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Concomitant Iron Deficiency with B-ThalassaemiaMinor in Preschool Children in Erbil City

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Abstract

Background and objectives: Iron deficiency anaemia and beta thalassaemia trait are the most common microcytic hypochromic anaemias, however, coincidence of both has been the topic of few studies. This study carried out to determine if iron deficiency coexists and to which extent, also influence on hemoglobinA2 level and link to demographical and biochemical parameters among β-thalassemia trait children aged 1 to 5 **Methods:** A cross-sectional observational study conducted on 112 children with thalassaemia minor diagnosed by blood counts and hemoglobin electrophoresis. The iron status of all children was measured, those with a cut-off value of serum ferritin level <15 µg/l considered to have coexistence of iron deficiency (group I), furthermore, different variables compared to the remaining children with normal serum ferritin levels (group II). **Results:** Out of 112 β-thalassemia trait children, 39 (34.82%) had concomitant iron deficiency, 35.9% females and 64.1% males, with no significant difference in sex between the two groups. The mean age ± SD was 38 ± 16 months, yet iron deficiency coincidence was significantly higher among the younger children. There was no significant difference between those with or without iron deficiency regarding hemoglobin A2 level. **Conclusions:** We found that more than one third of children with thalassemia minor are also iron deficient. Furthermore, serum ferritin level didn't impact the hemoglobin A2 in thalassaemic minor children with or without concomitant iron deficiency.

Keywords: β thalassemia minor; Iron deficiency anaemia; Hemoglobin A2.

Introduction

Anaemia is a global public health problem, according to the World Health Organization affects 25% of the world population, and 47% of children aged 0 to 5 years are anaemic[1]. Iron deficiency is the most common and widespread nutritional disorder in the world. In industrialized countries and in non-industrialized countries 10–20% and 50–60% respectively are iron deficient[1-3]. In Erbil city, Kurdistan region of Iraq, the prevalence of iron deficiency anaemia (IDA) in preschool children is 42.6%[4], reaching as high as 52% in the younger age groups[5]. In the development of iron deficiency, three stages can be defined, depleted iron stores, iron-deficient erythropoiesis, and iron-deficiency anaemia[6]. The third stage of iron deficiency develops when iron supply is no longer sufficient to maintain a normal concentration of haemoglobin and increase the red cell heterogeneity and a decreased mean cell volume (MCV), those changes indicated as increased red blood cell distribution width (RDW), and microcytic red blood cells[7]. Serum ferritin is the best and most widely used indicator for estimation of the iron status and diagnosing those with uncomplicated iron deficiency anaemia. Results of less than 12-15 µg/L are indicative of iron deficiency and of a lack of stainable iron in the bone marrow. Nevertheless, the relationship between serum ferritin and iron stores is affected by acute and chronic infections and inflammatory disorders, liver diseases, and malignancies[6, 8-10].

On the other hand, β-thalassaemias are disorders of haemoglobin synthesis often due to mutations in regulatory globin genes on the short arm of chromosome[11] resulting in decreased production of normal globin proteins. β-thalassaemia varies from minimal (mild β+-thalassaemia alleles) to a complete absence (β0- alleles) and is an extremely heterogeneous condition with more than 40 different lesions of the β-globin gene have been identified. With rare exceptions, heterozygotes for β-thalassemia (β-thalassaemia minor) are clinically

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asymptomatic people with thalassemia traits do not require medical or follow-up care after the initial diagnosis is made[11-13]. The thalassaemias have a high incidence in a broad band extending from the Mediterranean basin and parts of Africa, throughout the Middle East, the Indian sub-continent and into South-East Asia. The carrier frequency for β-thalassaemia trait (BTT) in these areas ranges from 1% to 20%[14], and is estimated to be around 7% within our populations in Erbil province[15,16]. Hemoglobin electrophoresis[17], is a blood test to check the different types of hemoglobin in the blood, and by comparing the pattern formed with that of a normal blood sample. An abnormal amount and/or an abnormal type of hemoglobin in the blood may cause mild diseases without symptoms, or cause diseases that can be life-threatening. Almost all heterozygous thalassaemias are characterized by an increased HbA2 content (≥ 3.5%) and a marked degree of microcytosis, which is frequently associated with mild anaemia. The increased HbA2 content is due to a compensatory increase of δ-chain synthesis leading to unstable α-chain tetramers which precipitate in cells and induce cell death with a shortened life span of red blood cells. Haemoglobin in the red blood cells consists of HbF and a small fraction of HbA2, varying from 1-3% in β0-thalassaemia to 7% in β+ thalassaemia[6, 8].

Both iron deficiency anaemia and thalassaemias are the most common microcytic and hypochromic anaemias which frequently leads to an incorrect diagnosis, however, diagnosing subjects with combined thalassaemia minor and iron deficiency is even more challenging8. It has long been considered that iron deficiency does not exist in thalassemia syndromes, including thalassemia trait, thus the exact role of thalassemia trait in iron metabolism still remains an area to be explored. However, few publications in the past have addressed the coexistence of b-thalassemia minor and iron deficiencies in pediatric age groups, particularly in the pre-school age group as in our study, whereas the highest rates of iron deficiency anaemia are found in the first few years of life. Our article was carried out to assess the serum ferritin level in a group of beta thalassaemia minor, hence determine the frequency of coincidence of iron deficiency anaemia, also to identify the influence of low serum ferritin on the HbA2 level and different red blood cell indices among children with β thalassemia trait aged 1 to 5 years.

Patients and methods

This is a cross sectional, observational study with prospective collection of demographic, clinical, diagnostic and laboratory data. The study was conducted in Erbil-Raparin pediatrics teaching hospital over a period of one year extending from December 2016 to December 2017. Those patients visited our faculty either for assessing anemia or from routine check-ups (detected by chance) with low mean corpuscular volume (MCV) and low mean corpuscular hemoglobin (MCH) by complete blood count were examined for the presence of β thalassemia trait by Hb electrophoresis, such methodology eventually identified a total of 112 patients within the age group of 1-5 years who were carriers of beta thalassemia. The data were collected by a direct interview of patient's caregivers through a special questionnaire, designed for the current study, containing demographic description, nutritional status assessment by Gomez classification and laboratory data. The purpose of the study was carefully explained to each caregiver, and an informed verbal consent was obtained from all enrolled individuals. Those younger than 1 year of age (due to the possible effect of Hb F quantitation) and those with other hemoglobinopathies, children with anaemia suffering from long standing systemic diseases, malignancies or inflammatory and infectious diseases based on clinical and personal information were excluded from the study. The study was approved by the scientific and ethical committees of the Kurdistan Board for Medical Specialties. All the included children underwent complete blood counts using an automated hematology analyzer (Sysmex XP-300™, USA) the analyzer was calibrated with reference methods and had regular quality control program. Haemoglobin analysis and estimation of HbA2 for thalassemia screening was done by high performance liquid chromatography (HPLC) using (D10, BIORAD Laboratories, Hercules, USA) those with HbA2% >3.5% were considered to have β-Thalassemia Trait. Iron studies, including serum iron screened by a kit (POINTE SCIENTIFIC Inc., CA, USA), and serum ferritin was measured using immunoassay (Roche Diagnostics GmbH, Mannheim,

Germany). The analyzer was calibrated with reference methods and had regular quality control program. A child was considered to have coincidental iron deficiency if serum ferritin level was <15 microgram/liter. Furthermore, the sample subdivided into two groups (according to the serum ferritin level), the first group of those with combined beta thalassaemia minor and iron deficiency (group I), while the remaining β-thalassaemic children with normal serum ferritin levels composed the second group (group II). Different demographic, clinical, diagnostic and laboratory variables compared between the two groups, the data will be recorded on a specially designed questionnaire, collected and entered in the computer and then analyzed using appropriate data system which is called Statistical Package for Social Sciences (SPSS) version 22 and the results of different variables, with a statistical significance level of < 0.05. The results presented as rates, ratio, frequencies, percentages in tables and figures and analyzed using T-test and Chi square test.

Results

One hundred and twelve children with beta thalassemia trait (BTT) were included in the study with a concomitant iron deficiency frequency of (34.82%). Distribution of the two groups according to the serum ferritin is shown in Figure 1.

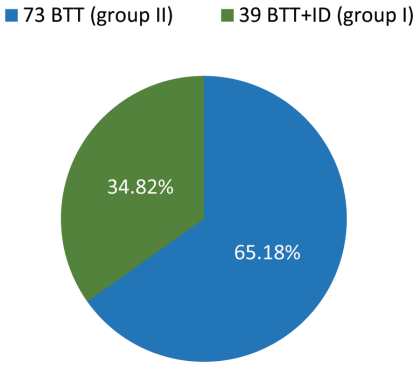

Figure (1): Frequency of concomitant iron deficiency (no. =112).

The mean age ± SD of the whole sample was 38 ± 16 months, ranging from 13 to 60 months. Table 1 shows that more than half (53.6%) of the whole sample aged > 3 years, yet the coincidence of iron deficiency was significantly (p-value < 0.001) higher among the younger age children.

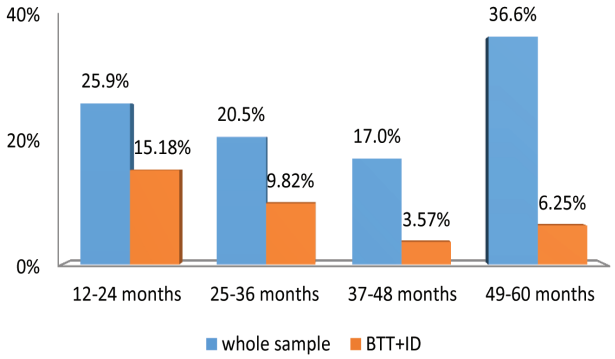

Figure (2): Age subgroups and frequency of combined iron deficiency.

The results show no significant association between the coexisting of iron deficiency in thalassemia trait with mother education (p-value = 0.16), father education (p -value= 0.07), mother occupation (p-value = 0.18), and father occupation (p-value = 0.64). In general, the majority of fathers and mothers were of intermediate educational levels, and work in a relatively lower rank occupation.

Table (1): Demographical variables and frequency of concomitant iron deficiency.

	Serum ferritin						
	BTT+ID		BTT		Total		
	No.	(%)	No.	(%)	No.	(%)	p-value
Gender							0.27
Female	14	35.9	34	46.6	48	42.9	
Male	25	64.1	39	53.4	64	57.1	
Residency							0.53
Rural	14	35.9	22	30.1	36	32.1	
Urban	25	64.1	51	69.9	76	67.9	
Known carriers							0.84
Yes	20	51.3	36	49.3	56	50.0	
No	19	48.7	37	50.7	56	50.0	
Consanguinity							0.46
Yes	21	53.8	34	46.6	55	49.1	
No	18	46.2	39	53.4	57	50.9	
Total	**39**	**100**	**73**	**100**	**112**	**100**	

*By Chi square test.

In Table 3; no significant association was detected between pattern of feeding during the first months of life with development of iron deficiency (p-value = 0.07) where it is evident in the Table that (28.2%) of I.D.+BTT cases had 1st degree malnutrition which was significantly higher than the proportion (8.2%) in the BTT group (p-value = 0.005). The same Table shows that only (30.8%) of the I.D. group had history of iron/folic acid intake, compared with (50.7%) of the BTT group (p-value = 0.04).

Table (2): Association between serum ferritin with nutritional and supplements use in the two studied groups.

	Serum ferritin						
	BTT+IDA		BTT		Total		
	No.	(%)	No.	(%)	No.	(%)	p-value
Feeding							0.07
Breast	20	51.3%	22	30.1%	42	37.5%	
Bottle	9	23.1%	29	39.7%	38	33.9%	
Mixed	10	25.6%	22	30.1%	32	28.6%	
Nutritional status							0.005
No malnutrition	28	71.8%	67	91.8%	95	84.8%	
1st degree malnutrition	11	28.2%	6	8.2%	17	15.2%	
Previous medications							0.04
Iron/Folic acid intake	12	30.8%	37	50.7%	49	43.8%	
Nil	27	69.2%	36	49.3%	63	56.3%	
Total	**39**	**100.0%**	**73**	**100.0%**	**112**	**100.0%**	

*By Chi square test.

Table (3): Data comparison between BTT with and without coexisting I.D.

Parameter	S. ferritin	N	Mean	S. D	p-value
RBC X 10^{12}/l	BTT+IDA	39	5.34	0.65	0.31
	BTT	73	5.45	0.46	
Hb g/dl	BTT+IDA	39	9.35	0.84	0.001
	BTT	73	10.76	0.84	
Platelets X10^{9}/l	BTT+IDA	39	439.60	119.41	0.004
	BTT	73	376.90	101.73	
MCV fl	BTT+IDA	39	57.20	3.82	0.001
	BTT	73	61.15	3.68	
MCH pg	BTT+IDA	39	17.69	1.41	0.001
	BTT	73	19.34	2.48	
RDW %	BTT+IDA	39	19.51	1.50	0.001
	BTT	73	15.88	1.44	
Hb A2 %	BTT+IDA	39	4.83	0.85	0.07
	BTT	73	5.16	0.94	
S. iron µg/dl	BTT+IDA	39	44.61	25.91	0.001
	BTT	73	77.74	23.41	
S. Ferritin µg/L	BTT+IDA	39	10.30	2.56	0.001
	BTT	73	66.33	31.92	

*By T- test and Chi square test.

Discussion

In 1995 a study done addressed not to presume that the trait protects iron status or that the two are in any way mutually exclusive, at least in the early years18, and Bruno Nobili et al study also found no difference in incidence of IDA in children with BTT compared to normal children[19]. In the current study the frequency of iron deficiency was (34.82%) among 112 children with β-thalassemia trait, the frequency of iron deficiency in our study is much higher than results of Anshuman et al of (13%)[20] and Asma et al where found as (17.5%)[21], but in agreement with Hinchcliffe et al who found coexisting iron deficiency in (34%) among British Asian children with BTT[18], and N. Madan et al based study remarked coincidental iron deficiency in 33 (37%) out of 88 BTT children[22]. Controversies are galore in medical literature about higher IDA prevalence in females (Asma et al, Economidou et al and Dolai et al) [21, 23, 24]. In our study there was no significance in contributions of gender to the results, this may be explained by lack of higher prevalence of IDA in females under 5 years due to nutritional deficiencies as well as the absence of excessive menstrual blood loss seen in teenagers and adults' females. In contrary to previous publication[25], the frequency of I.D in our sample was significantly negatively associated with age and in agreement to Hinchcliffe et al18 and Anshuman et al[20] published articles. Our results have demonstrated lower initial hemoglobin levels in patients with coexisting IDA and BTT in agreement with earlier authors[24, 26]. This has been explained by lower hemopoietic nutrients due to iron deficiency superimposing on the imbalance in globin chain synthesis[25]. As expected; statistical significant changes have also been shown in other red cell parameters, serum iron and ferritin Table3, compared to other publishers who showed same results, furthermore those changes also improved after adequate iron replacement therapy[26-28]. HbA2 levels have been reported to be lower in patients with coexisting IDA and BTT, and even with improvement in levels after iron therapy[26, 29]. However, our study results have shown no significant difference in HbA2 levels between the b-thalassaemic children with or without iron deficiency as in other earlier published treatise[30, 31]. The reduction in HbA2 levels in patients with concomitant BTT and IDA has been suggested to interfere in the diagnosis of the former. A recent study has hypothesized that such an occurrence can lead to these patients with BTT marrying another person with BTT with attendant risk of birth of thalassemia major child[32].

Conclusions

We found that iron deficiency anaemia co-existed in more than one third of children with beta thalassaemia minor, and may potentially increase the severity of anaemia among them. Hence, iron deficiency anaemia should be identified and treated in thalassaemic minor children. Furthermore, low serum ferritin didn't impact the hemoglobin A2 level in those children with concomitant iron deficiency anaemia and beta thalassemia trait.

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