prospective risk of cardiac dysfunction. Latest autopsy data showed that iron deposition in the myocardium in thalassaemia major patients occurs preferentially in the subepicardium and iron is highly representative of total cardiac iron in the interventricular septum.

Changes in the heart that occurs in addition to ventricular systolic impairment include the following:

a) decreased left atrial activity due to ventricular stiffening or direct atrial toxicity; (b) impaired right ventricular function that may result from increased sensitivity of the right ventricular to the consequences of iron deposition due to its thin wall; (c) impaired endothelial function in iron overload; (d) impaired diastolic function by tissue of the cardiac iron overload in Doppler imagery(15)

C) Pericarditis and myocarditis: Pericarditis is another common cardiac complication of the disease, along with the presence of cardiomyopathy.

Myocarditis additionally tends to play a vicinity within the pathological process of cardiomyopathy in thalassaemia patients [34].

D) Pulmonary hypertension: The main risk factors for developing pulmonary hypertension among β -thalassaemia major patients were with hypertension, older age, history of splenectomy and failure of iron chelation therapy. Increased age, low body mass index (BMI) and increasing size of splenomegaly and hepatomegaly were factors linked to pulmonary hypertension severity.

Symptoms for clinical evaluation of pulmonary hypertension can be counteracted into two categories, those reflecting elevated pulmonary vascular resistance and symptoms of right cardiac dysfunction and failure [(15).

11. **Endocrine Complications:** multiendocrine dysfunction - commonest is hypogonadotrophic hypogonadism reported in upto 75% of patient. The anterior pituitary is particularly sensitive to iron overload which disrupts hormonal secretion, leading to gonadal dysfunction. puberty, primary or secondary amenorrhea, menstrual irregularities and fertility problems later in life.

multiendocrine dysfunction, chronic anemia, infections, undernutrition, malabsorption of vitamin D, deficiencies of calcium, zinc and copper, and lower serum levels of insulin-like growth factor-1 (IGF-1) and IGF-binding protein-3 (IGFBP-3). diabetes in later life, due to iron deposition in the pancreas. diabetic ketoacidosis.

12. **Metabolic complications:** Cooley's original description of β -thalassemia major included marked bone deformities as a characteristic feature. There is a high prevalence of low bone mass in these patients. BMD is assessed using dual x-ray absorptiometry at three common sites including the lumbar spine, head of femur and forearm. bone deformities, osteoporosis, osteopenia, lower bone mineral density (BMD) in these patients include lack of spontaneous puberty, malnutrition, multiendocrine dysfunction and deficiencies of vitamin D, calcium, and zinc(16).

13. **Hepatic complications:** thalassemia-associated liver damage has been insufficiently characterized.³⁷ Liver disease in these patients can manifest as hepatomegaly, decreased albumen concentrations, increased aspartate and alanine transaminase activities, Hepatitis B and C. Hepatocellular carcinoma can complicate the course of hepatitis B and C. Significant fibrosis is frequent and its progression is mostly influenced by iron overload which may be attributable to, hypertransfusion, inadequate chelation, erythrocyte catabolism and iron hyperabsorption.

14. **Neurologic complications:** Neurological complications have been attributed to numerous factors such as chronic hypoxia, bone marrow expansion, iron overload, and desferrioxamine (DFO) neurotoxicity. Abnormal findings in the visual, auditory, and somatosensory evoked potential recordings are attributed to DFO neurotoxicity. On the other hand, nerve conduction velocity abnormalities are associated either to chronic hypoxia or to hemosiderosis(16).

A] Hypoxia: chronic anemia results in extramedullary hematopoiesis. Prolonged nerve hypoxia may also result in axonal sensorimotor neuropathy, as stated in a report by Stamboulis et al. Hypoxia due to chronic anemia has also been suggested to play a role in the development of ischemic stroke, a well-described, though infrequently reported complication of β -thalassemia. The incidence of brain damage is higher in non-treated patients with thalassemia-intermedia and increases with age.

It should be noted that multiple factors, besides hypoxia, are known to be involved in the hemorrhagic and thrombotic complications occurring in thalassemic patients.

B] Hemosiderosis: The effect of iron on neural pathways in thalassemic patients was initially connected to sensorineural hearing loss resulting from cochlear siderosis.

glucose metabolism impairment resulting from pancreas siderosis, is an important additional factor related to complications involving the central and/or peripheral nervous system in β -thalassemia patients(17).

C] DFO neurotoxicity: Regular chelation therapy with DFO has been shown to produce negative iron balance, reduce tissue iron stores, delay or prevent iron-induced organ damage and improve survival in patients with transfusional iron overload. Various possible mechanisms for DFO associated neuropathy - multiple trace element chelation, metalloenzyme activity inhibition, and oxygen based free radical generation. DFO ototoxicity, a long-term audiological evaluation reported by Kontzoglou et al. demonstrated the presence of high frequency sensorineural hearing loss in 20.2% of assessed patients – temporary treatment with drug discontinuation and dosage reduction.

clinical presentation includes parasthesias, myalgias, and muscle weakness, etc.

D] Nutrition deficiency: reports in relation to the levels of certain vitamins and trace metals in the blood of thalassemic patients, their deficiency state known to be associated with nervous system pathology. Well documented that the spinal cord, brain, optic nerves, and peripheral nerves may be affected by B12 deficiency. Increased zinc and copper fecal and/or urinary excretion, possibly related to or exacerbated by iron chelation treatment, has been demonstrated in certain studies (17).

15. **renal function abnormalities:** Renal manifestation - Etiology - Mechanism – Evaluation

a] Hematuria

- **evaluation:** Nephrolithiasis
- **mechanism:** Hypercalciuria, hyperuricosuria, cystinuria, struvite stones
- **excretion:** Dipstick urinalysis (12).

b] Tubular dysfunction

etiology: Chronic anemia/hypoxia/ Iron overload/ iron chelators/ Aminoglycoside, intravenous radiocontrast agents, NSAIDs/ Beta-lactams/ Ampicillin, ciprofloxacin, sulfonamides, acyclovir

mechanism: Oxidative stress, lipid peroxidation, endothelial damage and loss of peritubular capillaries/ Oxidative stress, lipid peroxidation/ Nephrotoxicity/ Cytotoxicity, renal vasoconstriction, acute tubular necrosis/ Mitochondrial dysfunction, lipid peroxidation, acute tubular necrosis/ Crystal precipitation within the distal tubular lumen resp.

evaluations: Serum β 2-M Urine calcium/creatinine Urine β 2-M/creatinine Urinary NAG Urinary NAGL Urinary α 1-microglobulin Urinary RBP etc (17).

c] Glomerular dysfunction:

etiology: Chronic anemia/hypoxia/ Iron overload/ Infections (e.g., HIV, HCV, HBV) / Iron chelators/ NSAIDs, COX-2 inhibitors/ ACE inhibitors, ARBs

mechanism: Reduced vascular resistance, elevated RPF/ Damage and loss of peritubular capillaries, epithelial-mesenchymal transdifferentiation of tubular cells to myofibroblasts, tubulointerstitial injury, glomerulosclerosis/ Damage and loss of peritubular capillaries, epithelial-mesenchymal transdifferentiation of tubular cells to myofibroblasts, tubulointerstitial injury, glomerulosclerosis/ Glomerulonephritis/ Relative iron depletion, mitochondrial dysfunction in tubular cells, tubuloglomerular feedback, vasoconstriction of the afferent arteriole/ Vasoconstriction of the afferent arteriole/ Vasodilation of the afferent and efferent arterioles

evaluation: Urine dipstick Serum creatinine Urine protein/creatinine Serum cystatin CrCl eGFR (17).

d] Nephrolithiasis:

Nephrolithiasis, the formation of kidney stones, can be attributed to several causes:

Etiology:

Vitamin D and Calcium Supplementation: Excessive intake of vitamin D and calcium supplements may contribute to kidney stone formation.

Deferasirox: The iron-chelating medication deferasirox can also be a factor in kidney stone development.

Tubular Dysfunction: Impaired tubular function, which can occur in certain conditions like thalassemia, can increase the risk of kidney stones.

Splenectomy: Removal of the spleen can lead to higher red blood cell turnover, potentially raising the likelihood of kidney stone formation.

Urinary Tract Infections: Infections caused by bacteria that produce urease (e.g., Proteus, Klebsiella, Staphylococcus epidermidis, Mycoplasma, and yeast species) can result in the formation of struvite stones in the urinary tract.

Mechanism:

Etiology:

Vitamin D and Calcium Supplementation: Excessive intake of vitamin D and calcium supplements may contribute to kidney stone formation.

Mechanism:

Hypercalciuria: Increased calcium levels in the urine can lead to the development of calcium stones.

Cystinuria: This condition can cause the formation of cystine stones due to impaired cystine reabsorption in the renal tubules.

Evaluation:

Healthcare professionals typically use the following methods to assess nephrolithiasis: Urine Dipstick: This test provides information about the composition of the stones.

16. **Carotid Endarterectomy in a Young Symptomatic Patient with B-Thalassemia Major:** Carotid occlusive disease as a part of a systemic atherosclerotic process is an age-related entity, exhibited mainly because of the engagement of the major atherosclerotic factors. Common carotid intima-media thickness, a currently applied marker for premature atherosclerosis, has been found to be increased not only in adults with b-thalassemia major but also in children. The proposed mechanism which induces premature atherosclerosis in b-thalassemic patients is iron overload. Because of the peripheral blood hemolysis, these patients require lifelong repeated blood transfusions to prolong survival. As a result, b-thalassemic patients develop iron overload initially in reticuloendothelial system and secondary to all parenchymal organs(17,18).
17. **Ocular abnormalities in multi-transfused beta-thalassemia patients:** All the thalassemic patients were asymptomatic, but abnormal ocular findings. The prevalence of ocular abnormalities in normal group, which was significantly lower than that in thalassemia patients. Not found any significant correlation between the prevalence of ocular abnormalities with serum ferritin level, hemoglobin concentration, and the type and dose of chelation therapy as life expectancy for beta-thalassemia patients extends, regular ophthalmological evaluation to detect early changes in their ocular system is recommended, in order to achieve a better life quality for this patient group(19).
18. **Cephalofacial Deformities in Thalassemia Major (Cooley's Anemia):** Osseous changes in thalassemia major (Cooley's anemia, homozygous β -thalassemia) with widening of medullary cavities, atrophy and trabeculation of the spongiosa, and cortical thinning follow hyperplasia of the red marrow. This occurs in response to marrow overstimulation because of ineffective erythropoiesis.1-4 These changes of the skeletal architecture are most typically reflected in the cephalofacial appearance of these patients. The prominent frontal and parietal bones along with the sunken bridge of the nose, the protruding zygomas and upward slant of the eyes are responsible for the mongoloid facial characteristics. Even more typical according to some authors is the "rodent facies" due to maxillary overgrowth with resulting overbite, protrusion of the exposed incisor teeth, and separation of the orbits.

Based on the above observations, we may conclude that delay in onset of transfusions and in performance of splenectomy, as well as failure to maintain at least moderate hemoglobin levels, have all contributed to the appearance of CFD.

The high incidence of a proximal type of muscular weakness in our patients with CFD, especially those with severe CFD, suggests that the underlying mechanism responsible for the skeletal changes may, under certain conditions, also affect muscles and lead to a myopathic-like condition. The positive correlations with the degree

of CFD included such indices as anemia, hepatosplenomegaly, skull thickness, rarefaction of the skull and other bones, head enlargement, stunting of growth, and liver dysfunction(20).

19. **Dentomaxillofacial Complications:**

A] Dental and Oromaxillofacial Features in TM: oromaxillofacial deformities observed in TM patients are frontal bossing, prominent cheek (malar) bones, saddle nose, maxillary protrusion, flaring of the maxillary anterior teeth, lip incompetence, and malocclusion. These changes give a distinctive “chipmunk”-like appearance.

Of the patients examined, 33% had almost normal appearance,

26% (grade I: slight depression of the nose, puffiness of the eyelids with no maxillary overgrowth),

24% (grade II: mild maxillary overgrowth and slight bulging of the frontal and cheek bones) 16.7% (grade III: “chipmunk” facies).

B] Dental Caries: dental caries is a multifactorial infectious disease with many contributory environmental factors, there is also convincing evidence for a genetic component in the etiology of this disease.

C] Periodontal Status and Oral Hygiene: Thalassemia major patients showed a higher plaque index and gingival index (GI) scores compared with the control group.

The GI showed that 49.2% of the thalassemic patients had mild gingivitis (no bleeding on probing), 34.7% moderate gingivitis (bleeding on probing), and 8.3% severe gingivitis (spontaneous bleeding).

D] Tooth and Mucosal Discoloration: Due to chronic jaundice associated with thalassemia, the incorporation of blood pigment bilirubin, degraded product of Hb, in the dentinal tubules during tooth formation results in yellow discoloration of teeth.¹⁵ Tooth discoloration and pallor oral mucosa has been found.

E] Tooth Crown Size and Tooth Size Ratio: In both thalassemic and control groups, males exhibited significantly larger MD than females in most instances. Canines displayed the most sexual dimorphic teeth in the dentition. Lateral incisors showed the greatest variable teeth.^{16,17} The tooth size ratio describes the discrepancy between the sums of MD of mandibular relative to the maxillary teeth.

Lateral incisors showed the greatest variable teeth.^{16,17} The tooth size ratio describes the discrepancy between the sums of MD of mandibular relative to the maxillary teeth. The anterior and overall ratios (sexes pooled) in thalassemic group were 79.1 and 92.0, respectively. The corresponding ratios of the control group were 79.4 and 92.4, respectively. The differences in tooth size ratio between thalassemic and control group were not statistically significant.

F] Dental Arches Dimensions: Measurements showed that the segmental arch lengths in the maxilla and mandible of thalassemic group were reduced by an average of 2.59 and 2.55 mm respectively, compared with the control group.

All arch widths in thalassemic patients were significantly reduced by an average ranging from 1.33 to 1.90 mm in the maxilla and 1.37 to 1.77 mm in the mandible. The mean maxillary and mandibular arch perimeters were reduced by 3.91 and 3.44 mm respectively, in the the Controls(10).

Most orofacial manifestations are in response to the severe hemolytic anemia, chronic hypoxia, and ineffective erythropoiesis, resulting in massive bone marrow hyperplasia and expansion of the marrow cavity.

These changes are mainly manifested as follows: (1) Bossing of the frontal bone, prominence of the malar bone, and maxillary protrusion; (2) thinning of mandibular inferior cortex, faint or absence mandibular canal; (3) enlarged marrow spaces, altered (reduced) trabecular pattern of the mandible; (4) partially obliterated maxillary sinus due to delayed pneumatization [(10).

G] Physical Growth: The cause of growth retardation in TM patients is multifactorial, including chronic anemia and hypoxia, iron overload, racial factors, endocrinopathies, and low socioeconomic status. A marked delay in physical growth of thalassemic patients has been documented in different population groups.

20. **LOW BACK PAIN IN BETA THALASSEMIA MAJOR REVEALING SACRAL EXTRA MEDULLARY HEMATOPOEISIS:** EMH is a well-established complication of thalassemia major and can manifest in variable forms ranging from asymptomatic hepatosplenomegaly to skeletal malformations causing serious adverse effects such as SCC which is rarely encountered but should always be held in mind when assessing patients with TDBT(21).

Conclusion: regular neuropsychological testing is essential for early diagnosis and appropriate management of cognitive dysfunction to improve the quality of life of patients with thalassems(13).

21. **Evoked potentials (VEPs, BAEPs, SSEPs):** Evoked potentials constitute a noninvasive method of evaluating the CNS. Evoked potentials lack disease specificity but remain sensitive tools in detecting even subclinical CNS lesions.

visual evoked potential (VEP): Gelmi et al. reported that visual evoked potential (VEP) abnormalities in b-TM patients correlated with iron overload. Pathological VEPs findings that were partially reversible were attributed to DFO neurotoxicity in several studies.

brainstem auditory evoked potentials (BAEPs): study with mild sensorineural loss & abnormal BAEP findings, mostly reversible and related to DFO neurotoxicity. The use of deferasirox or deferiprone [20] in the management of iron overload has not been implicated in causing such abnormalities, but a limited number of studies exist.

somatosensory evoked potentials (SSEPs): increased cortical latencies of median or posterior tibial somatosensory evoked potentials.

The results indicate that central nervous system lesions are not rare in either b-TM patients or in thalassemia intermedia, even if they remain subclinical and can be detected only by a careful assessment with specialized exams(13).

22. **Extramedullary hematopoiesis and neurological complications/ Extramedullary hematopoiesis (EMH):** a physiological compensatory phenomenon caused by insufficient bone marrow function that becomes unable to meet circulatory demands. EMH is seen in many hematological diseases; however, it commonly occurs in chronic anemias.

clinical presentations that have been reported includes back pain, lower extremity pain, paresthesia, abnormal proprioception, exaggerated or brisk deep tendon reflexes, Babinski response, Lasegue sign, paraparesis, paraplegia, ankle clonus, spastic gait, urgency of urination, and bowel incontinence.

The size and location of lesions and the extent of spinal cord involvement determine the severity, acuteness, and multiplicity of signs and symptoms.

Meara: reported extramedullary hematopoiesis of the middle ear in a patient with thalassemia intermedia resulting in conductive hearing loss.

Treatment options are transfusion therapy, irradiation of the masses, and synovectomy. Early diagnosis of EMH will affect the course of management and may reduce the incidence of irreversible neurological damage that would otherwise occur with prolonged undiagnosed(12,13).

23. **Cerebrovascular disease:** Patients with b-TM seem to suffer mainly from large hemispheric territorial infarcts. Cardioembolism due to siderotoxic cardiomyopathy and arrhythmias is assumed as one important etiology of stroke in b-TM.

Hemosiderosis-related disease, including cardiomyopathy, liver dysfunction, and diabetes mellitus, can be prevented by proper chelation therapy, and this therapy is also important in prevention of cerebrovascular accidents.

a hypercoagulable state is one of the most notable risk factors associated with thrombotic stroke in beta-thalassemia major, as well as in thalassemia intermedia patients.

Stroke: One complication in patients with β -thalassaemia who had prolonged survival is chronic hypercoagulable state. Cardioembolism seems to be the cause of stroke in cases of β -thalassaemia major(14).

24. **Peripheral neuropathy and myopathy:** clinical evidence of a sensory neuropathy (absent or diminished deep tendon reflexes and loss of sensation in a stock-glove distribution) additionally 25 % had decreased sensory conduction velocities, and only 10 % also had decreased motor NCVs. Peripheral neuropathy is a reality that reduces daily activities and hampers the quality of life of a high proportion of thalassemic patients.

25. **Chelation neurotoxicity:** three major iron chelators used in thalassemia namely Desferrioxamine, Deferiprone and Deferasirox. Of the three Desferrioxamine has been extensively studied for neurotoxicity. Porter et al., found a significant correlation between therapeutic index (mean daily DFO dose divided by serum ferritin level) and risk of sensorineural hearing loss in thalassemic patients.

Ocular toxicity - high-dose intravenous DFO.

26. **Sickle cell disease:** a hemolytic anemia caused by the presence of hemoglobin S (Hb S) in homozygous, depends on the associated genotype and other factors that alter the hemoglobin concentration or the blood flow. The mutation for Hb S occurs in the beta globin gene and it is responsible for the hemoglobin polymerization under conditions of hypoxia, acidosis or dehydration, altering the erythrocytes morphology for a sickling state(14).

27. **Cardiac Complications:** Cardiac disorders and, most notably, left-sided heart failure are responsible. Heart disease may manifest as hemosiderotic cardiomyopathy, heart failure, pulmonary hypertension, arrhythmias, systolic/diastolic dysfunction, pericardial effusion, myocarditis or pericarditis. Thalassemic cardiomyopathy and arrhythmias caused by myocardial siderosis are the most severe side effect of iron overload in patients with β -thalassaemia contributing to mortality and morbidity; The clinical presentation of cardiac failure varies from affecting ventricular pathology to pulmonary hypertension, to symptomatic supraventricular arrhythmias which will cause sudden death.

β -thalassaemia cardiomyopathy is typically characterised by two different phenotypes, a dilated type, left ventricular dilatation and reduced contractility, and a restrictive type of restrictive left ventricular filling, pulmonary hypertension and right heart failure.

a] **Arrhythmia:** Cardiac pathologies such as an increase in left atrial diameter, interventricular septum diameter, and left ventricular posterior wall diameter seem to contribute to the pathogenesis of arrhythmias, particularly supraventricular arrhythmias. In addition to atrial fibrillation and flutter, the most common thalassemiarelated arrhythmias were premature atrial contractions, premature ventricular contractions, ventricular hypertrophy and atrioventricular, ventricular tachycardia and cardiac arrhythmia.

In terms of electrocardiographic and echocardiographic parameters, thalassemia major patients displayed increase of the length of P wave, and increased length of QRS relative to normal controls. Additionally, prolonged P wave and dispersion of P wave are seen in patients with thalassemia major, and that they were related to increased risk of episodes of atrial fibrillation. It has been shown that increased length of QRS, even among normal limits, predicts mortality within the general population(15).

B] Heart failure: heart failure used to be the most common cause of death in thalassemia major patients undergoing daily transfusions. Magnetic resonance imaging assessment of iron overload using T2* imaging is used to measure iron loading in all organ systems, including the heart, prior to clinical manifestations. A cardiac T2* below 20 ms is indicative of cardiac iron and a T2* below 10 ms carries substantial prospective risk of cardiac dysfunction. Latest autopsy data showed that iron deposition in the myocardium in thalassemia major patients occurs preferentially in the subepicardium and iron is highly representative of total cardiac iron in the interventricular septum.

Changes in the heart that occurs in addition to ventricular systolic impairment include the following:

a) decreased left atrial activity due to ventricular stiffening or direct atrial toxicity; (b) impaired right ventricular function that may result from increased sensitivity of the right ventricular to the consequences of iron deposition due to its thin wall; (c) impaired endothelial function in iron overload; (d) impaired diastolic function by tissue of the cardiac iron overload in Doppler imagery(15)

C] Pericarditis and myocarditis: Pericarditis is another common cardiac complication of the disease, along with the presence of cardiomyopathy.

Myocarditis additionally tends to play a vicinity within the pathological process of cardiomyopathy in thalassemia patients [34].

D] Pulmonary hypertension:5 The main risk factors for developing pulmonary hypertension among β -thalassemia major patients were with hypertension, older age, history of splenectomy and failure of iron chelation therapy. Increased age, low body mass index (BMI) and increasing size of splenomegaly and hepatomegaly were factors linked to pulmonary hypertension severity.

Symptoms for clinical evaluation of pulmonary hypertension can be counteracted into two categories, those reflecting elevated pulmonary vascular resistance and symptoms of right cardiac dysfunction and failure [(15).

28. **Endocrine Complications:** multiendocrine dysfunction - commonest is hypogonadotropic hypogonadism reported in upto 75% of patient. The anterior pituitary is particularly sensitive to iron overload which disrupts hormonal secretion, leading to gonadal dysfunction. puberty, primary or secondary amenorrhea, menstrual irregularities and fertility problems later in life.

multiendocrine dysfunction, chronic anemia, infections, undernutrition, malabsorption of vitamin D, deficiencies of calcium, zinc and copper, and lower serum levels of insulin-like growth factor-1 (IGF-1) and IGF-binding protein-3 (IGFBP-3).

diabetes in later life, due to iron deposition in the pancreas. diabetic ketoacidosis.

29. **Metabolic complications:** Cooley's original description of β -thalassemia major included marked bone deformities as a characteristic feature. There is a high prevalence of low bone mass in these patients. BMD is assessed using dual x-ray absorptiometry at three common sites including the lumbar spine, head of femur and forearm. bone deformities, osteoporosis, osteopenia, lower bone mineral density (BMD) in these patients include lack of spontaneous puberty, malnutrition, multiendocrine dysfunction and deficiencies of vitamin D, calcium, and zinc(16).

30. **Hepatic complications:** thalassemia-associated liver damage has been insufficiently characterized.³⁷ Liver disease in these patients can manifest as hepatomegaly, decreased albumen concentrations, increased aspartate and alanine transaminase activities, Hepatitis B and C. Hepatocellular carcinoma can complicate the course of hepatitis B and C. Significant fibrosis is frequent and its progression is mostly influenced by iron overload which may be attributable to, hypertransfusion, inadequate chelation, erythrocyte catabolism and iron hyperabsorption.

31. **Neurologic complications:** Neurological complications have been attributed to numerous factors such as chronic hypoxia, bone marrow expansion, iron overload, and desferrioxamine (DFO) neurotoxicity. Abnormal findings in the visual, auditory, and somatosensory evoked potential recordings are attributed to DFO

neurotoxicity. On the other hand, nerve conduction velocity abnormalities are associated either to chronic hypoxia or to hemosiderosis(16).

A] Hypoxia: chronic anemia results in extramedullary hematopoiesis. Prolonged nerve hypoxia may also result in axonal sensorimotor neuropathy, as stated in a report by Stamboulis et al. Hypoxia due to chronic anemia has also been suggested to play a role in the development of ischemic stroke, a well-described, though infrequently reported complication of b-thalassemia. The incidence of brain damage is higher in non-treated patients with thalassemia-intermedia and increases with age.

It should be noted that multiple factors, besides hypoxia, are known to be involved in the hemorrhagic and thrombotic complications occurring in thalassemic patients.

B] Hemosiderosis: The effect of iron on neural pathways in thalassemic patients was initially connected to sensorineural hearing loss resulting from cochlear siderosis.

glucose metabolism impairment resulting from pancreas siderosis, is an important additional factor related to complications involving the central and/or peripheral nervous system in b-thalassemia patients(17).

C] DFO neurotoxicity: Regular chelation therapy with DFO has been shown to produce negative iron balance, reduce tissue iron stores, delay or prevent iron-induced organ damage and improve survival in patients with transfusional iron overload. Various possible mechanisms for DFO associated neuropathy - multiple trace element chelation, metalloenzyme activity inhibition, and oxygen based free radical generation. DFO ototoxicity, a long-term audiological evaluation reported by Kontzoglou et al. demonstrated the presence of high frequency sensorineural hearing loss in 20.2% of assessed patients – temporary treatment with drug discontinuation and dosage reduction.

clinical presentation includes parasthesias, myalgias, and muscle weakness, etc.

D] Nutrition deficiency: reports in relation to the levels of certain vitamins and trace metals in the blood of thalassemic patients, their deficiency state known to be associated with nervous system pathology. Well documented that the spinal cord, brain, optic nerves, and peripheral nerves may be affected by B12 deficiency. Increased zinc and copper fecal and/or urinary excretion, possibly related to or exacerbated by iron chelation treatment, has been demonstrated in certain studies(17).

32. renal function abnormalities: Renal manifestation - Etiology - Mechanism – Evaluation

a) Hematuria

- **evaluation:** Nephrolithiasis
- **mechanism:** Hypercalciuria, hyperuricosuria, cystinuria, struvite stones
- **excretion:** Dipstick urinalysis(12).

b) Tubular dysfunction

etiology: Chronic anemia/hypoxia/ Iron overload/ iron chelators/ Aminoglycoside, intravenous radiocontrast agents, NSAIDs/ Beta-lactames/ Ampicillin, ciprofloxacin, sulfonamides, acyclovir

mechanism: Oxidative stress, lipid peroxidation, endothelial damage and loss of peritubular capillaries/ Oxidative stress, lipid peroxidation/ Nephrotoxicity/ Cytotoxicity, renal vasoconstriction, acute tubular necrosis/ Mitochondrial dysfunction, lipid peroxidation, acute tubular necrosis/ Crystal precipitation within the distal tubular lumen resp.

evaluations: Serum β 2-M Urine calcium/creatinine Urine β 2-M/creatinine UrinaryNAG Urinary NAGL Urinary a1-microglobulin Urinary RBP etc(17).

c) Glomerular dysfunction:

etiology: Chronic anemia/hypoxia/ Iron overload/ Infections (e.g., HIV, HCV, HBV) / Iron chelators/ NSAIDs, COX-2 inhibitors/ ACE inhibitors, ARBs

mechanism: Reduced vascular resistance, elevated RPF/ Damage and loss of peritubular capillaries, epithelial-mesenchymal transdifferentiation of tubular cells to myofibroblasts, tubulointerstitial injury, glomerulosclerosis/ Damage and loss of peritubular capillaries, epithelial-mesenchymal transdifferentiation of tubular cells to

myofibroblasts, tubulointerstitial injury, glomerulosclerosis/ Glomerulonephritis/ Relative iron depletion, mitochondrial dysfunction in tubular cells, tubuloglomerular feedback, vasoconstriction of the afferent arteriole/ Vasoconstriction of the afferent arteriole/ Vasodilation of the afferent and efferent arterioles

evaluation: Urine dipstick Serum creatinine Urine protein/creatinine Serum cystatin CrCl eGFR(17).

d] Nephrolithiasis:

etiology: Vitamin D, calcium supplementation, deferasirox, tubular dysfunction/ Tubular dysfunction/ Splenectomy increased red cell turnover, tubular dysfunction/ Urinary tract infections by urease-producing bacteria (e.g., Proteus spp, Klebsiella spp, S. epidermidis, Mycoplasma spp, yeast species) resp.

mechanism: Hypercalciuria, calcium stones/ Cystinuria, cystine stones/ Hyperuricosuria, uric acid stones/ Struvite stones

evaluation: Urine dipstick Serum electrolytes Serum creatinine 24-hour urine collection Radiographic studies.

e] The role of iron chelating agents in renal disease: DFO chelates iron is located in plasma and ferritin by forming a metabolically inactive complex, which is renally excreted. DFO is poorly absorbed by the oral route. Consequently, intravenous, or subcutaneous administration is required. Acute renal failure necessitating dialysis following intravenous DFO overdose was described in patients who received 10- times the recommended dose due to administration pump failure or with inadequate monitoring.

33. Carotid Endarterectomy in a Young Symptomatic Patient with B-Thalassemia Major: Carotid occlusive disease as a part of a systemic atherosclerotic process is an age-related entity, exhibited mainly because of the engagement of the major atherosclerotic factors. Common carotid intima-media thickness, a currently applied marker for premature atherosclerosis, has been found to be increased not only in adults with b-thalassemia major but also in children. The proposed mechanism which induces premature atherosclerosis in b-thalassemic patients is iron overload. Because of the peripheral blood hemolysis, these patients require lifelong repeated blood transfusions to prolong survival. As a result, b-thalassemic patients develop iron overload initially in reticuloendothelial system and secondary to all parenchymal organs(17,18).

34. Ocular abnormalities in multi-transfused beta-thalassemia patients: All the thalassemic patients were asymptomatic, but abnormal ocular findings. The prevalence of ocular abnormalities in normal group, which was significantly lower than that in thalassemia patients. Not found any significant correlation between the prevalence of ocular abnormalities with serum ferritin level, hemoglobin concentration, and the type and dose of chelation therapy as life expectancy for beta-thalassemia patients extends, regular ophthalmological evaluation to detect early changes in their ocular system is recommended, to achieve a better life quality for this patient group(19).

35. Cephalofacial Deformities in Thalassemia Major (Cooley's Anemia): Osseous changes in thalassemia major (Cooley's anemia, homozygous β -thalassemia) with widening of medullary cavities, atrophy and trabeculation of the spongiosa, and cortical thinning follow hyperplasia of the red marrow. This occurs in response to marrow overstimulation because of ineffective erythropoiesis.1-4 These changes of the skeletal architecture are most typically reflected in the cephalofacial appearance of these patients. The prominent frontal and parietal bones along with the sunken bridge of the nose, the protruding zygomas and upward slant of the eyes are responsible for the mongoloid facial characteristics. Even more typical according to some authors is the "rodent facies" due to maxillary overgrowth with resulting overbite, protrusion of the exposed incisor teeth, and separation of the orbits.

Based on the above observations, we may conclude that delay in onset of transfusions and in performance of splenectomy, as well as failure to maintain at least moderate hemoglobin levels, have all contributed to the appearance of CFD.

The high incidence of a proximal type of muscular weakness in our patients with CFD, especially those with severe CFD, suggests that the underlying mechanism responsible for the skeletal changes may, under certain conditions, also affect muscles and lead to a myopathic-like condition.

the positive correlations with the degree of CFD included such indices as anemia, hepatosplenomegaly, skull thickness, rarefaction of the skull and other bones, head enlargement, stunting of growth, and liver dysfunction(20).

36. **Dentomaxillofacial Complications:**

A] Dental and Oromaxillofacial Features in TM: oromaxillofacial deformities observed in TM patients are frontal bossing, prominent cheek (malar) bones, saddle nose, maxillary protrusion, flaring of the maxillary anterior teeth, lip incompetence, and malocclusion. These changes give a distinctive “chipmunk”-like appearance.

Of the patients examined, 33% had almost normal appearance,

26% (grade I: slight depression of the nose, puffiness of the eyelids with no maxillary overgrowth),

24% (grade II: mild maxillary overgrowth and slight bulging of the frontal and cheek bones) 16.7% (grade III: “chipmunk” facies).

B] Dental Caries: dental caries is a multifactorial infectious disease with many contributory environmental factors, there is also convincing evidence for a genetic component in the etiology of this disease.

C] Periodontal Status and Oral Hygiene: Thalassemia major patients showed a higher plaque index and gingival index (GI) scores compared with the control group.

The GI showed that 49.2% of the thalassemic patients had mild gingivitis (no bleeding on probing), 34.7% moderate gingivitis (bleeding on probing), and 8.3% severe gingivitis (spontaneous bleeding).

D] Tooth and Mucosal Discoloration: Due to chronic jaundice associated with thalassemia, the incorporation of blood pigment bilirubin, degraded product of Hb, in the dentinal tubules during tooth formation results in yellow discoloration of teeth.¹⁵ Tooth discoloration and pallor oral mucosa has been found.

E] Tooth Crown Size and Tooth Size Ratio: In both thalassemic and control groups, males exhibited significantly larger MD than females in most instances. Canines displayed the most sexual dimorphic teeth in the dentition. Lateral incisors showed the greatest variable teeth.^{16,17} The tooth size ratio describes the discrepancy between the sums of MD of mandibular relative to the maxillary teeth.

Lateral incisors showed the greatest variable teeth.^{16,17} The tooth size ratio describes the discrepancy between the sums of MD of mandibular relative to the maxillary teeth. The anterior and overall ratios (sexes pooled) in thalassemic group were 79.1 and 92.0, respectively. The corresponding ratios of the control group were 79.4 and 92.4, respectively. The differences in tooth size ratio between thalassemic and control group were not statistically significant.

F] Dental Arches Dimensions: Measurements showed that the segmental arch lengths in the maxilla and mandible of thalassemic group were reduced by an average of 2.59 and 2.55 mm respectively, compared with the control group.

All arch widths in thalassemic patients were significantly reduced by an average ranging from 1.33 to 1.90 mm in the maxilla and 1.37 to 1.77 mm in the mandible. The mean maxillary and mandibular arch perimeters were reduced by 3.91 and 3.44 mm respectively, in the the Controls(10).

Most orofacial manifestations are in response to the severe hemolytic anemia, chronic hypoxia, and ineffective erythropoiesis, resulting in massive bone marrow hyperplasia and expansion of the marrow cavity.

These changes are mainly manifested as follows: (1) Bossing of the frontal bone, prominence of the malar bone, and maxillary protrusion; (2) thinning of mandibular inferior cortex, faint or absence mandibular canal; (3) enlarged marrow spaces, altered (reduced) trabecular pattern of the mandible; (4) partially obliterated maxillary sinus due to delayed pneumatization [(10).

G] Physical Growth: The cause of growth retardation in TM patients is multifactorial, including chronic anemia and hypoxia, iron overload, racial factors, endocrinopathies, and low socioeconomic status. A marked delay in physical growth of thalassemic patients has been documented in different population groups.

37. **LOW BACK PAIN IN BETA THALASSEMIA MAJOR REVEALING SACRAL EXTRA MEDULLAY HEMATOPOEISIS:** EMH is a well-established complication of thalassemia major and can manifest in variable forms ranging from asymptomatic hepatosplenomegaly to skeletal malformations causing serious adverse effects such as SCC which is rarely encountered but should always be held in mind when assessing patients with TDBT(21).
38. **Lumbar nerve root compression due to extramedullary hemopoiesis in a patient with thalassemia:** a patient suffering from heterozygous b-thalassemia who presented with paraparesis due to spinal cord compression caused by intrathoracic extramedullary hemopoietic masses. In all of them the authors described spinal cord compression syndromes due to epidural EMH. Presented with severe unilateral lumbar radiculopathy caused by an intra- and extraforaminal EMH mimicking far-lateral disc herniation syndrome. Extramedullary hemopoiesis should be considered in cases of sudden onset of nerve root compression syndrome. Limited exposure in most cases of disc surgery and profuse bleeding could make intraoperative diagnosis and subsequent total excision extremely difficult(22).
39. **Evaluation of Endocrine:** the different endocrine involvement between β -TI and β -TM highlights the different impact of iron overload on the two diseases. In effect, severe iron-overload related endocrine dysfunction is universally described in β -TM, while in β -TI the pattern of iron overload is preferentially hepatic, and it develops gradually throughout life(23).
40. **Vitamin D Levels in Thalessemia:** low Vitamin D levels in thalassemia patients. These were attributed to hepatic dysfunction, geographical attitude, and dysfunctions of endocrine tissues. Some researchers have attributed the etiology of Vitamin D deficiency to hepatic iron overload. This shows that thalassemics are at a greater risk for vitamin D deficiency and hence require a greater need for Vitamin D supplementation. the levels of vitamin D are deficient among β -thalassemia major patients on repeated blood transfusion. Hence, it is important to emphasize that treatment of thalassemia patients with aggressive nutritional support which include fortified cereals, fortified milk and supplementation with vitamin D are highly recommended. Supplementation with vitamin D in these children would also help in normalisation of various other growth markers such as calcium, phosphorous and ALP, as they are directly affected by vitamin D activity(24).
41. **Heamocrites:** hypochromic microcytic anemia with reticulocytosis and elevated levels of Hb F and Hb A2. The suppressed ratio of β /a-globin chain b. hypochromatosis are extremely rare in Japan (22). Previously, the causes of hemochromatosis in thalassemics had been considered to be due to excessive iron administration and frequent blood transfusion. Recent study showed that the increased iron absorption secondary to ineffective erythropoiesis could be the major cause of iron overload in thalassemics(25).
42. **Fetal cholelithiasis,** reported as echogenic material in fetal gallbladder in third trimester of pregnancy, is an infrequently encountered condition of uncertain clinical significance(26).
43. **IMPAIRED GLUCOSE TOLERANCE IN CHILDREN WITH BLOOD TRANSFUSION DEPENDENT BETA THALASSEMIA:** Iron overload may cause accumulation of iron in parenchyma tissue of liver and other tissues like heart and pancreas that leads to endocrine complications. Common manifestations are cirrhosis, cardiomyopathies, and damage to pancreas. Early diagnosis at the initial stages

with proper iron chelating therapy and well-timed use of deferoxamine, diabetes can be delayed for many years.³⁻⁷ Abnormal glucose tolerance is the commonest endocrine complication.

Late diagnosis of these cases may result in fatal complication that rise the need of glucose tolerance test and serum ferritin level for early diagnosis and prevention of those complications. Frequency of IGT is high amongst children with thalassemia major having regular blood transfusions (26).

44. **Infections:** spleen is part of your body's defense system against germs. It makes the white blood cells that protect you from infections. An enlarged spleen doesn't work as well as it should, which could make you more likely to get sick. And if you have surgery to remove your spleen, you or your child will be more likely to catch infections like the flu and pneumonia. Getting all your recommended vaccines and taking antibiotics will help to protect you from some of these illnesses. Let your doctor know if your child with beta thalassemia runs a fever. This could be a sign of a serious infection (27).

Conclusion:- In summary, thalassemia, identified by Cooley and Lee in 1925, is a prevalent monogenic blood disorder, with beta-thalassemia being the most common type globally. Beta-thalassemia major requires regular blood transfusions, leading to iron overload and complications. The disorder's epidemiology shows a higher prevalence in specific regions due to genetic diversity and intermarriage.

Beta thalassemia results from over 200 mutations, primarily point mutations in the beta globin gene. Clinical manifestations range from mild to severe, affecting organs beyond the hematological system. Understanding thalassemia's genetic basis is crucial for improved diagnostics and treatment. Ongoing research aims to alleviate the global burden of this disorder.

BIBLIOGRAPHY

1. Wong P, Fuller PJ, Gillespie MT, Milat F. Bone disease in thalassemia: A molecular and clinical overview. Vol. 37, Endocrine Reviews. Oxford University Press; 2016. p. 320–46.
2. Malik S, Syed S, Ahmed N. COMPLICATIONS IN TRANSFUSION-DEPENDENT PATIENTS OF β -THALASSEMIA MAJOR: A REVIEW Complications in transfusion-dependent patients of β -thalassemia major: A review. Pak J Med Sci 2009;25(4):678-682 [Internet]. Vol. 25, Pak J Med Sci. 2009. Available from: www.pjms.com.pk
3. Nemsas P, Arnaoutoglou M, Perifanis V, Koutsouraki E, Orologas A. Neurological complications of beta-thalassemia. Vol. 94, Annals of hematology. 2015. p. 1261–5.
4. Chiew JY, Thiruchelvam J, Bin Rahmat MA, William SP, Bin Shafien ZI, Banerjee KG. The key complications of beta thalassemia major: a review and update. Int J Res Med Sci. 2021 May 27;9(6):1846.
5. Demosthenous C, Eleftheriou P, Apostolou C, Sarafidis P, Perifanis V, Vlachaki E. β -Thalassemia and renal complications. A narrative review of pathophysiologic mechanisms. Integr Mol Med. 2018;5(4).
6. Wong P, Fuller PJ, Gillespie MT, Milat F. Bone disease in thalassemia: A molecular and clinical overview. Vol. 37, Endocrine Reviews. Oxford University Press; 2016. p. 320–46.
7. Kotsis T, Pappas E, Sarmas G, Basilopoulou S, Hatzioannou A, Theodoraki K, et al. Carotid endarterectomy in a young symptomatic patient with b-thalassemia major. Ann Vasc Surg. 2015 May 1;29(4): 838.e1-838.e5.

8. Wong P, Fuller PJ, Gillespie MT, Milat F. Bone disease in thalassemia: A molecular and clinical overview. Vol. 37, *Endocrine Reviews*. Oxford University Press; 2016. p. 320–46.
9. Bai N, Nasir S, Ahmed J, Malik F, Bin Arif T. Beta Thalassemia Major with Gaucher's Disease: A Rare Entity. *Cureus*. 2019 Jul 20.
10. Thalassemia Major and related Dentomaxillofacial Complications: Clinical and Radiographic Overview with Reference to Dental Care. *International Journal of Experimental Dental Science*. 2017 Dec;6(2):95–104.
11. Galanello R, Origa R. Open Access REVIEW BioMed Central Beta-thalassemia [Internet]. Vol. 5, *Orphanet Journal of Rare Diseases*. 2010. Available from: <http://www.ojrd.com/content/5/1/11>
12. Demosthenous C, Vlachaki E, Apostolou C, Eleftheriou P, Kotsiafti A, Vetsiou E, et al. Beta-thalassemia: renal complications and mechanisms: a narrative review. *Hematology (United Kingdom)*. 2019 Jan 1;24(1):426–38.
13. Nemtsas P, Arnaoutoglou M, Perifanis V, Koutsouraki E, Orologas A. Neurological complications of beta-thalassemia. Vol. 94, *Annals of hematology*. 2015. p. 1261–5.
14. Ansari B, Saadatnia M, Asghar Okhovat A. Watershed Infarct in Beta-Thalassemia Major Patient. *Case Rep Neurol Med*. 2017; 2017:1–4.
15. Chiew JY, Thiruchelvam J, Bin Rahmat MA, William SP, Bin Shafien ZI, Banerjee KG. The key complications of beta thalassemia major: a review and update. *Int J Res Med Sci*. 2021 May 27;9(6):1846.
16. Malik S, Syed S, Ahmed N. COMPLICATIONS IN TRANSFUSION-DEPENDENT PATIENTS OF β -THALASSEMIA MAJOR: A REVIEW Complications in transfusion-dependent patients of β -thalassemia major: A review. *Pak J Med Sci* 2009;25(4):678-682 [Internet]. Vol. 25, *Pak J Med Sci*. 2009. Available from: www.pjms.com.pk
17. Zafeiriou DI, Economou M, Athanasiou-Metaxa M. Neurological complications in β -thalassemia. Vol. 28, *Brain and Development*. 2006. p. 477–81.
18. Kotsis T, Pappas E, Sarmas G, Basilopoulou S, Hatzioannou A, Theodoraki K, et al. Carotid endarterectomy in a young symptomatic patient with b-thalassemia major. *Ann Vasc Surg*. 2015 May 1;29(4): 838.e1-838.e5.
19. Jafari R, Heydarian S, Karami H, Shektaei MM, Dailami KN, Amiri AA, et al. Ocular abnormalities in multi-transfused beta-thalassemia patients. *Indian J Ophthalmol*. 2015 Sep 1;63(9):710–5.
20. Logothetis J, Economidou J, Constantoulakis M, Augoustaki O, Loewenson RB, Bilek M, et al. Cephalofacial Deformities in Thalassemia Major (Cooley's Anemia) A Correlative Study Among 138 Cases [Internet]. Available from: <http://archpedi.jamanetwork.com/>
21. Ahmad R, Okar L, Almasri H, Sharaf Eldean MZ, Sharaf Eldean M, Elhiday A, et al. LOW BACK PAIN IN BETA THALASSEMIA MAJOR REVEALING SACRAL EXTRA MEDULLAY HEMATOPOEISIS: A CASE REPORT. 2020; Available from: <https://doi.org/10.22541/au.160133616.60792273>
22. article 26 by tsitsopoulos.

23. Baldini M, Marcon A, Cassin R, Ulivieri FM, Spinelli D, Cappellini MD, et al. Beta-thalassaemia intermedia: Evaluation of endocrine and bone complications. *Biomed Res Int.* 2014;2014.
24. Janardhanan J. Study of Vitamin D Levels in Thalessemia Major Patients in Children. *Journal of Medical Science and Clinical Research* [Internet]. 2019 Jul 11;7(7). Available from: <http://jmscr.igmpublication.org/v7-i7/49%20jmscr.pdf>
25. Uchihara M, Noucm T, Harano T, Yamane M, Sakai H, Takabe K, et al. å; CASE REPORT å; /T-
Thalassemia with Hemochromatosis. Vol. 31, *Internal Medicine.* 1992.
26. Roussou P, Tsagarakis NJ, Kountouras D, Livadas S, Diamanti-Kandarakis E. Beta-thalassemia major and female fertility: The role of iron and iron-induced oxidative stress. *Anemia.* 2013;2013.
27. article 30 by watson.

