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Research Article
Evaluation of Iron Deficiency Anemia as a Predisposing Factor in the Occurrence of Pneumonia in Children

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Abstract

Iron deficiency anemia is a major health problem in young children. It may be associated with increased risk of pneumonia. The present study is a prospective one conducted during the period from February, 2014 until February, 2015. The study included 300 children divided into two equal groups according to presence or absence of pneumonia. For each child, a detailed history, clinical examination, chest x-ray and laboratory investigations (complete blood count, Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), iron and serum ferritin) were performed. Compared to the control group, mothers of the study group lacked both high education and social class. However, there was a significant increase of ESR and WBCs in the study group compared to the control group and there was also a significant decrease of RBCs, hemoglobin, ferritin and iron in study group when compared to control group. Finally, there was a significant inverse (negative) correlation between iron from one side and each of ESR and WBCs from the other side. On the other hand, there was a positive (proportional) significant correlation between iron and both RBCs, ferritin and hemoglobin. Iron deficiency anemia was significantly associated with pneumonia in children. Thus, early and accurate diagnosis of iron deficiency in children is of utmost importance.

Key words: Iron, pneumonia, ESR, BMI, Low repiratory tract infection, CRP

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Hemoglobin (Hb) level is the most reliable indicator in the diagnosis of anemia among individuals. Anemia represents a major public health problem that can occur at any age, but is more prevalent in pregnant women and young children. Iron deficiency anemia is the most common cause of anemia in children (De Bernoist *et al*., 2008). A National Health and Nutrition Survey in 1995 found that 58% of primary school children were anemic when a hemoglobin concentration cutoff of <12 g dL^{-1} was used (Mudalige and Nestel, 1996). Anemic children are at a greater risk of developing various consequences of anemia including infections (Pasricha *et al*., 2010).

Lower Respiratory Tract Infections (LRTI) is defined as all infections of the lungs and the airways below the larynx (Green and McColley, 2004). The LRTI includes croup syndromes, bronchitis, bronchiolitis and pneumonia (Kabra, 2013). To estimate the burden of the problems, it was reported that, acute lower respiratory tract infections (pneumonia) is the biggest single cause of childhood death in developing countries (Graham *et al*., 2008). Recent studies have shown that nutritional factors such as zinc, iron, vitamin A and others are closely related to the body's resistance to infection. Decrease in such nutrients may be a risk factor for development of infection. However, there are controversies regarding the role of nutrients especially iron in respiratory tract infections in childhood (Zuo *et al*., 2014).

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 (Lozoff *et al*., 2000). Furthermore, iron deficiency is also associated with impaired immunocompetence and therefore can lead to increased morbidity (Thibault *et al*., 1993).

The relation between iron status and morbidity is controversial (Filteau and Tomkins, 1994). Some longitudinal studies with oral iron therapy showed a reduced prevalence of respiratory and gastrointestinal infections (Angeles *et al*., 1993). Other reports indicated that there was an increase or no change in the incidence of infectious diseases (Berger *et al*., 2000; Javaid *et al*., 1991).

Since infections of the lower respiratory tract are the major morbidity and mortality indicators among the children, attempts to control the risk factors would have a great effect on the wholesome growth and development of children. The present study was designed with the objective to know the association of iron status (and subsequently hemoglobin) levels among the children with pneumonia.

MATERIALS AND METHODS

The present study was a prospective one conducted in pediatric department, Al-Azhar university hospital (Damietta), during the period from February, 2014 till February, 2015. It included 300 children divided into two equal groups according to presence or absence of pneumonia. Pneumonia was diagnosed using the WHO criteria i.e., patients having fever, cough, fast respiratory rate for age, chest in-drawing and ronchi or crepitations on auscultation. The purpose of the study was explained to the parents or guardians before taking their consents to be subjected to investigations.

Exclusion criteria: Children with other systemic illnesses like congenital heart diseases, tuberculosis, protein energy malnutrition and children who had already received antibiotics from outside were excluded from the study. For each child, a detailed medical history was obtained and a clinical examination was carried out by the study pediatrician. Socioeconomic status was recorded. Height to the nearest 0.5 cm and weight to an accuracy of 0.5 kg were documented. Hemoglobin level <11 g% was considered low in this study.

Chest x-ray posteroanterior and lateral views were obtained for each child, routine laboratory investigations, ESR and CRP were conducted for each child in the study. A venous blood sample (5 mL) was obtained from each child between 9 and 11 AM by using sterile equipment. An aliquot (2.5 mL) was collected in tubes containing an anticoagulant (EDTA), placed on ice and processed within 3 h of collection. The remaining blood (2.5 mL) was collected in a tube without anticoagulants, serum was separated by centrifugation at 3000 rpm for 7 min at 28°C and aliquots were stored at -20°C till the time of analysis. A complete blood count including hemoglobin, hematocrit, mean cell volume and WBC count was obtained by using an automated analyzer (Cel-dyn 3500; Abbott Diagnostics, Abbott Park, IL). The ESR was measured by using a modified version of the Westergren method (Dispette 2, Ulster Medical Products, a division of Lukens Medical Corporation, Albuquerque, NM). Iron stores were assessed by serum ferritin determination (immunoradiometric assay; DPC Inc, Los Angeles). All samples were assayed in duplicate and a pooled serum sample was used as an internal control. Iron level was measured using the ferrozine method without deproteinization. The CRP was considered positive if >0.3 mg dL^{-1}.

Statistical analysis: Data analysis was performed using statistical package of social science (SPSS) version 16.0 of

windows. Numerical variables were reported in terms of mean and standard deviation. Categorical variables were reported in terms of numbers and percentages. Independent samples (t) test was used to compare two means and Chi square (χ^2) for comparison between categorical variables. The $p<0.05$ was considered statistically significant for interpretation of results.

RESULTS

In the present work, age ranged from 6-12 years and there was non-significant difference between study and control groups (10.88±1.35 vs 10.81±1.49 years respectively). In addition, there was no significant difference between study and control groups as regard to weight, height or Body Mass Index (BMI) (19.24±1.57, 1.144±0.031 and 14.68±0.81 vs 19.56±1.34, 1.145±0.033 and 14.89±0.51, respectively). On the other hand, mothers of the study group lacked high education in comparison with the control group (middle and higher education reported in 57.3 and 8.0% in study group, compared to 60.7 and 19.3% respectively). Similarly, there was significant decrease of social class in study group when compared to control group (22.7% 63.3 and 14.0% had low, middle and high social class in study group; compared to 7.3, 79.3 and 13.3% in control group respectively) (Table 1).

Regarding laboratory data, results of the present study revealed a significant increase of ESR and WBCs in study group when compared to control group (31.48±6.01 and 11.83±1.33 vs 10.62±1.87 and 3.69±1.39, respectively). On the other hand, there was a significant decrease of RBCs, hemoglobin, iron and ferritin in study group when compared to control group (3.13±0.12, 11.40±0.40, 111.74±3.63 and 29.86±2.68 vs 3.66±0.43, 12.07±0.50, 114.38±4.76 and 44.74±3.90, respectively), while CRP showed a significant increase of positive cases in study group when compared to control group (93.3 vs 8.7%, respectively) (Table 2).

As for the results of x-ray examination, it was negative in 17 cases (11.3%), pneumonia was lobar in 10 cases (3.3.0%), lobular in 119 cases (79.3) and pneumonia with effusion in 4 cases (2.7%) (Table 3). In the present work, there was no significant differences between different x-ray findings of pneumonia as regard to serum iron. However, the lobular pneumonia had the lowest levels of iron (Table 4). As regard correlation between iron and other variables, there was a significant inverse (negative) correlation between iron from

Table 1: Demographic and clinical characteristics of studied cases

	Study		Control			
	Mean	SD	Mean	SD	Test	p-value
Age	10.88	1.35	10.81	1.49	0.44	0.65NS
Weight	19.24	1.57	19.56	1.34	1.89	0.06NS
Height	1.144	0.031	1.145	0.033	0.38	0.69NS
BMI	14.68	0.81	14.89	0.51	1.77	0.09NS
Mother education						
None	13	8.7%	6	4.0%	13.34	0.004*
Primary	39	26.0%	24	16.0%		
Middle	86	57.3%	91	60.7%		
Higher	12	8.0%	29	19.3%		
Social class						
Low	34	22.7%	11	7.3%	14.47	0.001*
Middle	95	63.3%	119	79.3%		
High	21	14.0%	20	13.3%		

SD: Standard deviation, BMI: Body mass index

Table 2: Laboratory data of studied cases

	Study		Control			
	Mean	SD	Mean	SD	Test	p-value
ESR	31.48	6.01	10.62	1.87	40.565	0.001*
RBCs	3.13	0.12	3.66	0.43	14.29	0.001*
Hemoglobin	11.40	0.40	12.07	0.50	12.62	0.001*
WBCs	11.83	1.33	3.69	1.39	51.66	0.001*
Iron	111.74	3.63	114.38	4.76	5.40	0.001*
Ferritin	29.86	2.68	44.74	3.90	38.49	0.001*
CRP (n,%)						
Positive	140 (93.3%)		13 (8.7%)		215.13	0.001*
Negative	10 (6.7%)		137 (91.3%)			

ESR: Erythrocyte sedimentation rate, RBCs: Red blood cells, WBCs: White blood cells, CRP: C-reactive protein, SD: Standard deviation

Table 3: Distribution of studied cases as regard to x-ray findings

	No.	%
Negative	17	11.3%
Lobar	10	3.3%
Lobular (bronchopneumonia)	119	79.3%
Pneumonia with effusion	4	2.7%

Table 4: Serum iron in different x-ray findings

	Mean	SD	Minimum	Maximum
Negative	112.23	3.28	107.00	117.00
Lobar Pneumonia	111.93	3.48	104.00	122.00
Lobular (bronchopneumonia)	108.90	4.97	102.00	115.00
Pneumonia with effusion	111.00	3.74	107.00	116.00

SD: Standard deviation

Table 5: Correlation between iron and other variables

	Iron	
	r	p-value
Age	0.059	0.309
Height	0.007	0.906
Weight	0.015	0.802
BMI	0.013	0.821
ESR	-0.334	0.001*
RBCs	0.238	0.001*
Hemoglobin	0.181	0.002*
WBCs	-0.267	0.001*
Ferritin	0.31	0.001*

BMI: Body mass index, ESR: Erythrocyte sedimentation rate, RBCs: Red blood cells, WBCs: White blood cells

one side and each of ESR and WBCs from the other side; these results indicated that, with increased ESR and WBCs, there was a significant decrease of iron. On the other hand there was a positive (proportional), significant correlation between iron from one side and RBCs, hemoglobin and serum ferritin from the other side (i.e., with increased iron, there was significant increase of RBCs and hemoglobin and vice versa) (Table 5).

DISCUSSION

Pneumonia is one of the leading diseases threatening the health and lives of children, as the incidence and the mortality of pneumonia are significantly higher in childhood (Agweyu *et al*., 2012).

Anemia is the commonest disease affecting human's health and socio-economic development. The most common cause for anemia is nutritional deprivation in particular, iron deficiency (Kotecha, 2011). The prevalence of anemia varies between developed and developing countries. Reaching up to 50% of preschool children in some developing countries, ranging from 20-67% across several Arab Gulf countries and is principally caused by iron deficiency. As many as 20% of children in the United States and 80% of children in developing countries will be anemic at some point by the age of 18 years old (Muwakkit *et al*., 2008).

In children, major health consequences include impaired cognitive and physical development and increased mortality and morbidity related to occurrence of infections (WHO., 2001).

Balanced and adequate nutritional supplementation to the growing children is of utmost importance for development and maturity of immunity, consequently development of resistance against the infections. So, nutritional inadequacy including the iron deficiency forms an indirect risk factor for the contracting Acute Lower Respiratory Tract Infection (ALRTI) (Koch *et al*., 2003).

The interaction between iron and infection has been the subject of debate in nutritional immunology, primarily because iron deficiency impairs components of cell mediated immunity (Roth *et al*., 2008). Subsequently, iron does appear to participate directly to immunity and lung injury which suggest several different approaches to prevention and treatment of lung disease (Ghio, 2009).

The present study was conducted in the pediatric department, Al-Azhar university hospital (Damietta); during the period from February, 2014 till February, 2015. It included 300 children, divided into two equal groups according to presence or absence of lower respiratory tract infection. For each child, a detailed medical history was obtained and a clinical examination was carried out by the study pediatrician.

Socioeconomic status was recorded. Height to the nearest 0.5 cm and weight to an accuracy of 0.5 kg were documented. Then blood sample was drawn to measure serum iron, hemoglobin and ferritin. In the current study, hemoglobin level was statistically significantly decreased in study group when compared to control group (11.40±0.40 vs 12.07±0.50 g dL^{-1}, respectively). The results which are comparable to those reported by Mourad *et al*. (2010) who reported that, hemoglobin concentrations in study and control groups were 10.27±0.52 and 12.27±0.75 g dL^{-1}, respectively. However, the same author found non-significant increase of CRP in study group when compared to control group. This can be attributed to the fact that all their study and control subjects were from hospitalized children, the matter which explains the increased positivity of CRP in control subjects (hospitalized for causes other than pneumonia). In addition, the negative CRP cases in the present study may be attributed to etiology of pneumonia as viral pneumonia had normal levels of CRP.

As regard results of x-ray examination, it was negative in 17 cases (11.3%), pneumonia was lobar in 10 cases (3.3.0%), lobular in 119 cases (79.3) and pneumonia with effusion in 4 cases (2.7%).

These results are comparable to those reported by Brant and Helms (2012) who reported that x-ray presentations of pneumonia may be classified as lobar pneumonia, broncho-pneumonia (also known as lobular pneumonia) and interstitial pneumonia. In addition, Sharma *et al*. (2007) reported that, bacterial, community-acquired pneumonia classically show lung consolidation of one lung segmental lobe, which is known as lobar pneumonia. However, findings may vary and other patterns are common in other types of pneumonia. Radiographs of viral pneumonia may appear normal, appear hyper-inflated, have bilateral patchy areas, or present similar to bacterial pneumonia with lobar consolidation. Radiologic findings may not be present in the early stages of the disease, especially in the presence of dehydration, or may be difficult to be interpreted in the obese or those with a history of lung disease.

In the present study, serum iron was statistically lower in cases of pneumonia when compared to control group. These results are comparable to those reported by Hussain *et al*. (2014) who reported that, mean serum iron level was 35.3 mcg dL^{-1} in the anemic and 52.41 mcg dL^{-1} in the non-anemic acute lower respiratory tract infection (ALTRI; the majority of cases were pneumonia) cases ($p<0.01$), while in control group, the mean serum iron level was 57.1 mcg dL^{-1} in the anemic and 62.6 mcg dL^{-1} in the non-anemic subjects, ($p<0.01$) pointing an association of low serum iron in ALTRI, a hypothesis needs validation of the previously held research (De Silva *et al*., 2003; Openheimer, 2001). This hypothesis confirmed the association between low iron and lower respiratory tract infection, as proved by the correlation between iron and inflammatory biomarkers in the present study.

It seems that oxygen O_2 and carbon-dioxide CO_2 transport is primarily facilitated by Hb, besides Hb acts as buffer for nitric oxide (NO) and other body derangements (Ganong, 2005). Therefore, quantitative and/or qualitative reduction in Hb, may adversely affect the normal functions. Alveolar macrophages obtain iron primarily from the RBC metabolism and plasma pool and their function is may be hampered in iron deficient states (Mateos *et al*., 1998) and hence could be possible explanation for association of ALTRI and deficient iron state and consequently iron deficiency anemia (Hussain *et al*., 2014).

In addition, it had been reported that, iron is essential for the function of iron proteins that play a role in the innate immune response, such as hepcidin, lactoferrin, siderocalin, haptoglobin, hemopexin, Nramp1, ferroportin and the transferrin receptor (Johnson and Wessling-Resnick, 2012). Iron deficiency leads to reduced immunity and increases the incidence of infection. Collectively, these data suggest that zinc and iron deficiency in children may contribute to the development of pneumonia by increasing the chance of infection (Zuo *et al*., 2014).

Ramakrishnan and Harish (2006) found, in a study of 200 infants and children between 9 months to 16 years, that 74% of cases and 33% of controls were anemic (with 80 and 82% IDA, respectively). Boys were more anemic than girls and the anemic subjects were 5.7 times more susceptible to LRTI. Malla *et al*. (2010) in a study done on a total of 280 infants and children aged 1 months to 5 years, recorded 68.6% of anemic cases and 21.4% of anemic controls with mean Hb level of 9.8 and 12 g dL^{-1}, 82 and 60% of IDA, respectively. Eighty-three percent of the anemic group had a picture of pneumonia on chest radiograph. Anemia due to mainly IDA was a risk factor for LRTI with an Odds Ratio of 3.2. Bhaskaram *et al*. (2003) reported anemic cases with 71% IDA and 25% of anemic controls with 46 IDA. Out of 159 children aged 3-5 years, the mean Hb level was 9.5 and 11.4 g dL^{-1} in study and control group, respectively.

On the other hand, Broor *et al*. (2001) reported that, iron deficiency anemia was not found to be a risk factor for LRTI in 512 infants and children below 5 years of age and normal radiograph was found in 21% of cases. The possible explanation for this contradiction can be attributed to different age groups and different nutritional practices.

CONCLUSION

In short, iron deficiency anemia, was significantly found in children with pneumonia. Thus, early and accurate diagnosis of iron deficiency in children and treatment of iron deficiency will have a positive effect decreasing pneumonia in children.

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