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EVALUATION OF THALASSEMIC PATIENTS FOR HYPERURICEMIA, IRON STATUS AND THEIR IMPACT ON MUSCULOSKELETAL SYSTEM

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ABSTRACT

Background: Thalassemias, inherited hemoglobin synthesis defects, cause ineffective erythropoiesis, increased red blood cell destruction, reduced red blood cell life span, and chronic hemolytic anemia, with treatment involving blood transfusions leading to iron overload. **Objectives:** To assess serum uric acid and serum ferritin levels and their effect on the joints and their relation to the splenectomy and the gender in thalassemic patients. **Patients and Methods:** Case series study of 52 patients with beta thalassemia major (TM) from Thalassemia Center in Ibn-alatheer Teaching Hospital (34 males and 18 females) with age between 6 and 26 years. Venous blood samples were obtained from the patients and were analyzed for serum ferritin level, serum uric acid level and hemoglobin level. Any patient with articular or bone complain was sent for radiological assessment. **Results:** fifteen patients (28.9 %) with articular manifestation have only joint pain. The knee pain was in 13.5% of the patients, low back pain in 13.5 %, while the ankle affected only one patient (1.9%). In this study, it has been found that there is no significant relation between the serum ferritin and uric acid level with joint pain (p= 0.350 and 0.215 respectively). There is a significant effect of splenectomy on serum ferritin level p=0.042. Male patients showed a high serum ferritin level than female ones (p=0.033). The study also reveals that there is no significant relation between frequency of blood transfusion and the level of both serum uric acid and ferritin, yet significant relation exists with hemoglobin level p=0.029. **Conclusion:** Serum ferritin levels can be controlled with iron chelation agents, reducing iron overload impact on the musculoskeletal system. However, recurrent blood transfusions and improper chelating can lead to iron accumulation and secondary heamochromatosis. Most patients have normal uric acid levels.

KEYWORDS: Hyperuricemia, Iron Status, Musculoskeletal System, Thalassemia.

INTRODUCTION

Thalassemias are inherited hemoglobin synthesis defects causing ineffective erythropoiesis, increased red blood cell destruction, reduced red blood cell lifespan, and chronic hemolytic anemia. β thalassemia is the most common type, affecting the "thalassemia belt" from the Mediterranean Sea to Southeast Asia.[1,2] Treatment involves regular blood transfusions to maintain pre-transfusion levels between 9 and 10.5 g/dl, promoting growth, allowing normal physical activity, inhibiting bone marrow activity, and minimizing iron accumulation.[3,4]

Thalassemia can lead to iron overload due to Hb instability, RBC transfusion, and increased iron absorption. Over 20 g of excess body iron can accumulate in four years. Assessing iron overload after 10 packaged transfusions and at age 10 is crucial. Iron chelating therapies (ICTs) are used to balance excess iron loads and reverse heart failure.[5,6]

Deferoxamine, Deferiprone and Deferasirox are oral iron chelators used to treat iron overload in children. Deferoxamine can cause richitic bone changes and genu valgus in young children, while Deferiprone can cause serious complications like agranulocytosis, mild arthralgia, and arthritis. Deferasirox has no associated side effects.[7]

Thalassemia patients may experience joint arthropathy due to secondary iron overload, causing painful swelling without obvious inflammatory changes.[8] Distal

interphalangeal joint disease usually associated with osteoarthritis, affects wrist, elbow, shoulder, and knee joints. Changes include chondrocalcinosis, joint space loss, subchondral cysts, and osteophyte formation.[9] Hyperuricemia and gout in β-thalassemia patients increase with age and hyperuricemia degree, but most never experience symptoms like gouty arthritis, tophi, or kidney stones.[10]

The study aimed to evaluate the impact of hyperuricemia and hyperferritinemia on the musculoskeletal system and the effects of splenectomy on serum uric acid and ferritin levels in transfusion dependent thalassemia patients.

PATIENTS AND METHODS

Study Setting and Design

The study was conducted in the thalassemia center in Ibn Al-atheer Teaching Hospital in Mosul city.

A case-series study design was adopted to achieve the aim of the present study and the data collection duration was three months from the first of November 2020 to the end of January 2021.

Selection of the study samples

Cases: A group of 52 patients with transfusion dependent thalassemia were on frequent blood transfusion and on chelating therapy (Deferoxamine and Deferasirox) constitute the sample of the present study. Their age ranges between 6-26 years, and both sexes where included in this study. A written consent form was signed by these patient.

Any patient with thalassemia who had other heamoglobinopathies, malignancy, active infection, viral hepatitis, chronic renal disease, and Psoriasis Users of medication that interfered with serum uric acid level including uric acid-lowering drugs, diuretics, anti-tuberculous drugs in addition to the patients who did not give consent to participate in the study were excluded.

Data collection

A preformed questionnaire has been used to obtain information from the studied population. It includes general information about patients, their names, ages and gender, the frequency of blood transfusion, the chelating agent (the type and the dose). A detailed history on their musculoskeletal symptom has been taken. All the patients have been examined generally and systematically, and any positive finding had been recorded in the questionnaire.

A 5 ml of venous blood sample was obtained from the patients for investigations in the questionnaire, including hemoglobin level g/dl through using automated Swelab Alfa (manufactured by Boule medical AB product code 1420042 serial no. 21151), serum ferritin level ng/ml by using miniVIDAS Metabolite ferritin (FER kits) for miniVIDAS immunoassay analyzer (manufactured by bioMerieux, model vidas 3, REF 412590 SN VN03903) normal range in male 30-350ng/ml in female 20-250ng/ml. Serum uric acid level is detected manually by using uricase method by Biolabo reagent for quantitative determination of uric acid in humen serum and plasma or urine. The normal range for children is 119-327 µmol/l,male 208-428 µmol/l, and135-357 µmol/l for females.

X-ray for any joint problem was done by radiology institute device, (Digital AGFA/DX-D400, made in Belgium, 2013) for soft tissue swelling, joint space narrowing, osteophyte, erosion or subchondral cyst, chondrocalsenosis deformities, other findings (increase trabeculae, thin cortex, patellar breaking, flattening of the femoral condyle).

The Visual Analogue Scale (VAS) was used to assess the severity of pain, which represents quantitative measurement in terms of a straight line placed horizontally. Both ends of the line are labeled with descriptive terms to anchor the extremes of the scale on the left (no pain) and on the right (extreme pain). The patient is asked to mark their current pain level on the line. The line was 10 cm in length and each cm has its own number that reflected the amount of pain whether mild, moderate, or severe.[11]

Statistical analysis

The data were entered in computer using Microsoft Excel 2010 and the analysis was done using the software (MINITAB) version 10 for windows. One-way ANOVA-test and independent t-test for two means was used. P – Value regarded significant when it was < 0.05.

RESULTS

A total of 52 patients with β thalassemia major were included in this study, as shown in table (1), Their age ranges between 6-26 years with mean and standard deviation 11.8±3.69, 34 males (65.4 %) and 18 females (34.6 %), 6 patients had splenectomy.

Table 1: Personal characteristics of thalassemic patients on blood Transfusion and Chelating agents, [n = 52].

Characteristics	Mean	SD	Minimum	Maximum
Age (years)	11.8	3.69	6.00	26.00
			No.	**%**
Gender	Male		34	65.4
	Female		18	34.6
	Total		52	100.0
Splenectomy			6	11.5

The mean S. ferritin, S. uric acid and Hb level in thalassemic patients was demonstrated in table (2) and showed that the mean Hb was 8.8±1.2 g/dl, mean S. Ferritin was 3902±2939 ng/ml, and S. Uric acid was 239.7±91.0 µmol/l.

Table 2: The mean S. ferritin, S. uric acid and Hb level in thalassemic patients, [n = 52]

Parameters indices	Mean	SD	Minimum	Maximum
Hb (g/dl)	8.8	1.2	6.3	12.4
S. Ferritin (ng/ml)	3902	2939	106	11430
S. Uric acid (µmol/l)	239.7	91.0	59.0	461.0

The frequency of blood transfusion in this study was 11.5 %, taking packed RBC every 2 weeks, 11.5% every 4 weeks and 76.9 % every 3 weeks in the studied population, depending on hemoglobin level pre transfusion. As shown in table (3), there is a significant relation between blood transfusion and Hb level. Low Hb level requires more frequent blood transfusion (p value 0.029). There is no significant relation between the level of serum ferritin and uric acid level.

Table 3: The relationship between frequency of blood transfusion and Hb, S. ferritin and uric acid levels in thalassemic patients, [n = 52].

Parameters	Frequency of blood transfusion (weeks)			P-value*
	Every 2 Mean± SD	Every 3 Mean± SD	Every 4 Mean± SD	
Hb (g/dl)	7.6 ± 1.02	9.0 ± 1.14	9.0 ± 1.0	**0.029**
S. ferritin (ng/ml)	2590± 1836	4258±2563	2840±2152	0.282
S. Uric acid (µmol/l)	257.2± 68.2	233.8±60.5	262.2±84.8	0.693

Frequency of joint pain is shown in figure (1). In this study, 37 patients (71.2 %) have no joints or other musculoskeletal manifestation, 15 patients (82.9%) with articular manifestation have only arthralgia, the knee involved in 13.5%, low back pain in 13.5 %, while the ankle is affected only in one patient (1.9%).

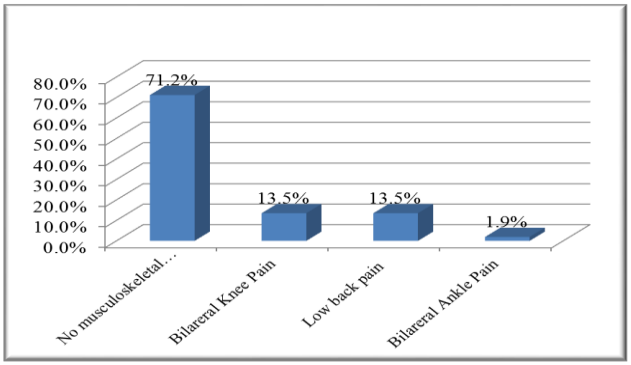

Figure 1: Frequency of joint pain in thalassemic patients, [n = 52].

By Using VAS for pain intensity, only one patient with low backache has moderate pain score while other patients with joint pain have mild score of pain.

Table (4) illustrates that there is no relation between patient complain of joint pain and the level of both serum ferritin and uric acid level in all age group in this study.

Table 4: The relations between S. ferritin and S. uric acid levels with joint pain among the three age groups in thalassemic patients, [n = 52].

Parameters	Age groups (years)*			P-value*
	6-10 Mean± SD	11-15 Mean± SD	16-26 Mean± SD	
Patients with joint pain	4	7	4	------
S. ferritin (ng/ml)	4021± 2645	4067±2741	6152±2989	0.350
S. Uric acid (µmol/l)	317.3± 75.4	301.3±85.2	225.0±87.9	0.215

There is a significant difference in S. ferritin between splenectomy and non-splenectomy thalassemic patients, as shown in table (5). There is a high serum ferritin level in patients with splenectomy than in those without splenectomy p=0.042, whereas no effect was found on uric acid in patients with or without splenectomy.

Table 5: The difference in S. ferritin and S. uric acid between patients with or without splenectomy, [n = 52].

Parameters	Thalassemic patients		P-value*
	Splenectomy [n = 6] Mean ± SD	Non-splenectomy [n = 46] Mean ± SD	
S. ferritin (ng/ml)	5917 ± 2418	3639 ± 2635	0.042
S. Uric acid (µmol/l)	240.0 ± 78.6	239.7 ± 93.2	0.992

***** Independent t-test for two means was used.

There is a significant relation between the sex of thalassemic patient and the level of serum ferritin level, which is higher in males than in females in the age group 16-26 (p=0.031). However, the relation with the level of uric acid is of no significance, as shown in table (6).

Table 6: Effect of the gender on S. ferritin and uric acid titer in thalassemic patients, [n = 52].

Parameters	Male [n=34] Mean ± SD	Female [n=18] Mean ± SD	P-value*
S. ferritin (ng/ml)	4529 ± 2998	2719 ± 2488	**0.033**
S. Uric acid (µmol/l)	257.0 ± 88.8	207.2 ± 88.2	0.060

*** Independent t-test for two means was used.**

DISCUSSION

In this study, 76.9 % of the patient were on transfusion every 3 weeks and 11.5 % every 2 and 4 weeks This is consistent with Choudhry study's recommendation of regular packed cell transfusions every 3–4 weeks. Each time, 10-15 ml/kg of blood can be transfused over 3-4 hours to keep hemoglobin levels between 9 and 10.5 g/dL before the transfusion.[12]

This study shows that the joint pain occurs in 15 patients (28.9 %) of the studied sample with no sign of inflammation the pain was in the knee, ankle and low back pain, all of the patients had normal x ray film. According to the VAS for the intensity of the pain, all patients with joint pain have mild pain intensity and only one patient with low back pain has a moderate intensity. These patients had a normal quality of life and seldom needed analgesics. This is in contrast with the study by Ismail et al in which there was a significant increase in VAS score of the thalassemia group compared with control group (p=0.0001).[11] The exact mechanism of pain in thalassemia has not yet been fully elucidated; however, iron overload, low hemoglobin level, and low bone mass may be the potential etiologies.

This study found that there is no significant relation between the serum ferritin level and the joint pain with p=0.272. This means that there is less deposition of iron in the joints may be related to the proper use of iron chelating therapy. This is similar to Noureldine *et al*.[13] which found no significant connection between iron deposition and arthritis in thalassaemic patients. Also, this study shows that there is no significant relation between the serum uric acid level and the joint pain the p=0.215, all of the patients have normal uric acid level and even if there is hyperuricemia need more time to cause acute attack of gout. The study by Mansi *et al*.[14] demonstrates that there are higher levels of uric acid in thalassemic group, which was predictable due to the higher cellular turnover. Chaloemwong et al. found that gout attacks depend on the duration of hyperuricemia and increase with age, gouty arthritis, and tophi were documented in seven cases (6.3%) and two cases respectively of 112 patient participate in the study. The median age of gouty arthritis onset was 30 years (range 20–44 years).[15] Sahithi et al. reported that the mean value of serum uric acid increased proportionately as the age of the subjects increased which was statistically significant (p=0.0129).[16]

In the current study, there is a highier level of serum ferritin in thalassemic patients who have splenectomy than patients without splenectomy. This is agreement with with Al-khero et al. in which a significant association was found between splenectomy and elevated serum ferritin level (P value 0.030).[1] This also goes with Ismail's study which shows that serum ferritin was statistically significantly higher in splenectomized patients P < 0.009. Also, 15 out of 18 splenectomized patients had iron overload (serum ferritin ≥ 1000 ng/ml),[17] Bashir *et al.*,[18] shows that splenectomised patients have higher ferritin mainly because they were older than non splenectomised and that they received more units of total blood transfusion.

The present study shows a significant difference in serum ferritin level in both sexes, which is higher in males than in females. In Mishra's et al study, it has been found that the serum ferritin level increases as the frequency of blood transfusion and the age of the patient increases.[6] other study conducted by Riaz *et al.* found that the values in males were similar compared to females.[19] Faruqi *et al.*,[20] referred that the difference in mean ferritin levels between genders was not found to be statistically significant (p=0.366). Additionally, Aghamaleki *et al.*,[21] revealed that there was no statistically significant relationship between mean serum ferritin level in terms of different variables (sex, age).

In this study, no significant relation has been found between the gender and the serum uric acid level (the p value 0.060), this is similar to Bazvand et al. that found elevated uric acid levels with no significant differences in gender.[22]

CONCLUSIONS

The current study concluded that the joints pain in the thalassemic patients has no relation with the serum ferritin and uric acid level. Also, male patients have higher serum ferritin level than female. Splenectomy cause increase in serum ferriten level but no effect on serum uric acid level.

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