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Copper Status in Patients with Thalassemia Major in Zahedan, Iran

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ABSTRACT

Introduction: There have been many reports and papers on deficient, normal and high levels of copper in patients with thalassemia major. The aim of this study is to evaluate copper status in a series of more than 300 patients with thalassemia major and determine the degree of copper deficiency or excess.

Methods: Three hundred and seventy patients with thalassemia major over 5 years of age were enrolled in this study. All patients were asked to fast for 12 hours before the test. Measurement was performed using atomic-absorption spectrophotometer in 2012 in southeast of Iran.

Results: The study included both males (n=192) and females (n=141). Of whom, 90 (27%) were aged 5-10 yrs, 80 (24%) were aged 10-15 yrs and 49% were above 15 years of age. Iron chelation therapy was dessferroxamine, deferasirox and dessferroxamine and deferiprone combinations in 61.5 %(204 cases), 24.2%(82 cases) and 14.3%(47 cases), respectively. Among the 370 cases, 107 (32.1%) had copper deficiency, 73 (21.9%) had copper excess and 153 (45.9%) had normal copper level.

Conclusion: High percentage of copper deficiency was documented in 333 patients with thalassemia major and about 50% of patients had normal copper level. This finding showed the importance of micronutrient measurement in thalassemic patients for treatment planning in every part of the world.

KEY WORDS: Major thalassemia, Copper.

INTRODUCTION

Thalassemia is the most common anemia with hereditary base.[1, 2] Iran is one of the most common countries for thalassemia major[3] and there are at least 20000 patients affected by thalassemia major.[4] This severe hereditary anemia necessitates lifelong blood transfusion and according to this modality of treatment metabolic, endocrine and growth abnormality occur.[5, 6] Chronic blood transfusion in thalasssemia major or other hemolytic disorders such as sickle cell anemia could decrease chronic hemolysis and change the micronutrient status.[7, 8] Copper is a trace element with high level in heart, kidney, brain, and also had an important role in the development of connective tissue, nerve and bone.[9] Other enzymatic reactions are reduction of superoxide dismutase, cytochrome oxidase, lysil oxidase, dopamine hydroxylase and other oxidases with reduction in molecular oxygen function.[10-12] Multiple nutrient products contain copper and high levels of copper find in meats, oysters, nuts, seeds, dark chocolate and whole grain.[13] In some reports, copper deficiency in major thalassemia patients has been described as a cause of retarded growth and delayed sexual maturity.[14-16] In the evaluation of copper status in patients with thalassemia major, some reports revealed paradoxical results with copper excess and deficiency.[15, 17] The aim of this study is to evaluate copper status in a large group of patients with thalassemia patients and determine how many and what types of patients need copper supplement.

MATERIALS AND METHODS

This prospective cross-sectional study was carried out on thalassemia patients in Ali-Asghar Hospital, Zahedan, Iran. The study was approved by the Ethics Committee, Medical University. Inclusion criteria included the following: (a) age over 5 years, (b) documented reports on diagnosis of thalassemia major, transfusion-dependent patients and (c) normal renal and liver function. Patients were not eligible for inclusion if they had liver, renal or gastrointestinal disease, special diet including vegetarian diet, or consumed multi-vitamin plus factitious mineral water. Blood samples were taken from eligible patients after an overnight fast of 12-14 hours. Blood samples were then centrifuged within 45 minutes of collection. Serum samples were stored at -80°C until analysis (at Razavi Hospital affiliated with Mashhad Medical University) by flame atomic absorption spectrometry Varian, Australia (AA240fs). According to this instrument, the normal level of copper is reported in the range of 70 to 150 µgr/dl. In this study, serum level lower than 70µgr/dl was defined as deficiency and higher than 150 µgr/ dl was defined as copper excess. All data were entered into an SPSS file and reported according to mean and standard deviation. The chi-square test, ANOVA and t-test were used for statistical analysis of data. Upon approval of the University Research Ethics Committee, the informed consent was obtained before the study.

RESULTS

Of 370 patients with thalassemia major over 5 years of age enrolled in this study, 333 were eligible and evaluated. The study included both males (n=192, 57.7%) and females (n=141, 42.3%). Of whom, 90 (27%) were aged 5-10 yrs, 80 (24%) were aged 10-15 yrs and 49% were above 15 years of age. The mean age was 15.63 ±7.4 years. The mean age was 15.52±5.99 years for males and 15.78±9.16 for females. Iron chelation therapy was dessferroxamine, deferasirox and dessferroxamine and deferiprone combinations in 61.5 %(204 cases), 24.2 %(82 cases) and 14.3 %(47 cases), respectively. The mean ferritin level was 4053.162± 2523.058. The mean copper level was 95.84±48.01 µgr/dl. The mean copper level in patients with normal, deficient and excessive accumulation was 153 (45.9%), 107 (32.1%), 73 (21.9%), respectively. There was a statistically significant difference (p=0.001) between female and male sexes with regard to copper deficiency. No significant difference was found between age and mean level of copper (p=0.09). The mean level of copper in patients aged 5-10 years, 10-15 years and those who were above 15 years of age was 97.6±50.07, 100.32±49.49, 92.66±46.15, respectively. The mean BMI was 16.55±3.31. There was no statistically significant difference between the mean copper level and BMI (p=0.48). No significant evidence was found between types of iron chelation drugs used in this study and mean copper level (p=0.56). The mean number of packed RBC transfusion was 2.48±1.06 per months. There is a significant relationship between serum copper level and packed red blood cell transfusion (p=0.059).

DISCUSSION

The prospective cross-sectional study on 333 patients with thalassemia major showed that copper deficiency is more prevalent (32.1%) in south-east Iran. This conclusion is inconsistent with the previous findings in Iran and other parts of the world. In comparison with previous studies, more thalassemia patients within different age ranges were recruited into this study. Mansi et al., studied 42 patients (20 males and 22 females) with thalassemia major in the age range of 4-14 years old.[18] Contrary to our conclusion in regard to number of patients, copper level and gender predominance, there was no significant difference between sex and serum copper level.

In a study conducted by Mahyar on 40 cases, the mean copper status was 152.42 ±24.17.[19] No copper deficiency was recognized and copper status was reported as normal in the study group. The copper range and mean copper status was 100-200.5 and 152.42±24.17µg/dl, respectively. No statistically significant difference was observed between copper status and demographic characteristics in patients with thalassemia major. There was also no significant difference between copper status and serum ferritin level or age, BMI, iron chelation therapy and blood transfusion.

In a study performed by Claster on patients with thalassemia major, copper level was above the upper limit of normal,[9] reflecting complete contrast to our findings. Another study conducted by Nasr et al., showed severe copper deficiency in patients with thalassemia major, while no normal copper level or copper excess was observed.[20] There was statistically significant difference between copper deficiency and mean serum mean copper status 60.60±15.71µgr/dl (p<0.001).

CAI Min-nin revealed that the copper status in patients with thalassemia major was higher than the normal range.[21] Canellas et al., found that copper concentration in sickle cell anemia patients was 20% higher than control group.[22] In a study conducted by Ellen, no copper abnormality or deficiency was observed in patients with thalassemia major.[23]

Table 1: Patients Characteristics' According to Copper Status

		Normal Copper		Copper deficiency		Copper Excess		P value
		No	%	No	%	%	No	
Sex	Male	89	46.4	64	33.3	39	20.3	0.685
	Female	64	45.4	43	30.5	34	24.1	
Age	5-10	45	50	25	27.8	20	22.2	0.689
	10-15	36	45	24	30	20	25	
	>15	72	44.2	58	35.6	33	20.2	
BMI	<20	130	44.8	94	32.4	66	22.8	0.643
	20-25	19	51.4	11	29.7	7	18.9	
	25-30	4	66.7	2	33.3	0	0	
Iron chelator	Desferal	72	47.1	49	32	32	20.9	0.101
	Deferasirox	43	44.8	26	27.1	27	28.1	
	Desferal&L1	29	44.6	25	38.5	11	16.9	

Table 2: Mean Copper Status According to Patients Characteristics According to Anova &T-test

Parameters		Mean	P value
Sex	Female	97±49.17	0.0001
	Male	94.95±25.47	
Age	5-10	97.60±50.05	0.09
	10-15	100.32±49.49	
	>15	92.66±46.15	
BMI	<20	96.01±48.19	0.48
	20-25	96.89±50.21	
	25-30	81.18±19.92	
Iron chelator	Desferal	94.07±44.85	0.89
	Deferasirox	104.83±56.90	
	Desferal&L1	88.63±41.44	

CONCLUSION

Copper status has been reported normal or high in the vast majority of studies. Previous studies were conducted with small sample sizes, while our study included a large number of thalassemic patients with copper deficiency, normal and elevated copper level. The results of this study show that what types of patients with thalassemia major can receive alternative treatment. Regarding the small amount of micronutrient supplement in daily regimen, future studies will likely attempt to develop a regimen including adequate amounts of micronutrient supplement for patients.

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