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Thalassemic child`s Bones, joints and skin

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Abstract:
Thalassemia an autosomal recessive disorder, it's the commonest monogenic disorder, its name derived from Greek words thalassa "sea" and haema "of blood", it was described in people lived around the Mediterranean, the Middle East, and Southeast Asia, but due to migration, now be found across the world.
The pathophysiology of the disease and its subsequent treatments affect almost every organ system, so the severe anemia, growth retardation, skeletal disturbances, iron overload, cardiac and endocrine abnormalities lead to shorting the life of thalassemic patients, bony and skin involvement is common but poorly understood ,affecting both younger and relatively older patient, presented diagnostic and therapeutic challenges.

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I. Introduction:

Thalassemia is the most common monogenic disorder[1], and it's mutations of either α or β globin chains results in abnormal structurally hemoglobin[2] causing reduced or absent in hemoglobin production, leading to reducing oxygen delivery[3].

α-Thalassemia :
caused by gene deletions on chromosome 16 of the α chain, inheritance in autosomal recessive manner, There are four clinical subtypes of α-thalassemia syndromes:
Alpha thalassemia silent carrier: one gene missing.
Alpha thalassemia carrier: tow genes missing.
Hemoglobin H disease: three genes are missing.
Alpha thalassemia major: all 4 genes missing.
It classified according to the number of the gene deletions, and also corresponding to their clinical severity[4].

β-Thalassemia:
mutations in the globin gene, on chromosome 11, which encodes the beta subunit of the most common form of adult hemoglobin HbA, mutations either abolish (β0) or reduce (β+) the β globin synthesis, results in ineffective erythropoiesis, chronic hemolysis, and profound life threatening anemia
Beta thalassemia major(Cooley's anemia): there are 2 damage genes.
Beta thalassemia minor or trait: only one gene damage, and it subdivided into; minima, and intermedia[5].
The hypochromic and microcytic erythrocytes aggregate and precipitate causing early destruction, and the bone marrow space enlarges to compensate for ineffective erythropoiesis[6].

Iron Overload:

Recurrent blood transfusion especially for β-thalassemia major improved the quality and the expectancy of the patients life[7], if no properly management with chelation therapy, the patients generally die in the second or third decade from the side effects of transfusion related hemochromatosis[8], deposition of the iron in parenchymal tissues starts within 1 year of regular transfusions which can be reduced by using subcutaneous deferoxamine[9], but this therapy by itself may induce dysplastic bone changes in the long bones and leas to short stature[10].

Normal body store of iron are 3–4g, it needed for many essential and basic cellular functions, the limited capacity of the body to excrete iron made any excess of iron, 20 g or more, lead to organic damage[11], so iron overload as well as iron deficiency may weakened the bones[12], as well as heart, liver, spleen, endocrine glands problems and increases risks of serious infections are also described in these patients due to the iron overload[13].

Each unit of packet red blood cells transfused contains approximately 200–250 mg of iron, leading to increased free iron and the overload occurs after 10 to 20 consecutive transfusions[14], which is highly toxic to

the cells[15], iron overload can be assessed by indirect markers serum ferritin and transferrin saturation, liver biopsy or MRI [16].

Bone and joint in thalassemia:

The osteoclasts and osteoblasts are the two major cell involved in bone remodeling, the osteoclasts for the resorption of bone tissue, and osteoblasts with a role of new bone tissue formation.

Differentiation and activity of these two cell are very important for preserve skeletal health integrity throughout life[17], abnormalities are multifactorial due to iron deposition, drug therapy, abnormal mineral homeostasis, bone turnover, and endocrine abnormalities[18].

Abnormalities in bone metabolism can be prevented in thalassemic child by adequate iron chelation, maintaining target hemoglobin, optimal calcium and vitamin D levels, with life style modification[19].

Osteoporosis

A common musculoskeletal problems due to the anatomic bones and joints proximity to the active centers of hematopoiesis[20],

In the untreated or poorly transfused thalassemic patients , chronic anemia increases erythropoietin secretion and this changes results primarily from marked erythroid hyperplasia which is secondary to ineffective erythropoiesis[21],lead to marrow proliferation, widening of the medullary space in both cortical and cancellous bones which can be expanded up to 15 - 30 times to the untreated patients[21], cortical thinning, resorption and generalized decrease in osseous density (osteopenia/ osteoporosis)[22], hand by hand with other factors for the reduction of bone mass, such as delayed sexual maturation, Growth Hormone (GH) and insulin growth factor-1 deficiency, parathyroid gland dysfunction, chronic liver disease[23], direct excessive iron toxicity on osteoblasts interferes with maturation of osteoid and deposits in hydroxyapatite crystals thus interfering with normal bone metabolism.

The desferoxamine inhibits DNA synthesis, proliferation, and maturation of fibroblasts and osteoblasts[24]

The Bisphosphonates, which have a good profile of safety and tolerability improve bone mineral density, reduce bone turnover, and decrease bone pain in patients with thalassemia-associated osteoporosis[25].

Joint problems:

1-Iron overload-related arthritis[26].

2-Septic arthritis: Salmonella enteritidis is an infrequent cause of septic arthritis, even in developing countries where the Salmonella infection is endemic.

The infection is usually caused by consumption of contaminated foods, most patients develop gastroenteritis resolves without any treatment [27].

3- Deferiprone-related arthropathy: Many thalassaemic patients are transfusion dependent and thus are managed with chelation therapy. Several studies have reported an increased incidence of arthropathy (16–30%)[28].

4- Crystal arthritis: hyperuricaemia is frequent but clinical gout is not, and because of renal function impairment it is important to consider gout in the differential diagnosis of soft-tissue lesions in thalassaemia patients with chronic arthritis[29].

5- Joint effusions: frequently developed secondary to non-inflammatory processes, some time because of vasoocclusion at articular surfaces [30].

B-Bony problems:

1-Fractures: Children and adolescents sustain more fractures than adults due to direct or indirect minor trauma, especially in the more severe variety of beta thalassemia major[31], and because of low bone mineral density fracture rates as high as 71% than non thalassemic child[32].

2-Aseptic necrosis of the femoral head: chronic recurring hypoxia and the rigid and ‘less-deformable’ red blood cells with marrow hyperplasia may compress the intramedullary branches of the nutrient artery and compromised blood flow, the multiple microfractures in osteoporotic bone contribute to osteonecrosis too[33].

3-Scoliosis: with small curves from5-19 degree that not need active orthopedic treatment[34].

4-Early fusion of epiphyses - Growth disturbances: It may be unilateral or bilateral, more frequently affects the proximal humeri and the distal femurs and rarely the proximal or distal tibia and fibula[35].

Skin manifestations

skin diseases especially pallor, pruritus, jaundice and xerosis are observed frequently in patients with beta-thalassemia major, in patients receiving desferoxamine.

Serum ferritin high levels associated with xerosis, hyperpigmentation.

Leukonychia (white streak), gingivitis are common nail and oral mucosa changes, and alopecia[36]

II. Conclusion:

The bone disease are unique compared to those of the more typical idiopathic osteoporosis, scoliosis, bone and joint seen in the general community.

Arthralgia and low back pain are among the most common complaints, ischaemic crampy pain, postural pulsating pain, synovitis post-transfusion haemosiderosis.

The purpose of this review is to highlight the musculoskeletal complications of thalassaemia, and rheumatologists and orthopaedic surgeons are strongly encouraged to take part in the multidisciplinary approach to the management of this debilitating disease.

Our understanding of thalassemia bone disease is incomplete, given the complex piecemeal collection of risk factors, which includes hormonal deficiency, marrow expansion, iron toxicity, chelator toxicity, and increased bone turnover.

Because cutaneous manifestations are common with beta-thalassemia major patients and are usually unfortunately neglected and underdiagnosed , regular dermatological follow up recommended in the early management.

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