IRON DIFFICIENCY ANEMIA AS A RISK FACTOR FOR LOWER RESPIRATORY TRACT INFECTIONS IN EGYPTIAN PRESCHOOL CHILDREN

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ABSTRACT

Background and Aim: Acute lower respiratory infection (ALRI) is one of the leading causes of illness and death in children below 5 years of age. Anemia is one of the most widespread public health problems, especially in developing countries[2]. We aim to study the relationship between anemia as a risk factor and acute lower respiratory tract infections in Egyptian preschool children aged 6 months to 6 years.

Subjects and methods: A case-control study was conducted on a total number of 172 infants and children aged 6 months to 6 years; in the period from January 2013 to December 2013, we recruited 86 cases hospitalized for lower respiratory tract infections in Children Hospital, Zagazig University comprising all newly diagnosed cases during the defined time period of the study (incident cases) to ascertain the temporal sequence of exposure and disease. 86 healthy controls without any respiratory problems, age and sex matched were selected by simple random sampling from the general population that gave rise to the cases . All patients were subjected to detailed history taking (including past medical or pharmacy records), full clinical examination, and investigations including CBC, Iron profile: serum ferritin, total iron binding capacity and serum iron for all children. CRP and Chest X ray are done for cases only.

Results: The percentage of anemia was higher among case than control, with 81.4 % of hospitalized cases and 32.5%of healthy controls and the percent of iron deficiency anemia was higher in cases than controls 69.8% and 23.2% respectively with a significant P-value of 0.001.There were significant lower medians of serum iron, ferritin and transferrin saturation in cases than controls with highly and significant higher total iron binding capacity (TIBC) in cases than controls , also There's significant lower serum iron and transferrin saturation in anemic cases than anemic controls with no significant difference as a regard TIBC and serum ferritin Approval of ethical committee in college, and written consent from patients′ parents were obtained.

Conclusion: we can conclude that anemia especially IDA is a risk factor for acute lower respiratory tract infections among Egyptian preschool children.

Key words: ferritin, total iron binding capacity, malnutrition, immunity.

INTRODUCTION

Acute lower respiratory tract infections (ALRTIs) include all infections of the lungs and the large airways below the larynx. On average, children below 5 years of age suffer from about 5 to 6 episodes of ALRTIs per year, and still a burden until 12 years of age and more [1].

Anemia is one of the most common and intractable nutritional problems in the world today. It has consequences on human health, social and economic development. It is also associated with increased risk of morbidity and mortality, especially in young children under the age of 5 years. Iron deficiency is considered as the most common cause of anemia especially in developing countries [2].

Iron deficiency anemia in children occurs most frequently between the age of 6 months and 3 years due to their higher requirements of iron required for their growth, and this is the same period of age when repeated infections occur [3].

OBJECTIVE

The aim of this work was to study the relationship between anemia as a risk factor and acute lower respiratory tract infections in Egyptian preschool children aged 6 months to 6 years.

PATIENTS AND METHODS

Study Design

A hospital-based group matched case control descriptive-analytical study was conducted on a total number of 172 infants and children aged 6 months to 6 years. 86 cases with median of age 15 months and range from 6-72 months, there were 56 (65%) males and 30(35%) females hospitalized for lower respiratory tract infections in Children Hospital, Zagazig University, cases were all incident cases that newly diagnosed and admitted during the period of the study (from January 2013 to December 2013) to ensure the time sequence of IDA as an exposure factor and LRTIs as an outcome, aided by previous medical and pharmacy records. Approval of ethical committee in college, and written consent from patients′ parents were obtained.

86 apparently healthy controls without any respiratory problems, selected by simple random sampling from the general population that gave rise to the cases, age and sex matched with median age of 25 months and

range from 6-67 months, they were 50 (58%) males and 36 (42%) females.

Inclusion criteria: We included in the study all hospitalized children aged between 6 months and 6 years with a diagnosis of LRTI; fever, cough, tachypnea, chest retractions, and ronchi or crackles on chest auscultation, as per WHO criteria [1].

Exclusion criteria: Exclusion criteria included children with prematurity, congenital chest wall malformations, severe systemic illness (congenital heart disease, tuberculosis, etc), chronic diseases (diabetes, hepatitis, liver failure, etc), intake of iron supplements, and previous history of infection in the control group

Technical Design

An approved consent from the Regional Ethics Committee was undertaken from the parents. All Children in this study passed through:

1. Full history taking, with special emphasis on: **A) Personal history:** name, age, sex, residence, social level. **B) Complaint and present** history**:** fever, cough, dyspnea, grunting, cyanosis, refusal of feeding and ask for onset, course and duration of each. **C) Past** history: Similar attacks, Treatment with anti T.B and History of blood transfusion. **D) Vaccination** history: BCG scar. **E) Family** history of chest diseases.

2- Clinical Examination:

A) General examination: level of consciousness, complexion (pallor, jaundice, cyanosis).

B) Vital signs:

I) Temperature.
II) Heart rate.
III) Respiratory rate: Thresholds for fast breathing depend on child's age, that if the child is:

■ Between 2-12 months the breath rate will be (50 or more breath/minute).

■ Between 12-60 months the breath rate will be (40 or more breath/minute) [4].

C) Anthropometric measurements**:** Height, Weight.

D) Local chest examination by:

I) Inspection for (retractions, chest movements, localized bulge or retraction and signs of respiratory distress).

II) Palpation for (tracheal shift, palpable bronchi).

III) Percussion.

IV) Auscultation for (breath sounds and adventious sounds).

3- Investigation:

Sample collection: Blood samples were obtained by vein-puncture about 5cc, and divided into 2 parts; one part was collected on Ethylene-diamine-tetra-aceticacid (EDTA) tubes for complete blood count assay, the other tubes were plain vacutainers for serum iron, total iron binding capacity, serum ferritin.

1. Complete blood count (CBC) by SYSMEX:
a) Hemoglobin concentration (anemia is considered when Hb is below 11 gm/dl according to WHO [5].
b) Determination of mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC).

2. Capsular reactive protein (CRP) and Chest X ray showing (opacity, hyperinflation, exaggerated bronchovascular markings, etc) are done for cases only.

3. Iron profile: serum ferritin, total iron binding capacity and serum iron for anemic childern.

Serum iron and Total iron binding capacity (TIBC): Using **:** Reference values for serum iron for infants 40-100µg/dl, while for children 50-120µg/dl. For TIBC: 100-140µg/dl for infants and 250-400µg/dl for children. So the child was considered as iron deficient if his Serum Iron was lower than **50** µg/dL, or his Serum TIBC was higher than **400** µg/dL [6]**.**

Serum ferritin: Was done by IMMULITE/ 1000 Ferritin (SIEMENS, Los Anglos, USA). For diagnosis of iron deficiency anemia, cutoff value of **<10 ng/mL** [7].

Mentzer index was calculated through the formula: Mean corpuscular volume (in fl) divided by RBCs count (in millions /microliter) {MCV/RBC}, used for differentiation between IDA and thalassemia. An index of less than 13.5 suggests that the patient has the thalassemia trait, and an index of more than 13.5 suggests that the patient has iron deficiency.

The transferrin saturation was calculated through the formula: IRON level/TIBC X 100 (normal values: 20-45%) [7].

Iron deficiency anemia was diagnosed in the **control** group by serum ferritin of <10 ng/mL [7].or serum iron lower than 50 µg/dL and serum TIBC higher than 400 µg/dL [6].

CRP was considered positive if more than upper limit of normal range for age and sex.

● Considering the fact that infection can affect iron panel studies by increasing ferritin level (usually by more than 50 μg/l if iron deficiency is absent), and decreasing iron level and TIBC, the diagnosis of iron deficiency anemia was done in cases when at least 3 of the below parameters were present:

1) Low MCV level with specificity around 96% (not affected by infections).
2) Smear showing hypochromic microcytic anemia
3) Red cell distribution width RDW > 14.5 with a sensitivity of 92.1% and specificity of 90.9% in detecting IDA.
4) Mentzer index > 13.5 (with around 85% specificity and sensitivity).
5) Transferrin saturation TS < 10% (with a specificity of 85% if below 15% and sensitivity around 80%) [8].

Statistical Methodology

Analysis of data was done by IBM computer using SPSS (statistical program for social science version 12) as follows:

Description of quantitative variables were summarized as mean and, standard deviation SD when data are parametric and t test was used to compare two means. Non parametric data was expressed as median and Mann-whitney u test was used to test its significance.

Description of qualitative variables as number and percentage.

Chi-square test was used to compare qualitative variables between groups. and

Fisher Exact test was recommended when expected cell was less than 5.

P value >0.05 was considered insignificant, P<0.05 was considered significant and P<0.01 was considered highly significant.

RESULTS

A total of 172 infants and children aged between 6 Months and 6 years were enrolled in the study. Eighty six patients were admitted to the pediatric ward at Children Hospital, Zagazig University with LRTI according to the inclusion criteria. 65% were males and 35 %females. Another 86 healthy controls were studied in the outpatient department, 58% were males and 42% females. Height and weight were recorded to all patients, and body mass index (BMI) was calculated for children above 2 years. All infants and children studied were well nourished.

Hemoglobin level was considered low when below 11g/dl, which is less than 2 standard deviation (SD)[7], Out of the total 172 infants and children in the study, 98 were found to be anemic (56.9%), with hemoglobin level below 11 g/dl in 81% of cases admitted to pediatric ward with a diagnosis of LRTI and in 32.5% of healthy controls, which was significantly different with a P-value of 0.001(Table 1).

P-value was highly significant (0.001) between hospitalized cases and controls with mean Hb level of 9.992 ± 1.33g/dl and 11.19 ± 0.87 g/dl, respectively.

Anemia was found to be a risk factor for LRTI with an Odds Ratio of 9 with 95% interval confidence of 3.3 - 24.5 and a significant P-value of (0.001). This means that children with Hb level below 11 g/dl were 9 times more susceptible to LRTI compared to the control group (Table 1).

P-value was significant (0.007) between anemic hospitalized cases and anemic healthy controls with mean Hb level of 9.44 ± 0.89g/dl and 10.15 ± 0.36g/dl respectively (Table 2).

Concerning the cases hospitalized for LRTI, anemic group had a positive CRP in 77% (54/70) and normal chest X-ray in 57% (40/70) comparing to 75% (12/16) and 62.5% (10/16) of non-anemic group, respectively, with a non significant P-value between the 2 groups as regards CRP and chest radiograph finding (Table 5).

Table (1): Percentage of anemia among cases & controls and Multivariate logistic regression analysis showing the risk factor of LRTI.

	Cases (86)		Controls (86)		OR (95%CI)	p. value
	N	%	N	%		
anemic	70	81.41	28	32.5	9	0.001
non anemic	16	18.6	58	67.5	(3.3-24.5)	

OR =odd ratio CI = confidence interval

As shown in table (1), there's statistically significant higher percent of anemia among cases than controls (p. value 0.001) & Anemia was found to be a risk factor for LRTI with an OR of 9 with 95% interval confidence of 3.3 – 24.5 and a highly significant P. vale. This means that children with Hb < 11 gm /dl were 9 times susceptible to LRTI compared to the controls.

Table (2): Mean hemoglobin (Hb) level in anemia cases & controls.

	Anemic cases (70)	**Anemic controls (28)**	**t. test**	**p. value**
Mean Hb	9.44	10.15		0.007
SD (g /dl)	± 0.89	± 0.36	2.83	

As shown in table (2), the mean Hb level among anemic cases is lower than that of anemic controls with highly significant p. value 0.007.

Table (3): Iron profile in cases& controls.

	Cases (86)	**Controls (86)**	**Mann-Whitney U test**	**P. value**
Serum Iron Median range (ug /dl)	36 14- 142	115 19- 187	4.92	0.001
Serum Ferritin Median range (ng /dl)	8 2- 60	24 4- 71	3.16	0.002
TIBC Median range (ug /dl)	446 141- 593	316 312- 515	4.09	0.001
Transferrin saturation median range	6.3 2- 53	37 3.3- 81.6	5.08	0.001

TIBC = total iron binding capacity

As shown in table (3), there are significantly lower medians of serum iron, serum ferritin and transferrin saturation in cases than controls with highly significant p –value and significantly higher TIBC in cases than controls.

Table (4): Iron profile in anemic case & anemic control.

	Anemic Cases(70)	anemic Controls(28)	Mann-Whitney U test	P. value
Serum Iron Median range (ug /dl)	29 14- 100	38 19- 171	2- 12	0.034
Serum Ferritin Median range (ng /dl)	7 2- 45	6 4- 60	1- 47	0.141
TIBC median range (ug / dl)	458 249- 593	439 249- 515	0.578	0.563
Transferrin saturation median range	5.9 2- 28	8.6 3- 63	2- 59	0.010

As shown in table (4), there's significant lower serum iron and transferrin saturation in anemic cases than anemic controls with no significant difference as a regard TIBC and serum ferritin.

Table (5): Comparison of C reactive protein (CRP) & chest X ray between anemic & non anemic cases.

	Anemic cases (70)		Non anemic case (16)		Chi square test	p. value
	N	%	N	%		
Positive CRP	54	77	12	75	Fisher	1.0
Negative CRP	16	23	4	25	Exact	
Normal chest x ray	40	57	10	62.5	Fisher	1.0
Abnormal chest x ray	30	43	6	37.5	Exact	

As shown in table (5), there's no statistically significant difference between anemic and non anemic cases as regards CRP and chest X ray.

DISCUSSION

Acute lower respiratory infection (ALRI) is one of the leading causes of illness and death in children below 5 years of age. WHO estimated that the annual number of Acute Lower Respiratory Tract Infections (ALRTIs) related deaths in children less than five years old was 2.1 million accounting for about 20% of all childhood death [9]. Most deaths from ALRIs are caused by severe pneumonia and 70% of them occur in low-income countries .Hence it is important to control the risk factors of LRTI like low birth weight, lack of breast feeding, severe malnutrition and low hemoglobin [3]. As identification of modifiable risk factors of LRTI may help in reducing the burden of disease [10].

Most anemia cases are due to iron deficiency. In early childhood, bad feeding habits, especially during the weaning period, exacerbate the problem. Anemia frequently develops as breast milk is replaced by foods that are poor in iron and other nutrients, including vitamin B12 and folic acid [11]. Infants, under 5-year-old children have greater susceptibility to anemia because of their increased iron requirements due to rapid body growth and expansion of red blood cells [12].

Our case – control study was conducted on a total number of 172 infants and children aged 6 months to 6 years with no significant difference between case and control concerning age and sex and this came in agreement with [13].

All our study cases were selected as incident cases, together with documented previous medical and pharmacy records to ensure the time sequence between exposure (IDA) and disease (LRTIs).

In our study, a history of recurrent chest infections was significantly higher in hospitalized cases than control and in anemic cases than non anemic cases 94% and 50% respectively with significant P-value of 0.007 and this was also noticed by [13].

In our study, the percentage of anemia was higher among case than control, with 81.4 % of hospitalized cases and 32.5%of healthy controls and the mean hemoglobin (Hb)level among cases was 9.92 ± 1.33g/dl which is lower than controls 11.19± 0.87g/dl with highly significant P value 0.001. So anemia was found to be a risk factor for ALRTI with an OR of 9 with 95% interval

confidence of 3.3-24.5 and highly significant P value. . This means that children with Hb < 11 gm /dl were 9 times susceptible to LRTI compared to the controls. These data came in agreement with Mourad et al [13]. study who reported that 32% of hospitalized cases and 16% of healthy controls in Lebanese children were anemic and the mean Hb level was lower in hospitalized cases than in healthy controls(11.35 ± 1.24g/dl & 11.95 ± 1.03g/dl) respectively mainly in children below 5 years of age with no difference between boys and girls. So anemic children were more susceptible to lower respiratory tract infection two time than the control group.

Malla et al [3] study done in Nepal on a total of 280 infants and children aged 1 months to 5 years, recorded 68.6% of cases and 21.4 % of controls were anemic and with mean Hb level of 9.8 g/dl and 12 g/dl, 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

Also Deng in Juba [14], Southern Sudan in a study of the risk factors for acute lower respiratory tract infections in children fewer than five years of age he found that anemia was present in 90.7% of cases as compared to 72.2% of controls and was significantly associated with ALRTI, p-value< 0.05. Harris et al [9] showed in a study done among Ecuadorian children, they studied anemia and air pollution as risk factors for ALRTIs. They explained their findings by that poor tissue oxygenation and anemia independently decreases oxygen delivery.

On the other hand a study performed by Broor et al reported that anemia was not found to be a risk factor for LRTI in 512 infants and children below 5 years of age. [10].

Hemoglobin facilitates oxygen (O2) and carbon dioxide (CO2) transport. It carries and inactivates nitric oxide (NO) and also play the role of a buffer Tissue ‘oxygen buffer’ function is very important one of hemoglobin system [15]. Quantitative and/or qualitative reduction in Hb, may adversely affect the normal functions. Probably it may be the reason for low hemoglobin level found to be as a serious risk factor for developing LRTI [16].

In the present study, the percent of iron deficiency anemia was higher in cases than controls 69.8% and 23.2% respectively with a significant P-value of 0.001

and this was also observed by Malla et al who found that iron deficiency anemia was 82%in cases and 60 % in controls respectively.

Among preschool children living in underprivileged communities in developing countries, infectious diseases such as LRTI and IDA are often coexistent. The effects of IDA on immune function, and increase in susceptibility to infections are well established. Researchers have argued that any inadequate supply of iron to body tissues is detrimental to immunity [17].

In our study, there were significant lower medians of serum iron, ferritin and transferrin saturation in cases than controls with highly significant P value and significant higher total iron binding capacity (TIBC) in cases than controls (Table 3) and There's significant lower serum iron and transferring saturation in anemic cases than anemic controls with no significant difference as a regard TIBC and serum ferritin **(**Table 4).

This came in agreement with Rahman et al which reported that mean serum iron, total iron binding capacity (TIBC), ferritin concentration in normal children were significantly higher (P<0.001) than non-infected severely malnourished children and mean serum iron concentration was reduced in acute respiratory infection (ARI) and parasitic infestation than other infection. [18].

In our study, anemic cases had a positive CRP in 77% and normal chest X-ray in 57% comparing to 75% and 62.5% of non-anemic cases respectively, with a non significant P-value between the 2 groups for positive CRP and normal chest radiograph finding. These data came in agreement with Mourad et al who found that anemic cases had a positive CRP in 84.4% and normal chest X-ray in 18.8% comparing to 75% and 30.9% of non-anemic cases respectively, with a non significant P-value between the 2 groups [13].

On the other hand Malla et al found that picture of pneumonia in chest radiograph was significantly higher in the anemic cases than non-anemic cases [3].

CONCLUSION

We concluded that anemia especially IDA is a risk factor for acute lower respiratory tract infections among Egyptian preschool children and the anemic children were 9 times more susceptible to LRTI compared to the control group.

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KEY MESSAGES

1. Screening for Hb or hematocrit level at the age of 9 or 12 months for all full terms infants and 6 months for premature and additional screening before the age of 5 years for patients at risk as American Academy of Paediatrics (AAP) recommends [19].
2. Assessing iron status by Hb and ferritin levels in hospitalized infected children, so we can diagnose properly and treat IDA in these patients, as recommended by CDC/WHO expert consultation [20].

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أنيميا نقص الحديد كعامل خطورة لعدوى الجهاز التنفسي السفلي في الأطفال المصرين تحت سن 6 سنوات

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المقدمة والهدف من الدراسة

تعتبر عدوى الجهاز التنفسى السفلى الحاد واحده من أهم أسباب الوفيات للأطفال تحت سن 5 سنوات. كما تعتبر الأنيميا من أحد أهم المشكلات الصحية المنتشرة فى الدول النامية. تهدف الدراسة الحالية إلى دراسة العلاقة بين الأنيميا كعامل للخطورة وعدوى الجهاز التنفسى السفلى الحاد للأطفال المصريين ما قبل سن الدراسة من سن 6 شهور وحتى 6 سنوات.

وسائل البحث

تمت الدراسة الحالية على 172 طفل تتراوح أعمارهم من 6 شهور وحتى 6 سنوات،86 طفل يتم علاجهم من عدوى الجهاز التنفسى السفلى الحاد بمستشفى الأطفال بجامعة الزقازيق خلال الفترة الزمنية(يناير 2013 حتى ديسمبر 2013) بينما الـ 86 حاله الأخرى كانت لأطفال أصحاء من نفس الجنس والعمر ولا يعانون من أى مشكلات فى التنفس. تم القيام بسرد دقيق للتاريخ المرضى لكل الحالات وكذلك كشف طبى كامل وتحاليل تشمل عد كامل لعناصر الدم، نسبة الفيريتين فى سيرم الدم، القدرة الكلية للارتباط بالحديد وكذلك نسبة الحديد فى الدم لكل الحالات.

النتائج

أظهرت النتائج ارتفاع نسبة الإصابة بالأنيميا فى حالات عدوى الجهاز التنفسى السفلى الحاد بالمقارنة بحالات الأطفال السليمة، حيث كانت نسبة الإصابة بالأنيميا 81.4% فى حالة الأطفال تحت الرعاية الطبية بالمقارنة بـ 32.5% فى الأطفال الأصحاء. وبالمثل ارتفعت نسبة الإصابة بأنيميا نقص الحديد فى حالات عدوى الجهاز التنفسى (69.8%) بالمقارنة بالأطفال الأصحاء (32.2%)

ارتفاع معنوى(p-value = 0.001)

كما لوحظ انخفاض معنوى فى كلا من نسبة الحديد فى سيرم الدم ، الفيريتين، وتشبع الترانسفيرين فى حالات عدوى الجهاز التنفسى بالمقارنة بالأطفال الأصحاء، بينما أظهرت

حالات عدوى الجهاز التنفسى ارتفاع معنوى فى القدرة الكلية للارتباط بالحديد بمقارنه بالأطفال الأصحاء. بالإضافة إلى ذلك، لوحظ انخفاض معنوى فى نسبة الحديد فى سيرم الدم وتشبع الترانسفيرين فى حالات عدوى الجهاز التنفسى المصابة بالأنيميا بالمقارنة بحالات الأطفال المصابين بالأنيميا وغير مصابين بعدوى الجهاز التنفسى، بينما لم يلاحظ فروق معنوية فى ألقدره الكلية للارتباط بالحديد ونسبة الفيريتين فى السيرم بين هاتين المجموعتين.

تم الحصول على الموافقة لأداء هذه الدراسة من قسم الأطفال و اللجنة الأخلاقية بالكلية وكذلك موافقة أولياء أمور الأطفال الذين تطبق عليهم الدراسة.

الخلاصة

تشير الدراسة الحالية إلى أن الأنيميا وخصوصا أنيميا نقص الحديد هى عامل خطورة لمرض عدوى الجهاز التنفسى السفلى الحاد بين الأطفال المصريين قبل سن الدراسة

الكلمات المفتاحية :

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