JKAU: Med. Sci., **Vol. 20** No. 1, pp: 3-13 (2013 A.D. / 1434 A.H.)
DOI: 10.4197/Med. 20-1.1

Is Iron Deficiency Anemia a Risk Factor in Asthmatic Children?

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Abstract. Asthma, a common problem worldwide with numerous risk factors; yet, few researchers mentioned iron deficiency anemia as a risk factor. This study evaluates prevalence of iron deficiency anemia among asthmatic children and adolescents. A cross sectional study conducted among patients attending asthma clinics at King Abdulaziz University Hospital, Jeddah, Saudi Arabia from January 2008 – June 2009. 117 children (0.7-15-years-old) were included in the study. All participants were subjected to complete history, clinical examination, laboratory and imaging investigations. Serum iron and ferritin were estimated using ELISA kits. 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 all asthmatic patients; low values were found for hematocrit (41.0%); mean corpuscular volume (41.9%) and hemoglobin (17.9%); platelets (0.9%); iron (5.1%); ferritin (12.0%), while high value was found for red cell distribution width (31.6%). 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 risk factor in asthmatic patients.

Keywords: Bronchial asthma, Iron deficiency anemia, Ferritin, Risk factor, Children.

Introduction

Asthma is a common medical problem encountered by clinicians dealing with children. Its incidence has substantially increased worldwide[1].It is a major cause of morbidity and mortality among the pediatric age

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Accepted for publication: 25 June 2012. Received: 05 November 2011.

group[2].Childhood asthma is associated with increased rates of doctor visits, hospitalizations, school absenteeism, parental work absenteeism, child activity limitations, and child disability[3,4]. Although family history of asthma and atopy is highly predictive of asthma in children[5], most researchers agree that environmental factors must play an important role, as genetic variation alone cannot explain such a steep increase in childhood asthma rates[6]. A study done by Hijazi, *et al*[7]suggested that dietary factors during childhood are an important influence in determining the expression of wheezy illness, such as living on urban/rural residence, sex, family history, and atopy. Their findings are consistent with previous studies in adults, and with the hypothesis that the change in diet has been a determinant of the worldwide increase of asthma and allergies[7]. Formula feeding and early food exposures predispose to increased risk for asthma and allergy[8,9]. For sodium intake, an unfavorable association is observed in asthmatics, however, the intake of fruit and vegetables, and fish is more likely to be beneficial[10].

Iron, an essential mineral is a component of hemoglobin, myoglobin, and a number of enzymes (*e.g.*, cytochromes, catalase, peroxidase). Iron is stored primarily as hemosiderin or aggregated ferritin, found in reticuloendothelial cells of the liver, spleen, and bone marrow. Approximately, two-thirds of the total body iron circulates the red blood cell mass in hemoglobin, the major factor in oxygen transport. Iron deficiency can affect muscle metabolism, heat production, and catecholamine metabolism, plus it has been associated with behavioral or learning problems in children. Iron deficiency anemia (IDA) is the most common nutritional disorder in the world, as it is in the Eastern Mediterranean Region (EMR). A total of 149 million in the EMR are iron deficient or anemic according to the World Health Organization (WHO) criteria. The prevalence of anemia was found to be especially high among children from low socioeconomic groups; such children live in crowded environments and are also prone to recurrent infections. Prevention of iron deficiency is essential as previous studies highlighted the adverse effects of iron deficiency on cognitive development, attention, behavior, school performance, and physical activity in children[11,12]. Furthermore, iron deficiency is also associated with impaired immune competence, and therefore, can lead to increased morbidity[13]. It has already been reported that low hemoglobin impairs

tissue oxygenation and acts as an independent risk factor for developing respiratory tract infections in children[14].

There are very few reports available in medical literature regarding the association of anemia and childhood asthma. Therefore, this study aims to assess the incidence of iron deficiency anemia in asthmatic pediatric patients in supporting the clinical findings at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia.

Methods

This cross sectional study was conducted in 117 asthmatic pediatric patients from the age group of 0.7-15 years old who attended the Pediatric Asthma Clinic at KAUH, Jeddah, KSA during the period January 2008 to June 2009. The study was approved by the Ethical committee of KAUH. Children were recruited into the study after obtaining written informed consent from their parents or guardians.

Symptomatic cases were seen and examined by the author of this study. For each child, a detailed medical history was obtained by interviewing the parents or (responsible persons) guardian. A thorough clinical examination, chest X-ray and pulmonary function tests for children more than 6 years were carried out by the study pediatrician. Information obtained from the interview includes family history, history of allergy and exposure to precipitating factors. Asthma was diagnosed by clinical examination and by applying the following criteria: (i) Episodic symptoms of airway obstruction, (ii) more than three episodes were present, (iii) airway obstruction was at least partially, reversible and (iv) alternative diagnosis were excluded[15]. Symptoms of airflow obstruction were defined as any of the following: (1) Recurrent episodic respiratory symptoms of cough, wheeze and chest tightness induced by precipitating factors characteristic of asthma; or (2) Pulmonary function tests (PFTs) indicating airway obstruction [forced expiratory volume in 1 second / forced vital capacity (FEV_1/FVC) ratio below the lower 95% confidence intervals (CIs) for age, race, gender, and height] or air trapping present on body plethysmography [residual volume (RV) / total lung capacity (TLC) ratio greater that 30%]. Reversibility of airflow obstruction was defined as either: (1) Symptoms that improve with administration of a bronchodilator; or (2) a 12% or greater increase in FEV_1 after bronchodilator administration. Excluded from the study were patients with congenital malformation of the chest wall, severe other systemic illness, protein energy malnutrition, those with chest diseases

other than asthma. Also, children with known hematological diseases except for IDA; children on iron medication at the time of or 30 days prior to material collection, and children with a history of prematurity or low birth weight.

A venous blood sample (5 ml) was obtained from each child by using sterile equipment. An aliquot (2.5 ml) was collected in a tube without anticoagulants, serum was separated by centrifugation at 3000 rpm (MSE Soniprep 150; MSE Scientific Instruments, Crawley, Sussex, United Kingdom) for 7 min at 28°C, and aliquots were stored at -20°C. A complete blood count (CBC) including hemoglobin, hematocrite, mean cell volume (MCV), and mean hemoglobin concentration (MHC) red cell distribution width (RDW) and platelets counts was obtained by using an automated analyzer (Cel-dyn 3500; Abbott Diagnostics, Abbott Park, IL). Iron stores were assessed by serum iron and ferritin determination (immunoradiometric assay; DPC Inc, Los Angeles). The operational definition of anemia, in terms of hemoglobin levels, was established by the World Health Organization, adopting the level of 11.0 g/dl for children < 6 years. For children of ages between 6 and 14 years, and non-pregnant adult women, the level was 12 g/dl, and 13 g/dl for adult men[16]. According to hemoglobin levels, asthmatic patients were divided into patient without anemia (n = 94, 80.30%) and patient with anemia (n = 23, 19.70%). The percentage of children with low iron stores, as indicated by a serum ferritin concentration < 20 µg/L[17] was determined.

Statistical analysis was performed using the SPSS version 12. Numerical variables were reported in terms of mean and standard deviations (SD). Categorized variables were reported in term of numbers (n) and percentages (%). The baseline characteristics of the children with or without anemia were compared using unpaired "student's" *t* test, and Chi-square tests for parametric and non-parametric parameters. *P* value less than 0.05 was considered to be statistically significant.

Results

Table 1 indicated the demographic and clinical characteristics of all asthmatic patents. In this study, 59.8% (n = 70) were male while, 40.2% (n = 47) were females. The hematocrite value was < 34% in 41.0% (n = 48) and between 34.0-48.0% in 59.0% (n = 69); MCV was < 75 (fl) in 41.9% (n = 49) and from 75-87 (fl) in 58.2% (n = MCH was < 23 (pg) in 17.9% (n = 21) and between 23-30 (pg) in 82.1% (n = 96); RDW was

from 11.6-14.8% in 68.4% (n = 80) and > 14.8% in 31.6% (n = 37); platelets counts was < 150 ($X10^9$/L) in 0.9% (n = 1); between 150-450 ($X10^9$/L) in 83.8% (n = 98) and > 450 ($X10^9$/L) in 15.4% (n = 18); serum iron was < 6 (µmo/L) in 5.1% (n = 6) and from 6-27 (µmo/L).

Table 1. Description of the participants.

Parameters	**Patients** (n = 117)
Age (years) [mean(SD)]	5.33 ± 3.56
0-2 [number (%)]	29 (24.8%)
3-5 [number (%)]	36 (30.8%)
6-8 [number (%)]	31 (26.5%)
9-11 [number (%)]	14 (12.0%)
12-14 [number (%)]	2 (1.7%)
> 14 [number (%)]	5 (4.3%)
Sex	
Male [number (%)]	70 (59.8%)
Female [number (%)]	47 (40.2%)
Hemoglobin (g/dl) [mean(SD)]	11.73 ± 1.35
Hematocrite(%)[mean(SD)]	33.61 ± 3.35
< 34 [number (%)]	48 (41.0%)
34-48 [number (%)]	69 (59.0%)
MCV (fl) [mean(SD)]	72.99 ± 7.61
< 75 [number (%)]	49 (41.9%)
75-87 [number (%)]	67 (58.2%)
MCH (pg) [mean(SD)]	25.50 ± 3.59
< 23 [number (%)]	21 (17.9%)
23-30 [number (%)]	96 (82.1%)
RDW (%)[mean(SD)]	14.18 ± 1.15
11.6-14.8 [number (%)]	80 (68.4%)
> 14.8 [number (%)]	37 (31.6%)
Platelets count ($X10^9$/L) [mean(SD)]	361.38 ± 102.39
< 150 [number (%)]	1 (0.9%)
150-450 [number (%)]	98 (83.8%)
> 450 [number (%)]	18 (15.4%)
Serum iron (umol/L) [mean(SD)]	8.68 ± 3.98
< 6 [number (%)]	6 (5.1%)
6-27 [number (%)]	11 (9.4%)
Missing [number (%)]	100 (85.5%)
Serum ferritin (µg/L) [mean(SD)]	33.76 ± 23.06
< 20 [number (%)]	14 (12.0%)
20-400 [number (%)]	7 (6.0%)
Missing [number (%)]	96 (82.1%)

Data are expressed as mean +/- standard deviation (SD) and number (%) as appropriate. MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; RDW, red cell distribution width.

in 9.4 (n = 11). Serum ferritin (an iron storage protein, provides a relatively accurate estimate of body iron stores) was < 20 (ng/mL) in 12.0% (n = 14) and from 30-400 (ng/ml) in 6.0% (n = 7).

Table 2 compared the demographic and laboratory finding between asthmatic patients with and without anemia. In asthmatic patients with IDA, MCH, platelets count, serum iron and serum ferritin were

Table 2. Description of the participants.

Parameters	Patients without Anemia (n = 94, 80.30%)	Patients with Anemia (n = 23, 19.70%)	Significance
Age (years) [mean(SD)]	5.79 ± 3.44	3.46 ± 3.51	p < 0.518
0-2 [number (%)]	19 (20.2%)	10 (43.5%)	
3-5 [number (%)]	30 (31.9%)	6 (26.1%)	
6-8 [number (%)]	26 (27.7%)	5 (21.7%)	
9-11 [number (%)]	13 (13.8%)	1 (4.3%)	
12-14 [number (%)]	2 (2.1%)	-	
> 14 [number (%)]	4 (4.3%)	1 (4.3%)	
Sex			
Male [number (%)]	58 (61.7%)	12 (52.2%)	p < 0.273
Female [number (%)]	36 (38.3%)	11 (47.8%)	
Hemoglobin (g/dl) [mean(SD)]	12.28 ± 0.82	9.45 ±0.59	p < 0.201
Hematocrite(%)[mean(SD)]	34.81 ± 2.06	28.68 ± 3.07	p < 0.232
< 34 [number (%)]	25 (26.6%)	23 (100%)	
34-48 [number (%)]	69 (73.4%)	-	
MCV (fl) [mean(SD)]	74.99 ± 5.70	64.78 ± 8.97	p < 0.096
< 75 [number (%)]	31 (33.0%)	18 (78.3%)	
75-87 [number (%)]	63 (67.0%)	5 (21.7%)	
MCH (pg) [mean(SD)]	26.45 ± 2.64	21.61 ± 4.34	**p < 0.001**
< 23 [number (%)]	8 (8.5%)	13 (56.5%)	
23-30 [number (%)]	86 (91.5%)	10 (43.5%)	
RDW (%)[mean(SD)]	14.05 ± 1.07	14.74 ± 1.28	p < 0.451
11.6-14.8 [number (%)]	73 (77.7%)	7 (30.4%)	
> 14.8 [number (%)]	21 (22.3%)	16 (69.6%)	
Platelets count ($X10^9$/L) [mean(SD)]	367.77 ± 90.37	335.25 ± 140.96	**p < 0.0001**
< 150 [number (%)]	1 (1.1%)	-	
150-450 [number (%)]	83 (88.3%)	15 (65.2%)	
> 450 [number (%)]	10 (10.6%)	8 (34.8%)	
Serum iron (umol/L) [mean(SD)]	9.51 ± 5.42	8.10 ± 2.77	**p < 0.009**
< 6 [number (%)]	3 (3.2%)	3 (13.0%)	
6-27 [number (%)]	7 (7.4%)	4 (17.4%)	
Missing [number (%)]	84 (89.4%)	16 (69.6%)	
Serum ferritin (µg/L) [mean(SD)]	41.09 ± 24.93	19.11 ± 7.11	**p < 0.008**
< 20 [number (%)]	3 (13.0%)	4 (17.4%)	
20-400 [number (%)]	11(11.7%)	3 (3.20%)	
Missing [number (%)]	80 (85.1%)	16 (69.6%)	

Data are expressed as mean +/- standard deviation (SD) and number (%) as appropriate. MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; RDW, red cell distribution width.

significantly lower than those without anemia ($p < 0.001$, $p < 0.0001$, $p < 0.009$, $p < 0.008$). Meanwhile, there was no significant difference amongst other measured data. Thrombocytosis or thrombocytopenia may sometime occur in asthmatics; hence, the mechanism of these platelet abnormalities is not clear.

Discussion

The prevalence of bronchial asthma has increased continuously since the 1970s, and now affects an estimated 4 to 7% of the people worldwide. Childhood bronchial asthma varies widely from country to country. At the age of six to seven years, the prevalence ranges from 4 to 32%. The same range holds good for ages 13 and 14 years. United Kingdom has the highest prevalence of severe bronchial asthma in the world[18]. It has also increased the number of preventable hospital emergency visits and admissions. Apart from being the leading cause of hospitalization for children, it is one of the most important chronic conditions causing elementary school absenteeism[19]. Childhood bronchial asthma has multifactor causation. Geographical location, environmental, racial, as well as factors related to behaviors and life-styles are associated with the disease[20,21].

In this study, 117 asthmatic patients were assessed over a 2-year period. The most common affected age was between 3-5 years old. Although this is not a true population based study, no ascertains by another source was carried out. Thus, it reflects that asthma is common in the western part of Saudi Arabia. Childhood asthma has nearly doubled in the last 2 decades to become one of the most common chronic childhood conditions in the United States, from 3.7% of children in 1980 to 6.9% in 1995[2,22]. Previous studies have suggested that doctor-diagnosed asthma occurs in 4-17% of urban children. Furthermore, education of the patient and/or child is mandatory to prevent, minimize and treat Asthma. This component should be included in the overall approach to asthma management. In this study, of asthmatics 59.8% ($n = 70$) were male while, 40.2% ($n = 47$) were females. Male predominance had been reported in a study made by Dodge and Burrows[23].

Anemia is defined as a pathological process in which hemoglobin (Hb) concentration in red cells is abnormally low, considering variations as to age, gender, and sea-level altitude. As a result of several situations, such as chronic infections, hereditary blood conditions, deficiency of one or more essential nutrients that are necessary for the formation of

hemoglobin *e.g.*, folic acid, B12, B6 and C vitamins, and proteins[16]. Therefore, there is no doubt that iron deficiency is the cause of most anemias (known as iron deficiency anemia[24]). Iron deficiency occurs at three stages. The first stage - iron depletion - occurs when iron content is not enough to meet body requirements. At the beginning, there is a reduction in iron deposition, characterized by serum ferritin below 12 µg/L, without functional changes. If the negative balance persists, the second stage begins - iron-deficient erythropoiesis - characterized by a reduction in serum iron, transferrin saturation below 16% and an increase in the free erythrocyte protoporphyrin level. At this stage, work capacity may be reduced. At the third stage - iron deficiency anemia – hemoglobin is below the standards for age and gender. This stage is characterized by the development of microcytosis and hypochromia[24].

Anemia and respiratory tract infections are common problems among primary school children of low socioeconomic status, and a complex relation exists between iron status and infection. Iron deficiency and anemia are associated with impaired immunocompetence and the increased morbidity[13], similarly infections can affect iron metabolism[17]. Thus, our interest was to examine the incidence of iron deficiency anemia and iron status among asthmatic pediatric patients. In this study, 19.70% of asthmatic patients were anemic. Some are of the opinion that an iron supplement significantly reduces the morbidity of upper respiratory tract infection (URTI) in children[25]. An increased incidence of anemia has been reported in chronic obstructive pulmonary disease (COPD)[26]. The increased incidence of asthmatic attacks in anemic children may be due to the following facts: Hb facilitates oxygen (O_2) and carbon dioxide transport. It carries and inactivates nitric oxide (NO) and also plays the role of the buffer[27]. Hemoglobin in the blood is mainly responsible for stabilizing the oxygen pressure and the tissues[28]. Qualitative and/or quantitative reduction in Hb may adversely affect the normal functions.

The percentage of children with low iron stores, as indicated by a serum ferritin concentration < 20 µg/L[17], was only 12.0% in the asthmatic group in this study, but unfortunately only 21 patients assessed their ferritin serum levels. This value probably underestimates the proportion with low body iron stores as ferritin is an acute-phase protein that increases during infections[29,30].

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 attach.

Acknowledgment

The authors wish to express their thanks and appreciation to Dr. Omaima Saad, who participated in collecting the data and showed passion in the work.

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هل فقر دم نقص الحديد عامل خطر في الأطفال المصابين بالربو؟

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جد ة – المملكة العربية السعودية

المستخلص. الربو مشكلة مشتركة حول العالم. وجدت عوامل خطرٍ عديدةٍ لحدوثه، هناك أبحاث قليلة أظهرت نقص مادة الحديد كإحدى هذه العوامل. تهدف هذه الدراسة إلى معاينة نسبة فقرَ دم بنقص الحديد بين الأطفال والمراهقين المصابين بالربو في مستشفي جامعة الملك عبد العزيز، جدة؛ المملكة العربية السعودية. اشتملت هذه الدراسة على ١١٧ طفلا يتراوح أعمارهم بين ٠،٧ إلى ١٥ سنة من الأطفال المترددين على قسم الأطفال بجامعة الملك عبد العزيز ما بين يناير ٢٠٠٨ إلى يونيو ٢٠٠٩. تم أخذ التاريخ المرضى من المشاركين وأيضا تم فحصهم وعمل التحاليل المطلوبة. تم قياس الحديد، الفرتيين في المصل بجهاز الممتز المناعى الضوئى. تبعا لنتيجة صورة الدم الكاملة تم تقسيم المرضى إلى مجموعة مصابة بفقرَ الدم بسبب نقص الحديد (١٩،٧٠٪، ١٣ مريضا) ومجموعة غير مصابة (٨٠،٣٠٪ ٩٤ مريضاً في كل مرضى الربو، وجد نقص في الهيماتوكريت (٤١،٠٪)، الحَجْمُ الكروي الوَسَطِيّ (٩،٤١٪)، هيموغلوبينُ الكُرَيَّةِ الوَسَطِيّ (٩،١٧٪)، الصفائح (٠٪،٩)، الحديد (١،٥٪)، الفريتين (١٢،٠٪) , بينما وجد ارتفاع في عرض توزيع الكرية (٦،٣١٪). في المرضى المصابين بفقر الدم وجد أن هيموغلوبينُ الكُرَيَّةِ الوَسَطِيّ، الصفائح، الحديد، الفرتيين قلوا مقارنة بالمرضى غير المصابين. نسبة مرضى فقرَ دم بسبب نقص الحديد بين مرضى الربو ١٩،٧٠٪. من خلال هذه الدراسة فإننا نوصي باعتبار فقر الدم بعوز الحديد عامل خطر في مرضى الربو.