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RESEARCH ARTICLE

Frequency of musculoskeletal and otorhinolaryngologic manifestations in children with B-thalassemia

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Abstract

Background : Beta-thalassaemias have a wide variety of musculoskeletal system manifestations. Spinal involvement related to disease course and treatment is common in patients with thalassemia syndromes. Also, a high frequency sensorineural hearing loss is observed in a large percentage of patients during intensive desferrioxamine therapy. **Aim :**To study the clinical and radiographic skeletal changes in transfusion-dependent beta-thalassaemia patients and to present a comprehensive overview of spinal involvement in those patients. **Patients and Methods :**This cross sectional study was carried out on **240** patients with β-thalassemia major who came weekly for blood transfusion at the hematology outpatient clinic of Pediatric Department at Zagazig University hospital during a period from 2012-2013. In all patients studied, detailed history regarding musculoskeletal involvement was taken and locomotor examinations were performed. Also, preliminary auditory perceptual assessment of patient's voice and careful laryngeal examination. All patients underwent all routine laboratory investigations (CBC, Serum iron and ferritin, Liver and renal functions) , Imaging study with standing anteroposterior and lateral X-rays of the spine, Ultra sonography on affected knee (s) joint , augmentation and documentation of the glottic picture and high-fidelity voice recording and acoustic analysis was done. **Results :** locomotor system involvement was found in 56 patients (23.3 %). Most frequent complaints were arthralgia and low back pain in 21.3% and 6.3% of patients respectively. Scoliosis was detected radiologically in 8 patients (3.3%). The most common curve pattern in thalassemia was the left lumbar (62.5 %) followed by the right lumbar (37.5). Ultrasonography of affected knee (s) joint showed synovitis , effusions , signs of metaphysis dysplasia and increased power Doppler signals in (23.8% ,14.3 %,85.7% ,19 % respectively). There was mild to moderat laryngeal congestion nearly in all cases but the vocal fold mobility (crico-arytenoid joint) is not affected. **Conclusions :**Patients with beta thalassemia have a variety of musculoskeletal problems and spinal involvement is common. Further studies will be needed to detect the risk factors involved in the development of these musculoskeletal problems.

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INTRODUCTION

β-thalassemia, an inherited disorder of hemoglobin synthesis, is the most common monogenetic disease worldwide. Patients with thalassemia major (TM) suffer a severe anemia that requires regular blood transfusions for survival and iron chelation therapy to control transfusional iron overload [(1)].

Increased survival in patients with β-thalassemia major (TM) allowed for several complications of the disease and its treatment to manifest , one of which is bone disease. [(2)]. The pathogenesis of bone changes in patients with βTM is not yet completely understood. However, an unbalance in bone mineral turnover resulting from increased resorption and suppression of osteoblast activity has been detected in βTM patients. The abnormal regulation of bone metabolism may be related to hormonal and genetic factors, iron overload and iron chelation therapy, nutritional deficits, and decreased levels of physical activity [(3)].

β-thalassaemias have a wide variety of musculoskeletal system manifestations. Most frequent complaints were arthralgia and low back pain and in 40% of patients with a lateral curve of at least 5° Cobb [(4)]. Back pain is common in adult patients with homozygous thalassaemia and degenerative disc disease is increasingly recognized as a cause [(5)]. osteoporosis, growth retardation, platyspondyly and kyphosis also reported as skeletal changes in untreated thalassemia [(6)] **.**

Ear impairment due to extramedullary marrow growth in the middle ear has been reported, especially in those patients where transfusion was avoided. Marrow expansion may lead to pathological fractures and sinus and middle ear infection due to ineffective drainage. Also, a high frequency sensorineural hearing loss is observed in a large percentage of patients during intensive Desferrioxamine therapy[(7)].

The Aim of this study is to assess the clinical and radiographic skeletal changes in transfusion-dependent beta-thalassaemia patients and to identify a comprehensive overview of spinal involvement in those patients.

PATIENTS AND METHODS

This descriptive cross-sectional study was carried out at Hemotology outpatients clinic of Pediatric department, ENT department and Rheumatology and Rehabilitation department of Zagazig University Hospitals, during a period from the beginning of November 2012 to the end of November 2013. The study included 240 transfusion dependent thalassemic patients on their regular follow up visits in outpatient clinic of hematology unit of Pediatric Department at Zagazig University Hospital.

An informed written consent of participation in the study was signed by the parents or legal guardians of the studied subjects. This study was approved by the Ethical Research Committee , Faculty of medicine , Zagazig University.

A detailed history was taken from all the patients and they underwent complete musculoskeletal examination including examination of the spine by a rheumatologist.

All patients were subjected to:

- **Examination of musculo-skeletal system:** 1-Inspection: swelling (effusion or bony swelling), deformity, muscle wasting. 2- Palpation: hotness, tenderness, crepitus, 3- Range of movement: active and passive .4- The following joints were examined: shoulders, elbows, wrists, metacarpophalangeal (MCPs), proximal and distal interphalangeal (PIPs and DIPs), hips, knees, ankles, metatarso-phalangeal joints.
- **Examination of the spine:** It includes examination of cervical, dorsal and lumbosacral regions as regard: curvature, deformity, swelling, tenderness, muscle spasm, scar of operation and special tests as tests for Low back pain as straight leg raising test and femoral stretch test[(8)]**.**
- **Elementary Diagnostic Procedures:** This includes the patient's interview, the preliminary auditory perceptual assessment of patient’s voice and careful laryngeal examination.
- **Clinical Diagnostic Aids:** This includes augmentation and documentation of the glottic picture and high-fidelity voice recording.
- **Additional Instrumental Measures:** At this level, acoustic analysis was done using the Vocal Assessment Program from Dr. Speech 4.5 software [(9)].
- **Laboratory investigations:** ESR, CRP , CBC ,Fasting blood sugar, ferritin level.

- **Imaging study:** X-ray for The spine both antero-posterior and lateral views, X-ray for both knees, Musculoskeletal ultrasound of both Tempro-mandibular joint (TMJ), knees, elbows, ankles, SCJ, hip joints.
- **Knees Ultrasound:** US of the inflamed knee was performed with a 5-12 MHz linear probe (madison R3). Synovitis and knee effusion was defined according to the published OMERACT definitions [(10)]. Active synovitis was defined with intra_articular power Doppler signals. Longitudinal images of the peripheral physis and metaphysis of the distal left femur and the proximal tibia and fibula were obtained for evaluation. The sonographic diagnosis of dysplasia was based on the detection of 2 of the following 3 features: (1) notching at the metaphyseal corner, (2) a blurred or irregular peripheral juxtaphyseal metaphyseal contour, and (3) widening of the peripheral juxtaphyseal metaphyseal echogenic interface [(11)].

Score Definitions: [(12)].
Grey Scale (GS) – hypoechoic synovial thickening
• **Grade 0:** None
• **Grade 1:** Mild [filling the angle between the peri- articular bones without bulging over the line linking tops of the bones]
• **Grade 2:** Moderate [bulging over the line with predominantly flat or concave upper surface]
• **Grade 3:** Severe [bulging over the line with a convex upper surface]
Power Doppler (PD) - vascularisation of synovium
• **Grade 0:** No flow in the synovium
• **Grade 1:** Isolated spots of signal (up to 3 single or 2 confluent)
• **Grade 2:** Vessel signals in <50% of the area of the synovium
• **Grade 3:** Vessel signals in ≥50% of the area of the synovium

Statistical Analysis:

Analysis was performed using Statistical Package for Social Sciences version 15.0 (SPSS, inc., Chicago, USA). Complementary statistical methods, independent-t test Mann-Whitney U and Chi-square tests were used. All of the results were demonstrated as mean ± standard deviation. A p value less than 0.05 was considered as statistically significant.[(13)]

RESULTS

Table (1): Demographic and clinical data of the studied cases

	Number (Total=240)	Percentage (%)
Sex		
Male	**133**	**55.4 %**
Female	**107**	**44.6 %**
Age (year)		
Mean ± SD	**11.73 ± 6.98**	
(Range)	**(7– 20)**	
Duration of transfusion (year)		
Mean ± SD	**10.53 ± 5.99**	
Median (Range)	**10 (0.25 – 30.4)**	
Chelating agent use		
Irregular	**105**	**43.8 %**
Regular	**135**	**56.3 %**
Spleenectomy		
No	**198**	**82.5 %**
Yes	**42**	**17.5 %**
Ferritin level (ng/dl)		
Median (Range)	**2100 (95 – 18758)**	
Hemoglobin level (g/dl)		
Mean ± SD	**7.308 ± 1.46**	

ENT examination

-ve	**229**	**95.4 %**
+ve	**11**	**4.58 %**
Joint affection		
-ve	**184**	**76.7%**
+ve	**56**	**23.3%**
Knee joint affection		
-ve	**219**	**91.25 %**
+ve	**21**	**8.75 %**
Elbow joint affection		
-ve	**237**	**98.75 %**
+ve	**3**	**1.25 %**
Ankle joint affection		
-ve	**223**	**92.9 %**
+ve	**17**	**7.1 %**
Tempromandibular joint affection		
-ve	**234**	**97.5 %**
+ve	**6**	**2.5 %**
Sacroiliac joint affection		
-ve	**225**	**93.75 %**
+ve	**15**	**6.25 %**
Spine affection		
-ve	**228**	**95 %**
+ve	**12**	**5 %**
Hip joint affection		
-ve	**236**	**98.3 %**
+ve	**4**	**1.7 %**
Cricoarytenoid joint affection		
-ve	**240**	**100 %**
+ve	**0**	**0 %**

Table (2): Distribution of peripheral joints involvement among cases with locomotor system affection

	Right (n = 20)	**Left (n = 25)**	**Bilateral (n = 21)**
Knee joint (n = 21)	**6 (28.5 %)**	**7 (33.4 %)**	**8 (38.1 %)**
Elbow joint (n = 3)	**1 (33.3 %)**	**1 (33.3 %)**	**1 (33.3 %)**
Ankle joint (n = 17)	**5 (29.4 %)**	**3 (17.7 %)**	**9 (52.9 %)**
TMJ (n = 6)	**1 (16.7 %)**	**5 (83.3 %)**	**0 (0 %)**
Sacroiliac joint (n = 15)	**4 (26.7 %)**	**8 (53.3 %)**	**3 (20 %)**
Hip joint (n = 4)	**3 (75 %)**	**1 (25 %)**	**0 (0 %)**

TMJ : Tempromandibular joint affection

Table (3): Frequency of spinal involvement among studied cases

	Number (Total = 240)	**Percentage (%)**
Congenital deformity	**0**	**0**
Spinal fracture	**0**	**0**
+ve FNST	**4**	**1.66**
Scolosis	**8**	**3.33**
Right lumbar (Total = 8)	**3**	**37.5**
Left lumbar (Total = 8)	**5**	**62.5**

FNST: Femoral nerve stretch test

Table (4) : ultrasonographic finding s of the affected knee joint

	Number (Total =21)	Percentage (%)
Synovitis	**5**	**23.8 %**
Effusion	**3**	**14.3 %**
Normal power doppler signals	**0**	**0 %**
Increase power doppler signals	**4**	**19 %**
Signs of metaphysis dysplasia	**18**	**85.7%**
- Signs of dysplasia at distal femoral metaphysis	**11**	**61.1 %**
-Signs of dysplasia at proximal tibial metaphysis	**12**	**66.6 %**
-Signs of dysplasia at proximal fibular metaphysis	**3**	**16.6 %**

Table (5): Relation between serum ferritin level and peripheral joint affections

	Ferritin level			**P**
	Mild (n=4)	**Moderate (n=27)**	**Marked (n=29)**	
Knee affection (n=21)	**1 (4%)**	**10 (48%)**	**10 (48%)**	**0.892**
Elbow affection (n=3)	**0 (0%)**	**2 (66.7%)**	**1 (33.3%)**	**0.709**
Ankle affection (n=17)	**2 (11.8%)**	**8 (47%)**	**7 (41.2%)**	**0.549**
TMJ affection (n=6)	**0 (0%)**	**2 (33.3%)**	**4 (66.7%)**	**0.574**
SCJ affection (n=15)	**0 (0%)**	**4 (26.7%)**	**11 (73.3%)**	**0.055**
Hip affection (n=4)	**0 (0%)**	**1 (25%)**	**3 (75%)**	**0.523**
Spine affection (n=12)	**0 (0%)**	**4 (33.3%)**	**8 (66.7%)**	**0.287**

Table (6): Relation between joint ultra-sonography and serum ferritin level

	Ferritin level			*P*
	Mild (*n*=4)	**Moderate (*n*=25)**	**Severe (*n*=27)**	
Knee arthritis				
Grade I (*n*=12)	**1 (8.3%)**	**6 (50%)**	**5 (41.7%)**	**0.609**
Grade II (*n*=9)	**0 (0%)**	**4 (44.4%)**	**5 (55.6%)**	
Elbow arthritis				
Grade I (*n*=2)	**0 (0%)**	**1 (50%)**	**1 (50%)**	**0.386**
Grade II (*n*=1)	**0 (0%)**	**1 (100%)**	**0 (0%)**	
Ankle arthritis				
Grade I (*n*=14)	**2 (14.3%)**	**8 (57.1%)**	**4 (28.6%)**	**0.074**
Grade II (*n*=3)	**0 (0%)**	**0 (0%)**	**3 (100%)**	
TMJ arthritis				
Grade I (*n*=2)	**0 (0%)**	**1 (50%)**	**1 (50%)**	
Grade II (*n*=3)	**0 (0%)**	**0 (0%)**	**3 (100%)**	**0.153**
Grade III (*n*=1)	**0 (0%)**	**1 (100%)**	**0 (0%)**	
SCJ arthritis				
Grade I (*n*=4)	**0 (0%)**	**2 (50%)**	**2 (50%)**	
Grade II (*n*=10)	**0 (0%)**	**1 (10%)**	**9 (90%)**	**0.071**
Grade III (*n*=1)	**0 (0%)**	**1 (100%)**	**0 (0%)**	
Hip arthritis				
Grade I (*n*=3)	**0 (0%)**	**1 (33.3%)**	**2 (66.7%)**	**0.505**
Grade II (*n*=1)	**0 (0%)**	**0 (0%)**	**1 (100%)**	

Mild ferritin level : ≤ 1000 (ng/dl)
Moderate ferritin level : 1000 -3000 (ng/dl)
Severe ferritin level : > 3000 (ng/dl)

Table (7):Relation between joint ultra-sonography grading and the use of chelating agent

	Chelating agent use		*P*
	Irregular (*n*=32)	**Regular (*n*=24)**	
Knee arthritis			
Grade I (*n*=12)	**6 (50%)**	**6 (50%)**	**0.801**
Grade II (*n*=9)	**5 (55.6%)**	**4 (44.4%)**	
Elbow arthritis			
Grade I (*n*=2)	**0 (0%)**	**2 (100%)**	**0.083**
Grade II (*n*=1)	**1 (100%)**	**0 (0%)**	
Ankle arthritis			
Grade I (*n*=14)	**8 (57.1%)**	**6 (42.9%)**	**0.072**
Grade II (*n*=3)	**0 (0%)**	**3 (100%)**	
TMJ arthritis			
Grade I (*n*=2)	**1 (50%)**	**1 (50%)**	
Grade II (*n*=3)	**2 (66.7%)**	**1 (33.3%)**	**0.513**
Grade III (*n*=1)	**0 (0%)**	**1 (100%)**	
SCJ arthritis			
Grade I (*n*=4)	**4 (100%)**	**0 (0%)**	
Grade II (*n*=10)	**6 (60%)**	**4 (40%)**	**0.122**
Grade III (*n*=1)	**0 (0%)**	**1 (100%)**	
Hip arthritis			
Grade I (*n*=3)	**1 (33.3%)**	**2 (66.7%)**	**0.505**
Grade II (*n*=1)	**0 (0%)**	**1 (100%)**	

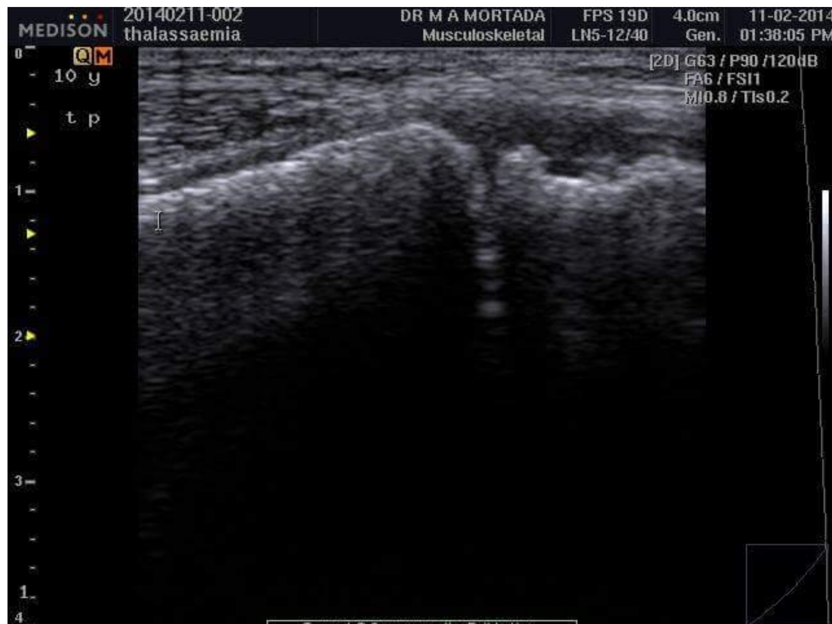


Figure (1): Grey scale US of right knee of 10 years old boy shows irregular peripheral juxtaphyseal metaphyseal contour corner

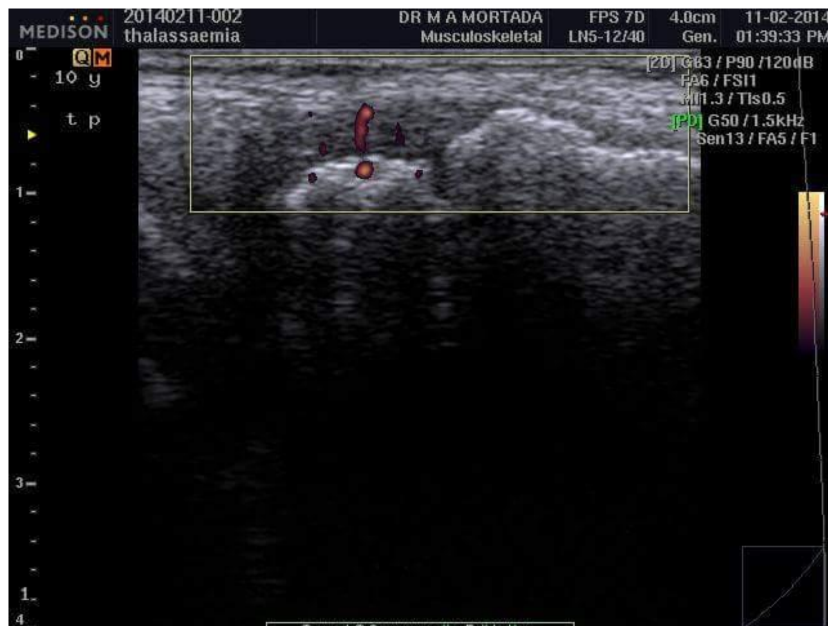
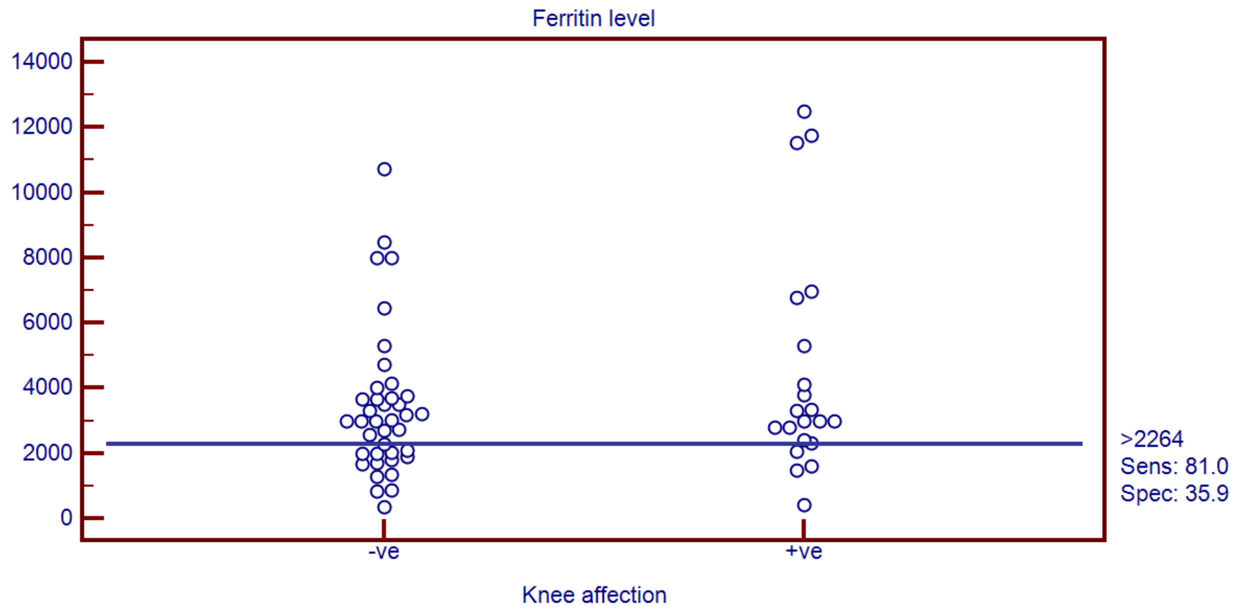


Figure (2): Doppler scale US of right knee of 10 years old boy shows grade I Doppler activity

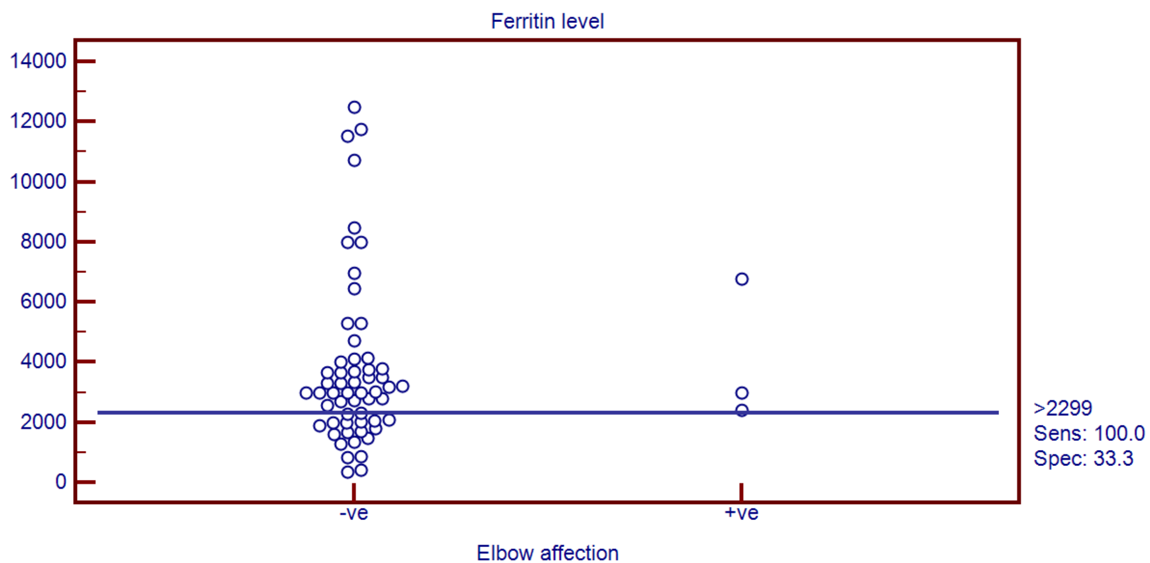
Knee affection



Cutoff	Sens.	Spec.	PPV	NPV	Accuracy
> 2264	81 %	35.9 %	40.5 %	78 %	0.573

Figure (3): correlation between serum ferittin and knee joint affection.

Elbow affection



Cutoff	Sens.	Spec.	PPV	NPV	Accuracy
> 2299	100 %	33.3 %	7.3 %	100 %	0.553

Figure (4): correlation between serum ferittin and elbow joint affection.

Results

Two hundred forty thalassemic patients (133 males and 107 females) with a mean age of 11.73 ± 6.98years (Range 7 – 20) were recruited into our study. They were on blood transfusion for 10.53 ± 5.99 years. One hundred thirty five patients (56.3%) were regularly on iron chelating therapy, table (1).

Joint involvement was found in 56 of our patients (23.3%), with the most affected joint was the knee (21 patients)followed by ankle then sacroiliac joints and spine 17, 15, 12 respectively, table (1).

Our results showed that bilateral joint affection was more frequently affecting knee and ankle joints, table (2).

Scoliosis was found in only 8 paients; five of them with left sided curvature, table (3).

Ultrasonography of affected knee (s) joint showed synovitis , effusions , signs of metaphysis dysplasia and increased power Doppler signals in (23.8% ,14.3 %,85.7% ,19 % respectively, table (4).

Our results showed no significant relation between serum ferritin level and peripheral joint affections. About 66.7% of cases with tempro-mandibular joint and spine affections was associated with marked elevation of serum ferritin. table (5).

There was no statistical significant correlation between the level of serum ferittin and the grade of joint affection by ultrasonography, with more joint affection in moderate and severe elevation of serum ferittin, table (6).

There was no statistical significant correlation between the regularity of iron chelators and the grade of joint affection by ultrasonography, table (7)

There was mild to moderate laryngeal congestion nearly in all cases but the vocal fold mobility (crico-arytenoid joint) is not affected.

DISCUSSION

The underlying mechanisms of skeletal involvement in thalassemia are complex. Patients suffer hemolysis and subsequent tissue hypoxia, as a result of their globin dysfunction[14,15]. As other regulatory mechanisms are preserved, patients develop intramedullary bone marrow hyperplasia in reaction to this hypoxia. It is now recommended that patients be transfused to hemoglobin levels of 110-120 g/I to decrease tissue hypoxia and erythropoietin secretion. Splenectomy is also indicated in severe forms of hemolysis [,16,17].

The spine is commonly affected by scoliosis ,kyphosis and osteoporosis. Despite supportive treatment fractures are common affecting around 30% of patients (with 20% suffering multiple fracture) [18] .

In patients with TM, genetic and acquired risk factors lead to osteoporosis, pathologic fractures of the spine and back pain. Osteoporosis in TM patients is progressive; thus, early diagnosis and treatment are recommended. Characteristic intervertebral disc degeneration is also seen in patients with TM who have evidence of severe iron overload or those who receive the subcutaneous iron chelator deferoxamine. Spinal asymmetry and overt scoliosis are common in patients with TMJ [1].

locomotor system involvement was found in 56 of our patients (23.3%). Most frequent complaints were arthralgia and low back pain in 21.3% and 63% of patients respectively. This data is in agreement with Onur et al who found that locomotor system involvement was found in 12 of 20 patients (60%) and most frequent complaints were arthralgia and low back pain in 30% and 25% of patients respectively [4].

Our study showed that scoliosis was detected radiologically in 8 patients (3.3%). This data disagrees with Onur et al who reported that scoliosis was detected radiologically in 40% of patients with a lateral curve of at least 5° Cobb ([4]). Haidar et al reported that spinal asymmetry and overt scoliosis are common in patients with TM and the prognosis seems favorable, with many patients showing spontaneous resolution without the need for intervention (1).

About 66.7% of our cases with spine affections was associated with marked elevation of serum ferritin. Korovessis et al found that the level of ferritin was significantly ($p = 0.025$) higher in the thalassemic patients with scoliosis than in those without scoliosis(18).

The most common curve pattern among our thalassemic patients was the left lumbar (62.5%) followed by the right lumbar (37.5%). Korovessis et al reported in their study that the most common curve pattern in thalassemia was the left lumbar (38%) followed by the right lumbar (21%), and no patient with thalassemia showed radiographic signs of congenital spinal deformities and spinal fractures [18].

Among the spinal deformities observed, Papanastasiou et al suggest that an increased prevalence of frontal curves was reported of at least, 5° in 67% of patients with TM. However, scoliosis curvatures of more than 10° and less than 14° were observed in 21.7% of examined patients. The prevalence of scoliosis was not gender related, irrespective of age and curve magnitude [19].

Arthropathy is the most common side effect of chelation therapy. various studies report joint symptoms to be observed in 20% of patients [20]. The condition affects mainly the knees, but other joints may be involved as well, like ankles, wrists, elbows and shoulders[21]. It is speculated that deferiprone-induced shifts of iron to synovium resulted in tissue damage and was accelerated by free radical formation during incomplete complexation of iron and this bidentate chelatoin [22].

Our study found non significant relation between the regular use of iron chelators and joint affections . This is in agreement with Drakonak et al who reported that there was no significant correlation between the presence of joint abnormalities and the therapy protocol [23].

In our patients ultrasono-graphy of affected knee (s) joint showed synovitis, effusions, signs of metaphysis dysplasia and increased power Doppler signals in (23.8%, 14.3%, 85.7%, 19%) respectively. Kellenberger et al. studied 14 patients receiving DFP and observed radiographic changes in 86% of cases. The changes (which they classified as mild, moderate, or severe) were joint effusion, patellar beaking, and subchondral flattening of the femoral condyles. The metaphyses were normal and the growth plates were not widened [21].

Also , Drakonak et al found an abnormalities in 21/40 (52.5%) knees of thalassemic patients and included small suprapatellar effusion (21/40, 52.5%) with the presence of supra- or parapatellar synovial folds (8/40, 20%) [23].

In a report case indirect laryngoscopy showed marked edema of the left arytenoid mucosa and false vocal cord. The true vocal cord was obscured by a ventricular band. The glottic opening was diminished on deep inspiration. The right side of the larynx, however, appeared normal(24). In our patients there was mild to moderate laryngeal congestion nearly in all cases but the vocal fold mobility (crico-arytenoid joint) is not affected.

Conclusions

spinal involvement in patients with β-thalassemia is common and further research is warranted to evaluate the mechanisms, clinical implications, and optimal management of bone disease in this patient population.

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