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ORIGINAL ARTICLE

Assessment of Blood Manganese Concentration in Children with Iron Deficiency Anemia.

Nahed Mahmoud Helmy Khater [1], Nehad Ahmed karam[1], Noha Abd el Haleem Mohammed[1], Asmaa Ibrahim Ahmed [1]*

[1]*Department of Pediatrics , Faculty of Medicine, Zagazig University*

***Coresponding author:**
Name: Asmaa Ibrahim Ahmed
M.B.B.CH, Resident of Pediatrics , Department of Pediatrics , Faculty of Medicine, Zagazig University
Email:
drasmaa.ibrahim90@gmail.com

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ABSTRACT

Anemia is a global health problem, which affects not only developing countries, but also developed countries as well. Iron deficiency affects about 30% of the world's population, making it one of the most prevalent nutritional problems worldwide. A nutritional iron deficiency may cause high absorption of Mn. Overexposure to Mn can cause an overwhelming neurologic impairment that is clinically called "manganism". The aim of this study was to assess blood manganese concentration in children with iron deficiency anemia. Patients and methods: This is a prospective cohort study carried out in department of Pediatrics, faculty of medicine, Zagazig University, in a 6 months duration, on 50 children with iron deficiency anemia. CBC, ferritin and TIBC are used for diagnosis of iron deficiency anemia. Assessment of manganese levels was done with division of patients into normal and high manganese level.**Result:** most cases of iron deficiency anemia associated with increase blood manganese level.**Conclusion:** Blood manganese concentration is elevated in children with iron deficiency anemia.

Key words: iron deficiency anemia; manganese; iron; transferrin

INTRODUCTION

Simply, anemia occurs when hemoglobin (Hb) concentration is 2 standard deviations (SD) below the mean Hb concentration for a normal population of the same sex and age range [1]. Iron deficiency (ID) is a status in which there is deficient iron to keep the maintenance of normal physiologic functions. It occurs as a result of inadequate iron absorption to satisfy an elevated growth requirement or as a consequence of prolonged negative iron balance, any of these conditions can lead to decreased iron stores as measured by serum ferritin (SF) concentrations or iron content in bone marrow.[2]

Manifestations of IDA include: anorexia, low-weight percentiles and depression of growth, irritability, fatigue and decreased activity, reduced cognitive performance, palpitations. [3]

Manganese (Mn) is a vital element for humans, animals, and plants and is essential for growth, development, and preservation of health. It is found in most of all living organisms' tissues and is existing naturally in stones, earth crust, water and food. [4] .

The brain sites which are mostly influenced by Mn accumulation are the globus pallidus and the substantia nigra. [5] .

The early symptoms of high blood Mn level are mostly behavioral and include anorexia, mood swings, and irritability, in addition to attention disturbances and reduced response times. As the illness develops, the patient begins to show many of the symptoms of idiopathic Parkinson's disease including disturbed speech, bradykinesia, rigidity, and walking difficulty[6].

An increased absorption of Mn in iron-deficient cases may be the cause of the fivefold increase in blood Mn observed in anemic patients [7] Strong suggestion exists that iron and Mn compete for absorption into the mucosal cells [8].

PATIENTS AND METHODS

Study design: is a prospective cohort study, which examined the iron and manganese

status of children attending the Department of Pediatrics, Faculty of Medicine, Zagazig University, in a period of 6 months duration from July 2017 to January 2018.

Patients: 50 children with iron deficiency anemia.

Inclusion criteria: Children 6 months old and above, both sexes included, Children with IDA (diagnosed by decrease serum ferritin, iron level and elevated TIBC).

Exclusion criteria: individuals with evidence of infection, cholestasis, receiving total parenteral nutrition, patients being treated for malignancy, individuals with renal disease, malabsorption syndromes.

Method: Details of procedure and aim of work were explained to all patients before any intervention. All possible outcomes, complications were also explained and written informed consents were obtained from all parents of children included in this study. Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University (IRB).The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Full medical history was taken throughout physical examination and CBC, ferritin and TIBC are used for diagnosis of IDA. Assessment of Mn levels was done with division of patients into normal and high Mn level,normal Mn level = 0.09 – 0.29 microgram / dl [9] .This study was carried out over a period of 6 months from July 2017 to January 2018.

procedures: Non-fasting blood (5 ml) was collected. 1ml was transferred into a lithium heparin tube for blood Mn determination, 1ml was transferred into an EDTA tube for a full blood count and 3ml was transferred to a tube with a blood clotting gel for the remaining tests (C-reactive protein (CRP), iron, ferritin and TIBC).

All specimens for hematology and CRP and were analyzed immediately in duplicate, whereas blood samples for Mn analysis were stored at -70°C. A full blood count was determined by automated analysis using a hematology analyzer (Nihon Kohden, Tokyo, Japan) and included measurement of red blood cell count (RBC), white blood cell count (WBC), Hb, hematocrit, mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC) and mean cell volume (MCV).

Serum Fe was determined using a kit method based on the colorimetric reaction of Fe with FerroZine (Roche Diagnostics).

C-reactive protein: determined within an hour of sample collection using the Tina-quant CRP (Latex) immunoturbidimetric assay (Roche Diagnostics, Basel, Switzerland).

Total iron binding capacity (TIBC): determined using a colorimetric kit method (Randox Laboratories, Crumlin, UK). Serum ferritin was measured using the Tina-quant ferritin immunoturbidimetric kit method (Roche Diagnostics) and transferrin saturation was calculated using the formula:

Transferrin saturation (%) = (serum Fe ÷TIBC) × 100.

Manganese was determined by atomic absorption spectrometry by direct aspiration of the sample into an air-acetylene flame without pre-concentration or pretreatment.

Statistical analysis

Data were analyzed by Statistical Package of Social Science (SPSS), software version 24.0 (SPSS Inc., 2016).

Continuous data were presented as the Mean ± SD if normally distributed or Median (Range) if not normally distributed. Normality was checked by Shapiro test. Categorical data were presented by the count and percentage.

- Paired-samples t-test (dependent t-test): is used to compare the means between two related groups on the same continuous, dependent variable.
- Chi-squared test: is used to discover if there is a relationship between two categorical variables.
- Independent-samples t-test: is used to determine if a difference exists between the means of two independent groups on a continuous dependent variable.
- Mann-Whitney u test (nonparametric alternative to independent-samples t-test).
- Multiple regression analysis: is used to predict a continuous dependent variable (serum Mn) based on multiple independent variables. It allows determining the overall fit

of the model and the relative contribution of each of the predictors to the total variance explained. Variables that have a *P*-value of <0.05 in univariable analysis were included in multivariable analysis.

All statistical comparisons were two-tailed.

Significance level:

P-value <0.05 indicates significant, *P*<0.01 indicates highly significant difference, *P*<0.001 indicates very highly significant difference while, *P*≥0.05 indicates non-significant difference. *(Petrie and Sabin, 2009)*

RESULTS

The median age of the studied children was 16.5 months **(**Table 1).

10 patients had normal Mn level and 40 patients had high Mn level. None of our patients had low Mn level. Mn level higher in females (65%) than males (35%) (Table2). 54% of our patients were of low socioeconomic standards and 46% of moderate standards **(**Table 1). Children with high Mn level showed no statistically significant differences in age, sex and socioeconomic standards compared with children with normal Mn level (Table2).

No statistically significant differences in all CBC data in the studied children except for RDW and serum Mn level where statistically significant elevations were observed in children with high Mn level compared with children with normal Mn level (Table 3).

No statistically significant differences in all iron indices and C-reactive protein in the studied children except for transferrin saturation where a statistically significant reduction was observed in iron deficient anemic children with high Mn level compared with iron deficient anemic children with normal Mn level (Table 4).

Multiple stepwise regression analysis revealed that transferrin saturation is the independent determinant serum Mn level in the studied children (Table 5).

Table 1: Demographic characteristics of the iron- deficient children.

Variables			
Age (months)			
Median (Range)	16.5(6-156)		
Sex		*n*	%
Female		17	(34%)
Male		33	(66%)
Socioeconomic standards		*n*	%
Low		27	54%
Moderate		23	46%

Table 2: demographic characteristics of the iron-deficient children grouped according to serum Mn level.

Variables	**Normal Mn**		**High Mn**		**Test of significance**	***P*-value**
	n=10		*n=40*			
Age(months)					MW=204.5	0.91
Median (Range)	13.5(50-156)		18(6-156)			
Sex	*n*	(%)	*n*	(%)	Chi-squared test (^{2}) = 0.09	0.77
Male	3	30%	14	35%		
Female	7	70%	26	65%		
Socioeconomic standards					Chi-squared test (^{2}) = 1.29	0.26
Low	7	70%	20	50%		
Moderate	3	30%	20	50%		

MW, Mann-Whitney u test

Table 3: Complete blood count data and serum Mn of the iron-deficient children grouped according to serum Mn level.

Variables	Normal Mn	High Mn	Test of significance	*P*-value
	n=10	*n=40*		
TLC (10^3/uL)			MW=235.5	0.4
Median(Range)	8.55(5.2-15)	9.35(4.4-16.6)		
HT (%)			Independent sample-t test=1.8	0.095
Mean±SD	30.7±3.6	28.4±3.3		
HB (gm/dL)			Independent sample-t test=1.4	0.17
Mean±SD	9.6±1.2	9±1.3		
MCV (FL)			MW=148	0.21
Median (Range)	67(51-71.1)	64.9(49-71)		
MCH (Pg)			Independent sample-t test=1.3	0.19
Mean±SD	20.8±3.3	19.4±2.7		
RDW (%)			MW=287	**0.035***
Median (Range)	17(16-23.5)	19.2(16.9-27.2)		
Platelets (10^3/uL)			MW=206.5	0.88
Median (Range)	347 (185-551)	378(112-1047)		
Serum Mn (microgram/dL)			Independent sample-t test=8.7	**<0.001*****
Mean±SD	0.22±0.05	0.37±0.028		

MW, Mann-Whitney u test, TLC, total leukocytic count, HT, hematocrit, HB, hemoglobin, MCV, mean corpuscular volume, MCH, mean corpuscular hemoglobin, RDW, red cell distribution width, *= significant(*P*<0.05),**=very highly significant(*P*<0.001)

Table 4: Iron indices and inflammatory biomarker of the iron-deficient children grouped according to serum Mn level.

Variables	Normal Mn	High Mn	Test of significance	*P*-value
	n=10	*n=40*		
Iron (microgm/dL)			Independent sample-t test=1.8	0.071
Mean±SD	41.1±12.1	34.7±9.3		
TIBC (microgm/dL)			MW=269	0.097
Median (Range)	357.5(345-401.2)	367(345-529.4)		
Ferritin (ng/mL)			MW=132.5	0.10
Median (Range)	31.65(24-332.31)	19.3(7.2-505)		
Transferrin saturation (%)			Independent sample-t test=2.4	**0.023***
Mean±SD	11.4±3.3	9.2±2.5		
C-reactive protein (mg/L)			MW=122.5	0.059
Median(Range)	5.9(2-17)	4.8(0.5-13)		

*= significant(*P*<0.05), **=very highly significant(*P*<0.001)

Table 5: Summary of regression analysis for serum Mn level in the iron-deficient children.

Variables	Multivariable stepwise regression		
	Unstandardized Coefficients		*P*-value
		SE	
Intercept	0.43	0.032	
Transferrin saturation (%)	-0.010	0.003	**0.004**

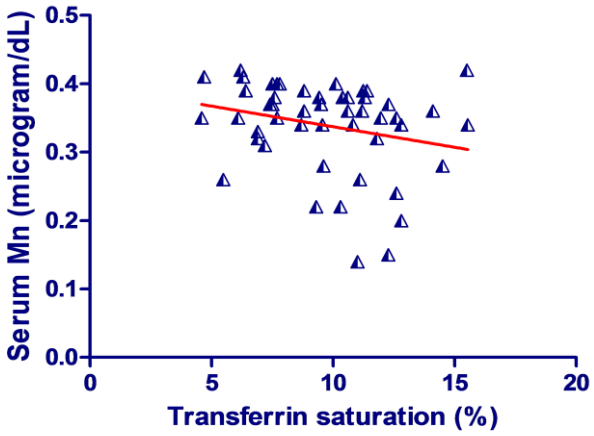

Figure 1: A scatter plot with a regression line of serum Mn level against transferrin saturation% of the iron-deficient children

DISCUSSION

Iron deficiency results mostly from nutritional causes such as exclusive feeding of infants with breast milk, feeding of infants with cow milk, or drinking tea soon after a meal, resulting in three-fold decrease in dietary iron absorption. [10]

Manganese (Mn) is crucial for a number of biological and physiological processes, including body growth, immune function, enzymatic regulation reactions, bone growth and metabolism. [11]

Despite its vital role in brain growth and development, excessive exposure to Mn can result in neurotoxicity[12]

Our study done on fifty patients of iron deficiency anemia, 66% males and 34% females. Also, the frequency of IDA higher in males (53%) than females (47%),). In a Syrian study, the similar results obtained (males 85.33% and females14.6%) [13] . Median age of our studied group was 16.5 months. Younger children (under 2 years) were more likely to be anemic compared to their older peers and prevalence rate of anemia among under-fives was found to be 84.6%.[14].

Patients were grouped according to serum manganese level into normal (20%) and high (80%) manganese level. Children with high Mn level showed no statistically significant differences in age, sex and socioeconomic standards compared with children with normal Mn level.

Oulhote et al.,(2014) revealed a significant inverse association with Mn levels only in individuals with iron concentrations below 75 µg/L. This inverse association was also more pronounced among women than for men which similar to our study as 65% females and 35% males [15].

In our study, there were no statistically significant differences in all CBC data in the studied children except for RDW and serum Mn level where statistically significant elevations were observed in children with high Mn level.

A large Korean National Health and Nutritional Examination Survey (KNHANES) done in 2008, demonstrated that blood Mn concentration was significantly higher in the low ferritin groups of both males and females as compared to the normal ferritin groups' values[16]

In Norwegian study done on females, the results indicated that a low serum ferritin concentration is a predictor of high Mn concentrations independent on whether anemia is present or not. The high blood Mn concentrations shown for several of the studied women indicate the importance of assessing iron and hematological status when addressing occupational or environ- mental exposures to Mn and related neurotoxic effects [17] .

Highly statistically significant positive correlation between iron and transferrin saturation showed in correlations between serum Mn level children and Multiple stepwise regression analysis revealed that transferrin saturation is the independent determinant serum Mn level in the iron-deficient children. Multiple regression analysis showed a weak relationship between Fe and blood Mn. The only independent relationship was Mn with TIBC. In a stepwise regression analysis, ferritin and TIBC had the most significant relationship with Mn [18].

Conclusion: Blood manganese concentration is elevated in children with iron deficiency anemia.

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