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Research Article

Assessment of Iron Deficiency Anemia as a Prognostic Factor for Childhood Asthma

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Received: September 13, 2019; **Published:** October 29, 2019

Abstract

Background: Dietary factors are implicated in the development of asthma exacerbations in children as well as adults. Iron deficiency anemia has been stated as a prognostic factor for childhood asthma attacks and severity.

Objectives: This study was conducted to determine the association between iron deficiency anemia and bronchial asthma among children. Also, to compare the prevalence of iron deficiency anemia between non-asthmatic and asthmatic children at the same age group.

Subjects and Methods: A diagnostic cross-sectional analytical study was conducted during the period from June 2016 to March 2018. This study was carried out on 56 asthmatic patients and 56 normal children. The study was conducted in the pediatric department, Suez Canal University hospital, Ismailia city, Egypt. Both study and control groups were subjected to a detailed history included the personal data, present history, nutritional history, past history and family history. All children included in the study were subjected to a full clinical examination including chest examination, along with the anthropometric measurements. Laboratory investigations in the form of CBC, serum Ferritin, and total IGE were ordered. An information leaflet was offered to children family and informed consent was taken from both parents (father and mother).

Results: IDA was prevalent in the cases group 39.29% rather than in the control group 35.71% ($P > 0.05$). Also, there was a moderate negative correlation between serum ferritin level and asthma severity ($R = -0.517$, $P = < 0.001$) with a mild negative correlation between severity and serum HB level ($R = -0.422$, $P = < 0.001$)

Conclusion: From the data of this study, it can be concluded that incidence of iron deficiency anemia is not uncommon in pediatric patients with bronchial asthma. In our study the increasing number of asthmatic attacks was noticed in the study group especially with those with decreased serum ferritin levels as an indicator of depleted iron stores; therefore, Iron deficiency anemia is a contributing factor to the severity of asthmatic attacks.

Keywords: *Iron Deficiency; Anemia; Asthma*

Introduction

Asthma is a common, chronic respiratory disease affecting 1-18% of the population in different countries. Asthma is characterized by variable symptoms of wheeze, shortness of breath, chest tightness and/or cough, and by variable expiratory airflow limitation. Both symptoms and airflow limitation characteristically vary over time and in intensity. These variations are often triggered by factors such as exercise, allergen or irritant exposure, change in weather, or viral respiratory infections [1].

Symptoms and airflow limitation may resolve spontaneously or in response to medication and may sometimes be absent for weeks or months at a time. On the other hand, patients can experience episodic flare-ups (exacerbations) of asthma that may be life-threatening and carry a significant burden to patients and the community. Asthma is usually associated with airway hyper-responsiveness to direct or indirect stimuli, and with chronic airway inflammation. These features usually persist, even when symptoms are absent or lung function is normal, but may normalize with treatment [1].

Dietary factors are implicated in the development of asthma in children as well as adults [2]. It was proposed that anemia may explain some part of this pattern [3].

Iron deficiency anemia (IDA) is the most common nutritional disorder in the world especially Eastern Mediterranean Region. The prevalence of anemia was found to be especially high among children from low socioeconomic groups who live in crowded environments and prone to recurrent infections [4]. Iron deficiency is a state in which there is insufficient iron to maintain the normal physiological function of tissues such as the blood, brain, and muscles. Iron deficiency can exist in the absence of anemia if it has not lasted long enough or if it has not been severe enough to cause the hemoglobin concentration to fall below the threshold for the specific sex and age group [5].

Few reports described association between anemia and bronchial asthma [6]. Anemia has been shown to be a risk factor for lower respiratory tract infection (LRTI) [7] and asthma [8]. Maternal anemia was found to be associated with increased risk of wheezes and asthma in children [9].

The relation of anemia to atopic diseases has been studies in some reports. Drury., *et al.* 2014 found association of eczema, asthma, food allergy with anemia particularly microcytic hypo-chromic anemia. Whether anemia is the result of chronic inflammation associates atopy or it risk factor of atopic diseases. This needs further investigation [10].

Iron has variable role regarding asthma and respiratory function. Some reports described iron as free radicle and potentially toxic, impair pulmonary function, and potentiate asthma. On other hand, iron is component of cellular enzyme with respiratory function, hemoglobin and myoglobin, its deficiency (ID) may impair respiratory function and associate asthma development [11]. Some reports described anti allergic role of iron in experimental animals. Iron deficiency was identified as a trigger for increased mast cell activation that was associated with mast cell-dependent hair loss in IL-10-deficient mouse pups [12].

Subjects and Methods

Study design

This is a diagnostic cross sectional analytical study.

Study setting

The study was conducted at the Pediatric Department, Suez Canal University Hospital, and Ismailia city.

Target population

Children aged 4 - 12 years admitted at the inpatient unit or visiting the outpatient chest clinic of the Pediatric department in Suez Canal University Hospital. Two groups were recruited:

- **Group I (study group):** Asthmatic children according to GINA guidelines definition of asthma [1].
- **Group II (comparative group):** Children of the same age and gender as the study group were selected from the outpatient Paediatric clinic for routine follow up with no personal, family history or evidence of asthma.

Inclusion criteria

Asthmatic children aged 4 - 12 years old (considered being asthmatic according to the definition of GINA 2017.

Exclusion criteria

1. Any child receiving iron supplementation.
2. Any child presented with lower respiratory tract infection.
3. Any child with other types of anemia.
4. Any child on inhaled steroid for at least 12 months.
5. Any child with recent chest, heart, and abdominal surgery.
6. Any child with chronic heart, liver and kidney disease or any condition that can alter hemoglobin level.

Methods and procedures

Both study and control groups were subjected to:

Full history taking

The data was collected in a case sheet. It was divided into five sections; personal data, present history, nutritional history, past history and family history.

Personal data encompasses name, sex, age, consanguinity, address, telephone number.

Present history including presenting symptoms, alarming symptoms, and the number of episodes of wheeze or shortness of breath. A history of asthma exacerbations, asthma medications, chest tightness, and cough has been reviewed.

With special attention to intermittent attacks, cough, and expectoration, wheezy chest, dyspnea, chest tightness, tachypnea, signs of hyperinflation, prolonged expiratory phase, expiratory Rhonchi, and pallor.

Hospital records were also examined for relevant data & Chest radiographs will be examined and added if present.

Clinical examination:

- General examination including: general appearance and vital signs.
- Anthropometric measurements: weight, height, and BMI.
- Chest examination.

Laboratory investigations:

1. **Complete blood count**: Hb level was estimated in the blood samples using an automatic blood cell counter. The cutoff point for low Hb level was 11 g/dl for children < 5 years and < 12 g/dl in children five years and older; meeting the definition of anemia as Hb level being two standard deviations (SDs) below the mean for age and gender, as fixed by the WHO [13].
2. **Serum ferritin level** (a measure of iron stores): As for ferritin, the Enzyme Linked Immuno-Sorbent Assay (ELISA) was used with a cutoff point of ferritin < 12 micrograms/L in children up to five years old, and < 15 micrograms/L in individuals five years and older [14].
3. **Serum total IgE:** Total IgE levels were obtained from serum and measured using RIDA allergy screen panel 2 or 3 test kit (R-Biopharm AG, Darmstadt, Germany) [7,15].

Procedure:

1. Blood samples were obtained from the antecubital vein of each child for complete blood count, serum ferritin level and total IgE.
2. Sterile, disposable syringes and needles and proper tubes were used.
3. The samples were Serum, free of hemolysis and separated from cells as rapidly as possible.

4. Stability of the sample: Ferritin kits are stable at 2 - 8°C for 7 days after opening.
5. The samples were analyzed by Micro lab instrument 300.
6. Blood samples were sent to the laboratory, processed, and examined immediately for a complete blood count by DIAGONRLTD (D-Cell60).
7. Serum ferritin level and were measured by ELISA (Sandwich-technique) using Enzyme Immuno-Assay Test Kit. No.10601. Perfect Company.
8. Collection of samples includes information on the name, age, and sex of the children

Data analysis

The data was coded, organized and final study results were stated using SPSS [statistical package for social sciences] version 20 and data were presented through tables and graphs.

The data was compared by using Chi-square test for qualitative variables as absolute (n) and relative (%) frequency values while Independent T-Test were used for quantitative variables as mean, standard deviation, median, minimum and maximum values.

Statistical significance was considered at p-value < 0.05.

Results

Table 1 shows baseline demographic characteristics of the two studied groups showing that there is no significant difference between the two groups ($P > 0.05$).

Title No.		Control (N = 56)		Cases (N = 56)		P. value
		%	No.	%		
Gender	Male	23	41.1%	26	46.4%	0.572
	Female	33	58.9%	30	53.6%	
Age (Year)	Mean ± SD	7.69 ± 2.4		8.71 ± 2.66		0.162
	Range	4 - 12		4-12		
Residence	Urban	19	33.9%	21	37.5 %	0.438
	Rural	37	66.1 %	35	62.5%	

Table 1: *Socio-demographic characteristics of the studied populations.*

Table 2 demonstrates that among the two groups there was no significant difference regarding the anthropometric measurements ($P > 0.05$).

Measures		Cases (N = 56)	Cases (N = 56)	P value
Weight (kg)	Mean ± SD	24.75 ± 7.17	27.66 ± 9.34	0.06
	Range	15 - 42	16 - 40	
Height (cm)	Mean ± SD	117.07 ± 12.59	124.71 ± 14.31	0.633
	Range	95 - 142	97 - 162	
BMI (kg/m^2)	Mean ± SD	17.7 ± 2.46	17.3 ± 2.87	0.341
	Range	10.88 - 22.71	11.89 - 22.86	

Table 2: *Anthropometric measures among the two groups.*

**BMI: Body Mass Index.*

Table 3 demonstrates the clinical data of the asthmatic cases.

Measures		Cases (N = 56)
Onset of asthma (years)	Mean ± SD	3.38 ± 2.35
	Range	0.5 - 9
*Duration of wheeze (GINA, 2017)	Prolonged early wheeze	18 (32.14%)
	Intermediate onset wheeze	11 (19.64%)
	Late onset wheeze	11 (19.64%)
	Persistent wheeze	16 (28.57%)
*Asthma pattern (GINA, 2017)	Infrequent intermittent	6 (10.7)
	Frequent intermittent	18 (32.1)
	Mild persistent	16 (28.6)
	Moderate persistent	14 (25)
	Sever persistent	2 (3.6%)
*Severity (GINA, 2017)	Mild	36 (64.3%)
	Moderate	15 (26.8%)
	Severe	5 (8.9%)
Hospital admission	No previous admission	34 (60.7%)
	Once	16 (28.6%)
	Twice	3 (5.4%)
	Three times	3(5.4%)
*Asthma control (GINA, 2017)	Well controlled	15 (26.8%)
	Partially controlled	23(41.1%)
	Uncontrolled	18(32.1%)

Table 3: *Clinical data of the patients group.*

**The assessment of duration of wheeze, asthma pattern, asthma severity, and asthma control according to GINA, 2017 guidelines.*

Among the 56 studied asthmatic patients, the mean disease onset was 3.38 ± 2.35 years. Also, it demonstrates that 36 children were suffering from mild attacks of asthma while 5 children were severe asthmatic.

Table 4 demonstrates the use of reliever medication during the attack and controller treatment onwards by the 56 studied asthmatic patients; 5.4% of the patients tended to use combined Inhaled CS + LTRA while 94.6% weren't on any controller medication. 94.6% children used SABA to relieve their attacks, 3.6% of cases used a combination of inhaled SABA + CS as a reliever medication, while 1.8% did not use any reliever medications.

	Measures	Cases (N = 56)
Control treatment	No control treatment	53 (94.6%)
	ICS +LTRA	3 (5.4%)
Reliever treatment	No	1 (1.8%)
	SABA via nebulizer	44 (78.6%)
	SABA via spacer	4 (7.1%)
	Inhaled SABA	5(8.9%)
	SABA + ICS via nebulizer	2 (3.6%)

Table 4: *Medication data of the studied asthmatic patients.*

Table 5 demonstrates that among the two groups, there was no significant difference in the laboratory investigations as ($P > 0.05$) regarding CBC, HB levels, and S. ferritin levels.

Characteristics		Control (N = 56)	Cases (N = 56)	P value
Type of anemia	Normal	19 (33.93%)	23 (41.07%)	0.827
	Microcytic, hypochromic anemia	20 (35.71%)	22 (39.29%)	
	Normocytic normochromic anemia	17 (30.36%)	11 (19.64%)	
TLC×10^3	Mean ± SD	7.19 ± 1.98	7.33 ± 2.14	0.146
	Range	2.6:12.4	2.8:13	
Ferritin (µg/L)	Mean ± SD	28.51 ± 29.5	20.84 ± 21.09	0.115
	Range	3.34:145	3.76:87.3	
HB (g/dL)	Mean ± SD	11.72 ± 1.06	11.85 ± 1.16	0.522
	Range	9.85:14.6	9.4:14.5	

Table 5: *Cases versus controls regarding the laboratory data.*

Table 6 demonstrates:

1. A moderate negative correlation between severity and serum ferritin level (R = -0.517, P = < 0.001).
2. A moderate positive correlation between severity and serum IgE level (R = 0.591, P = < 0.001).
3. A mild negative correlation between severity and HB level (R = -0.422, P = < 0.001).

		Severity
Ferritin	Pearson Correlation	-.517**
	Sig. (2-tailed)	.000
	N	56
HB	Pearson Correlation	-.422**
	Sig. (2-tailed)	.001
	N	56
IgE	Pearson Correlation	.591**
	Sig. (2-tailed)	.000
	N	56

Table 6: *Correlation analysis between severity of asthma and different laboratory investigations.*

*** Correlation is significant at the 0.01 level (2-tailed).*

Table 7 shows a significant negative correlation between the mean values of serum ferritin concentration and serum hemoglobin level and severity of asthma; low values were in concordance with severe asthma while normal values were relatively related to mild asthma. A significant positive correlation between the mean level of serum IGE and asthma severity was noted.

Mean	Severity		
	Mild	Moderate	Severe
Ferritin (µg/L)	33.98	15.54	7.47
IGE (IU/L)	237.89	546.93	784.00
HB (g/dL)	12.34	11.71	10.56

Table 7: *Correlation analysis between the mean values of different lab investigations and asthma severity.*

Discussion

Asthma is a chronic inflammatory condition of the lung airways resulting in episodic airflow obstruction. Different etiological factors including genetic, environmental factors are involved in development of asthma. Among risk factors for asthma exacerbation: infection, Allergen exposure, non-use of controller medication, non -white race and winter season. Dietary factors are implicated in the development of asthma in children as well as adults [2]. It was recently proposed that anemia may explain some part of this pattern [3].

Iron deficiency anemia (IDA) is the most common nutritional disorder in the world especially Eastern Mediterranean Region. The prevalence of anemia was found to be especially high among children from low socioeconomic groups who live in crowded environments and prone to recurrent infections [4]. Iron deficiency is a state in which there is insufficient iron to maintain the normal physiological function of tissues such as the blood, brain, and muscles. Iron deficiency can exist in the absence of anemia if it has not lasted long enough or if it has not been severe enough to cause the hemoglobin concentration to fall below the threshold for the specific sex and age group [5].

Few reports described association between anemia and bronchial asthma [6]. Anemia has been shown to be a risk factor for lower respiratory tract infection (LRTI) [7] and asthma [8]. The relation of anemia to atopic diseases has been studies in some reports.

Drury., *et al*. 2016 found an association of eczema, asthma, food allergy with anemia particularly micro-cytic hypo-chromic anemia. Whether anemia is the result of chronic inflammation associates atopy or it is a risk factor of atopic diseases. This needs further investigation [10]. Thus, our interest was to examine the impact of iron deficiency anemia and iron status on asthmatic pediatric patients.

Our study hypothesizes that iron deficiency anemia has a good relation with increased incidence and number of asthmatic attacks in children. In order to test this hypothesis, iron deficiency was assessed in pediatric asthmatic patients. Complete blood count and serum ferritin level (as an indication of iron stores) were measured in patients with bronchial asthma and compared with normal children of the same age and sex.

In the current study, the age of both cases and control groups ranged from 4 to 12 years and the mean was 8.71 ± 2.66 and 7.69 ± 2.4 respectively. The cases group included 26 males (46.4%) and 30 females (53.6%), while the control group included 23 males (41.1%) and 33 females (58.9%). The study showed no statistically significant difference between the two groups regarding age and sex (P > 0.05).

In a study done by [6] who studied anemia as a risk factor for childhood asthma, their study included 200 children in the age group of 2 - 18 years with upper or lower respiratory tract infection, 100 children with asthma were taken as the study group and another 100, age and sex-matched children without asthma were taken as the control. PFTS were performed on those over six years showing evidence of asthma and the study showed that asthma was present in 74 (74%) children in the study group and in 33 (33%) children in the control group. It also stated that anemic children were 5.75 times more susceptible to asthmatic attacks when compared with non-anemic children.

The reason for such difference is that they studied the occurrence of asthma in previously diagnosed anemic children and the sample size was relatively large in comparison with ours. Also, the type of study was a prospective cohort study. In addition to the variety of investigations used to assess iron deficiency anemia, besides using PFTs to assess the severity of asthma.

In the present study, the BMI in the cases group ranged from 11.89 - 22.86 with a mean 17.3 ± 2.87. On the other hand, the BMI in the control group ranged from 10.88 to 22.71 and a mean was 17.7 ± 2.46. The study showed that there was no significant statistical difference between the studied groups with a P-value > 0.05. The results were in concordance with that by [16] who assessed iron deficiency anemia as a risk factor for childhood asthma and its possible effect on pulmonary functions. The BMI in group I ranged from 22 to 30 and mean was 25.6 ± 8.9 and in group II the BMI ranged from 21 to 29 and mean was 24.8 ± 7.3. The study showed that there was no significant statistical difference between the studied groups with P value > 0.05.

According to the Australian Asthma Handbook; a rapid asthma severity classification of acute attack has been launched. Applied in our study (64.3%) were mild cases, (26.8%) were moderate, and (8.9%) severe asthmatics. Our results were in agreement with a similar study done by [17], who conducted a case control study and investigated iron deficiency and iron deficiency anemia in children with bronchial asthma to study possible association of both conditions and the possible role of IDA in development of bronchial asthma and its exacerbation in children. There study included 40 asthmatic cases, and 16 healthy children taken as controls; among 40 cases of asthma, 8 cases (20%) presented with the mild attacks, 22 cases (55%) moderate attack and 10 (25%) cases presented in the severe acute attack.

In the current study, IDA was prevalent in the cases group 39.29% rather than in the control group 35.71% but with no statistical significant difference (P = 0.827). Lower Hb, Hct, MCV, MCHC, MCH were found in asthmatic cases to controls. These results indicate that hypo-chromic microcytic anemia is more prevalent in our asthma cases. Association of anemia with asthmatic children was found in other reports. Ramakrishnan K and Borade A suggested that anemia is a possible risk factor of asthma. They found that the incidence of asthma in Indian anemic children was 74% compared to 33% of non-anemic controls with predominance of IDA (85% of anemic asthmatics). Our results were also in agreement with Fida and Kamfar 2013 who conducted a cross sectional study on 117 asthmatic children. According to complete blood count, asthmatic patients were divided into patients with iron deficiency anemia [19.70% (n = 23)] and without iron deficiency anemia [80.30% (n = 94)]. In asthmatic patients with iron deficiency anemia; mean corpuscular hemoglobin, platelets count, iron and ferritin were significantly lower than those without anemia. The prevalence of iron deficiency anemia in asthmatic patients was 19.70% summarizing that iron deficiency anemia needs to be considered as a risk factor in asthmatic patients. Eissa SA., *et al.* [16] found children with IDA have more risk of asthma exacerbations (66%) compared to non-asthmatics (24%).

There was a moderate negative correlation between serum ferritin level and asthma severity with a mild negative correlation between severity and serum HB level. Various studies have shown that deleterious effect of anemia on various systems of the body like the involvement of nervous system leading to insomnia, mental irritation, lightheadedness, impaired cognitive functions etc. It also affects the immune system of the body and reduces immunity. A decrease in strength of respiratory muscles including diaphragm reduces the pulmonary functions [18].

On contrary to our results, IDA can be a risk factor of asthma rather than a prognostic in a previously mentioned study by [17], IDA was significantly more frequent in asthma cases than healthy controls. This was attributed to the smaller sample size and strict exclusion criteria as mentioned before.

Asthma in children has different phenotypes: 1-Transient non atopic types (infrequent intermittent and frequent intermittent asthma) which start in preschool age, provoked by viral URTI, resolves by school age. 2- Persistent atopy associated type which start in early preschool age, associated with atopic manifestation, elevated IgE, provoked by allergen sensitization, and may persist into late childhood (persistent asthma). Inflammatory reaction is evident in this type. Most of our patients are of atopic persistent type 83.9%, compared to non-atopic transient phenotype of asthma 16.1%, where chronic inflammation is not present. The results were different with that by [17], who found that most of the studied asthmatic patients are of non-atopic transient phenotype of asthma where chronic inflammation is not present.

The percentage of children with low iron stores, as indicated by a serum ferritin concentration < 12 µg/L [19], was only 48% in the asthmatic group in this study, compared to 35.7% in the control group. Among the studied asthmatic group; serum ferritin level ranged from 3.34:145 with a mean of 28.51 ± 29.5, while those in the control group serum ferritin ranged between 3.76 and 87.3 with a mean of 20.84 ± 21.09, showing no statistically significant difference (P < 0.05). Although there is no statistically significant difference between both groups regarding Iron deficiency anemia, the iron deficiency was little bit higher in studied asthmatic group than in the controls. These results were in agreement with that of Fida and Kamfar 2013, who conducted a cross sectional study among patients attending asthma clinics at King Abdul-Aziz University Hospital, Jeddah, Saudi Arabia from January 2008 - June 2009. In asthmatic patients with iron

deficiency anemia; mean corpuscular hemoglobin, platelets count, iron and ferritin were significantly lower than those without anemia. The prevalence of iron deficiency anemia in asthmatic patients was 19.70%. In conclusion, iron deficiency anemia needs to be considered as a predictor for childhood Asthma.

Regarding asthma management plans in the study group; there were two management lines: reliever medications and controller medications. 94.6% of cases used SABA as a reliever medication for acute attacks whether via nebulizer, or spacer or inhalation, while 3.6% used a combination of SABA + ICS and this stood for the severe cases. Although 94.6% were not on controller medications, only 5.4% used a combination of inhaled CS + LTRA to prevent occurrence of further attacks.

From the data of this study, it can be concluded that incidence of iron deficiency anemia is not uncommon in pediatric patients with bronchial asthma. Further studies are needed to assess the relationship between severity of asthma and the degree of anemia, and likewise, if the treatment of anemia could improve asthmatic attacks.

Asthma and respiratory diseases are the leading causes of death in children, and identification of modifiable risk factors of asthma and respiratory may help in reducing the burden of diseases [20]. Literature revealed a few studies on anemia in patients with acute asthma. To the best of our knowledge, our study is one of the few studies evaluating Hb level in asthma and allergic diseases, and the first one to be conducted among children in Suez Canal Region.

Conclusion

The present study investigated the role of iron in childhood asthma. Hemoglobin deficiency was common among study group. The increasing number of asthmatic attacks was significantly higher in patients with iron deficiency anemia compared to control group, particularly among asthmatic children who had decreased serum ferritin level a biomarker of depleted body iron stores.

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Volume 8 Issue 11 November 2019