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Role of sickling crisis with serum zinc in children with sickle cell anemia

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Abstract

Background and objectives: Sickle cell anemia causes painful crises by the occlusion of small blood vessels by spontaneous intravascular sickling. The aim of this study is to determine the possible association of Zinc deficiency with painful crises among patients with sickle cell anemia.

Methods: A case – control study included 50 children with sickle cell anemia during painful crisis, 50 with Sickle cell anemia without painful crisis and 50 normal children (control group). Serum zinc was measured for all participants and statistically analyzed to test the presence of a possible significant relation between serum zinc and painful crises in sickle cell anemia.

Results: The mean age of all study population was 9.79 ± 4.54 years and male to female ratio was 1.2:1. Weight, height, body mass index, Hemoglobin and packed cell volume are lower in those with sickle cell anemia as compared to controls but the difference is not statistically significant. White blood cells count is significantly higher in those with sickle cell anemia and painful crisis than those with sickle cell anemia but no painful crisis and the normal controls. Liver enzymes alanine aminotransferase and aspartate aminotransferase are significantly higher among patients than controls. Serum zinc is lower in patients with sickle cell anemia and painful crisis than those with sickle cell anemia but without painful crisis and the normal controls (88.84±31.20, 98.62±20.78, 101.38±24.49 µg/dl respectively) and the difference is statistically significant.

Conclusion: Zinc deficiency is significantly associated with predisposition to painful crises in children with sickle cell anemia.

Key words: Painful; Crisis; Zinc; Sickle; Occlusion.

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Introduction

Sickle cell disease (SCD) is one of the most prevalent hematological diseases in the world. Despite the immense progress in molecular knowledge about SCD in the last years, few therapeutic sources are currently available[1].Zinc is known to inhibit the activity of calmodulin which activates the calcium-ATPase that controls the calcium pump system of the erythrocytes. During sickling, there is an influx of calcium into the erythrocytes and this occurs, probably, due to the fact that the calmodulin is so over activated that the membrane is destroyed. It is suggested, therefore, that during zinc therapy, its anti-calcium action, (through its effect on calmodulin) produces anti-sickling effect[2].Although it has been suggested that zinc therapy could reduce painful crisis; however, it has not been shown with certainty that zinc deficiency in sickle cell anemia is directly related to the development or severity of vasoocclusive crisis[3].Various studies have shown that zinc is deficient in patients with SCD. One study showed that oral zinc supplements improved severe crises in patients with SCD[4]. Another study of hematology; reported the significant lower levels of zinc and an association of clinical complexity in sickle patients[5]. There is a lack of data on the deficiency of zinc amongst inherited disorders and their prevalence. The importance of zinc deficiency to the risk of SCD has not better understood. There is a paucity of data on the prevalence of zinc deficiency in SCD patient[6]. A study done in Melaka, Malaysia found that evidence of benefit is seen with the reduction in the number of sickle cell crises among sickle cell patients who received one year of zinc sulphate supplementation and with the reduction in the total number of clinical infections among sickle cell patients who received zinc supplementation for both three months and for one year[7].Previous research strongly indicates a relationship between micronutrient deficiencies and the severity of SCD, but, there is a paucity of information on their role in pathogenesis and management of SCDs. There is need to determine micronutrient levels in patients with sickle cell because if indeed deficiencies are discovered to be a contributing factor to ill health, it will provide a treatment intervention which will have a lot of benefits to the patient who will experience an improved health, better quality of life, less severe episodes of crises, faster recovery from crises; all at a more affordable cost than some currently

available treatment/prevention strategies[8]. The aim of this study is to determine the possible association of Zinc deficiency with painful crises among patients with sickle cell anemia.

Subjects and methods

A case – control study was accomplished at Heevi Pediatric Teaching Hospital in Duhok, Iraq from 1st April 2016 to the 1st of October 2016.The population of this study was 100 children aged 6 months – 18 years with sickle cell anemia with no recent transfusion of blood or blood products in the previous three months and no symptoms or signs of infection, 50 of them had a painful crisis in the limbs or the back within 2 days and 50 did not have such a crisis over the last 3 months in addition to 50 age- and sex-matched children without sickle cell disease taken as control group from the healthy children who visited the hospital with their parents. None of the participants received any zinc-containing medications. Data were collected including the mother's and father's educational status and occupation, 24-hour meal recall, date of last blood transfusion, and the presence or absence of pain in the limbs. Physical examination included assessment for the presence or absence of fever (temp > 37.0◦C), jaundice, pallor, finger clubbing, liver size, spleen size, and tenderness in the limbs. Weight and height were measured for all participants and Body mass index (BMI) was calculated for each participant as the ratio of weight (kg) to height (m) squared (kg/m²). If BMI 18.5 to < 25 normal, 25 to < 30 Overweight and ≥ 30 Obese. Five mL of blood was collected from each subject by venepuncture after appropriate skin preparations with a 21-gauge stainless steel needle with a polypropylene syringe**.** Hemoglobin (Hb), Packed cell volume (PCV), and White blood cell were measured using standard laboratory procedures. The zinc concentrations in serum were measured by means of flame atomic absorption spectrometry. Zinc status was assessed as follow: Severe zinc deficiency (serum Zinc < 50 µg /dl), marginal zinc deficiency (serum zinc 50-≤70 µg /dl), Normozincaemia: serum zinc concentration > 70 -130 µg /dl and Hyperzincaemia (serum zinc ≥130 µg /dl). A cut off point of < 70 µg /dl of Zinc was used to classify individuals as on low zinc status. Ethical approval of the study was taken from the Research ethics committee in the Directorate

of Health of Dohuk. Statistical analysis was done with aid of the computer program SPSS (statistical package for the social sciences) for windows version 22. The data were presented as percentage and continuous variable as means & standard deviation with 95% CI. Differences between two groups for continuous variables were determined by Odds Ratio & independent student t test, while difference between more than two groups determined by one way ANOVA test. Chi square test were used for categorical variables. Statistical significance was set at a p- value of less than 0.05

Results

The age range of all study population was between (20 months – 16.5years). The group with sickle cell and painful crisis hag an age range of 20 months-14 years, those with sickle cell without crisis was 2-15 years while for the control group was 26 months-16.5 years. From the cases, 55 were male and 45 were female. Of those with painful crisis, 30 cases were male and 20 cases were female, those with no painful crisis, 25 cases were male and 25 cases were female and from the normal controls, 28 cases were male and 22 cases were female.The mean age of all study population was 9.79 ± 4.54 years and male to female ratio was 1.2:1.

Table (1): Mean hematologic, biochemical and anthropometric parameters in cases and controls

Parameter	Sickle with crisis	Sickle without crisis	Control	p- value
Height(cm)	125.42±23.30	130.68±22.51	131.16±24.85	0.4
Weight(Kg)	26.18±11.83	28.40±12.69	30.43±16.27	0.3
BMI(Kg/m^2)	15.55±2.22	15.63±2.54	16.50±3.77	0.1
Hb (g/dl)	8.21±1.42	8.47±1.24	12.91±1.66	0.01
PCV(%)	24.44±4.71	24.72±4.39	37.34±4.58	0.01
WBC(×10^9/L)	18.67±6.59	15.74±6.81	9.32±6.41	0.01
S.GPT(I.U/L)	38.54±26.58	27.54±14.89	32.32±13.09	0.01
S.GOT(I.U/L)	58.92±25.35	53.73±16.52	31.54±13.39	0.01
S.Zinc(μg/dL)	88.84±31.20	98.62±20.78	101.38±24.49	0.04

As it's apparent in table 1, the mean growth parameters including weight, height and BMI are lower in those with sickle cell anemia as compared to controls but the

difference is not statistically significant. Hemoglobin and PCV are significantly lower in those with SCA than those with normal hemoglobin type. WBC count is significantly higher in those with SCA and painful crisis than those with SCA but no painful crisis and the normal controls.Liver enzymes S.GPT and S.GOT are significantly higher among patients than controls. Serum zinc is lower in SCA with painful crisis than those with SCA but no painful crisis and the normal controls and the difference is statistically significant.

Table (2): Relation between serum Zinc and the clinical presentation among all patients with sickle cell anemia.

Clinical presentation		**Low serum zinc NO. (%)**	**Normal serum zinc NO. (%)**	**p-value**
Jaundice	Present	18(94.7%)	78 (96.3%)	0.7
	Absent	1(5.3%)	3 (3.7%)	
Pallor	Present	8 (42.1%)	53 (65.4%)	0.05
	Absent	11 (57.9%)	28 (34.6%)	
Hepatomegaly	Present	18 (94.7%)	67 (82.7 %)	0.1
	Absent	1 (5.3%)	14 (17.3%)	
Splenomegaly	Present	11 (57.9%)	27 (33.4%)	0.04
	Absent	8 (42.1%)	54(66.6%)	

The relation of serum zinc level with clinical presentation of all those with SCA (with and without painful crisis) is shown in table(2), pallor and splenomegaly are significantly related to serum zinc level while jaundice and hepatomegaly are not. Among patients with SCA and painful crises as in table (3), those with low serum zinc level had lower weight, height, BMI, Hb, PCV and number of blood transfusion per year but no clinical significant was found; leukocytosis is not significantly related to low serum zinc level. No significant relation to S.GPT and S.GOT was found.

Table (3): The Relation Between zinc level and other factors in those with painful crisis .

Factors	Patients with low zinc mean	Patients with normal zinc mean	p-value
Weight(Kg)	23.23±14.82	27.33±10.47	0.2
Height(cm)	115.42±26.42	129.30±21.11	0.05
BMI(Kg/m²)	15.50±2.56	15.56±2.11	0.9
Num. of transfusion /year	3.07±3.54	3.88±4.24	0.5
Hb (g/dl)	8.17±1.50	8.22±1.42	0.9
PCV (%)	25.49±4.89	24.03±4.64	0.3
WBC(×10^9/L)	19.90±7.39	18.20±6.31	0.4
S.GPT(I.U/L)	42.07±35.48	37.16±22.69	0.5
S.GOT(I.U/L)	51.21±20.45	61.91±26.68	0.1

Discussion

Zinc is an important factor for RBC maintenance[9,10]. In SCA, the chronic hemolysis and cell death leads to red marrow expansion. Our study revealed significantly lower serum zinc level in patients with SCA and painful crisis than those with SCA but no painful crisis and the normal controls. This is in agreement with many studies all over the world[11-14]. A study by Garba that included 101 participants divided in to 3 groups like our study revealed a significantly lower serum zinc level in SCA with painful crisis than SCA patients without painful crisis and normal controls[15]. Hasanato in his study dealt with 25 SCA patients and 25 controls measured serum zinc level along with antioxidants and found a significantly lower serum zinc level in SCA patients than controls[16].A study by Martyres that estimated nutritional deficiencies in SCA children also found 57% of the 91 participants with SCA to have zinc deficiency[17]. Vijenthira studied zinc and vitamin D level in serum of 43 patients with SCA also revealed a significantly lower serum zinc level in 64% of cases[18]. A study by Idonije that dealt with 213 participants divided similarly as in our study also proved that zinc level is significantly lower in SCA with painful crisis as compared to SCA patients without painful crisis and with normal controls[13]. Besides, there is defective zinc homeostasis due to excessive zinc excretion in urine or abnormal renal tubular absorption due to sickling phenomena, increased demand and consumption[25].Since patients with SCA have a higher potential for oxidative damage and zinc inhibits lipid peroxidation on sickle cells which is a form of oxidative damage which increases

clearance of zinc from circulation[19].On the other hand, zinc deficiency impairs T-helper cell function and cell mediated immunity leading to reduced interleukin-2 production leading to increase rate of bacterial infection and vasooclusive crisis[19-22].Contrary to previous studies on the growth of SCA patients that show impaired growt[24], patient in our study had normal growth. A similar result was also found in a study by Martyres as well[17]. This can be explained by that growth needs are met in our population since the overall the nutritional status of children in our locality is good and this includes those affected by SCA.

Conclusions

Zinc deficiency is an important factor predisposing to painful crises in children with sickle cell anemia.

Conflicts of interest

The authors report no conflict of interest.

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