Institute of Postgraduate Childhood Studies
Department of Medical Studies For children

Iron Deficiency Anemia as a Risk Factor for Lower Respiratory Tract Infections

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ABSTRACT

Background: Lower respiratory tract infection (LRTI) with anemia occurs in children than in adults, with anemia affecting approximately 30% of children all over the world. Iron deficiency anemia in children occurs most frequently between the age of 6 months and 3 years, the same period of age when repeated infections occur. **Aim**: This study aimed to evaluate the role of iron deficiency anemia as a risk factor for lower respiratory tract infections. **Design**: Case-control study. **Methods**: a case control cross sectional study that carried out on 74 children hospitalized in Pediatric Department, Agouza Police Hospital in a period from March to December 2013. These children suffering from LRTI and subdivided into two groups according to the presence or absence of respiratory distress, they were matched with another 36 apparently healthy children with the same age and sex served as control group. History taking, general and local examination were performed. CBC, ESR and CRP were determined with serum iron, ferritin and TIBC. Plain chest x-ray was also performed. **Results**: No significant difference according to sex among all groups where the p-value =0.4 where male patients were affected by acute lower respiratory tract infections more than females, with a percentage of 56% to 44%.frequency and percent of different x-ray findings in cases of L.R.T.I. Showed that increase bronchovascular marking was the most common x-ray finding (34.5%) The mean of the age is more in control group (45.9) and less in R.D group (2,73). Fever was significant more common in no respiratory distress group (91.1%) there were statistical significant differences between the two patient groups and control as regard to HCT and MCV levels ($P<0.05$),with no significant difference between them as regard to R.B.Cs,HB and other blood indices($P>0.05$) there were statistical significant differences between control and patient groups as regard to Monocytes and Eosinophils levels ($P < 0.05$). There was high statistical significant difference between control and patient groups as regard to CRP levels ($P = 0.01$), with no significant difference between them as regard to ESR values ($P>0.05$). There was high statistical significant difference between control and patient groups as regard to serum iron and TIBC levels ($P < 0.01$), with no significant difference between them as regard to serum ferritin levels ($P>0.05$).

Conclusion and recommendation:

Alertness should be increased towards L.R.T.I with no fever, young age and male. C.R.P to be from routine investigation in L.R.T.I. Further larger study is recommended to investigate the magnitude of the problem.

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Key words: LRTI, children, respiratory distress, iron, ferritin, TIBC.

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Maisa Hasan

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LIST OF ABBREVIATIONS

ACD	Anemia of chronic disease
ALA	Aminolevulinic acid
ARTI	Acute respiratory tract infection
BM	Bone marrow
BTS	British thoracic society
CHr	Content of hemoglobin in reticulocyte
CMV	Cytomegalovirus
CRP	C-reactive protein
CT	Computerized tomography
CXR	Chest x ray
DMT-1	Divalent metal transporter 1
EP	Erythrocyte protoporphyrin
ESR	Erythrocyte sedimentation rate
FOBT	Fecal occult blood test
Hb	Hemoglobin
HbA	Adult hemoglobin A
HbA2	Hemoglobin A2
HbF	Fetal hemoglobin
HbH	Hemoglobin H
Hct,	Hematocrit
Hib	Homophiles influenzae type b
HMPV	Human metapneumovirus
HSV	Herpes simplex virus
ID	Iron deficiency
IDA	Iron deficiency anemia
IOM	Institute of Medicine
LRTI	Lower respiratory tract infection
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
NSW	New South Wales
PCR	Polymerase chain reaction
PERCH	Pneumonia Etiology Research for Child Health
PPV	Positive predicted value
RBC	Red blood corpuscular
RDW	Red distribution width
RLS	Restless Legs Syndrome
RSV	Respiratory syncytial virus
SARS	Severe acute respiratory syndrome virus
TfR	Transferrin receptor
TIBC	Total iron binding capacity
TNF	Tumor necrosis factor
TSST-1	Toxic shock syndrome toxin-1
VMNIS	Vitamin and mineral nutrition information system
VZV	Varicella-zoster virus
WHO	World Health Organization
ZnPP	Zinc protoporphyrin

INTRODUCTION

Lower respiratory tract infection (LRTI) includes all infections of the lungs and the large airways below the larynx. On average, children below 5 years of age suffer about 5 to 6 episodes of LRTI per year, and still a burden until 12 years of age and more ***(Christi et al., 2009).***

Acute respiratory tract infection (ARTI) is a major cause of morbidity and mortality worldwide, particularly in children ***(O'Grady et al., 2010)***. An estimated 1.9 million children die from ARTI every year, with 70% of the mortality occurring in Africa and Southeast Asia ***(Williams et al., 2002)***. Most respiratory tract infections are caused by viruses ***(Khor et al., 2012)***.

Bronchitis is a clinical term implying a self-limited inflammation of the large airways of the lung that is characterized by cough without pneumonia. Bronchitis is prevalent throughout the world and is one of the top 5 reasons for childhood physician visits in countries that track such data. The incidence of bronchitis in British and German schoolchildren is reported to be 20.7% and 28% respectively ***(Weigl et al., 2005).***

While bronchiolitis is defined as the first episode of wheezing in a child younger than 12 to 24 months who has physical findings of a viral respiratory infection and has no other explanation for the wheezing, such as pneumonia or atopy. While the broader definition is an illness in children <2 years of age characterized by wheezing and airway obstruction due to primary infection or reinfection with a viral or bacterial pathogen, resulting in inflammation of the small airways/bronchioles ***(Hanson et al., 2006).***

Pneumonia is defined as an acute infection of the lung parenchyma that is accompanied by symptoms of acute illness. Typically, the gold standard for diagnosis is the presence of new pulmonary infiltrates, as observed by X-ray, in combination with compatible clinical symptoms, and laboratory and microbiological findings ***(Polverino and Marti, 2011).***

Pneumonia is the biggest single cause of childhood death under the age of 5 years in developing countries ***(Graham et al., 2008).*** Globally there are about three million deaths, less than 5 years of age, each year due to pneumonia. Of these deaths, 90 to 95% are in the developing countries ***(Murad et al., 2010).***

LRTI associated with anemia occurs more commonly in children than in adults, with anemia affecting approximately 30% of children all over the world ***(Brotanek et al., 2007).*** Iron deficiency anemia in children occurs most frequently between the age of 6 months and 3 years, the same period of age when repeated infections occur ***(Malla et al., 2010).***

Iron deficiency exerts adverse effects on immune response and alters the metabolism and growth of pathogens ***(Ramakrishnan and Borade, 2010).***

Whatever the etiology of anemia, the relation between iron deficiency anemia and LRTI has not been fully evaluated, and only few reports are available evaluating this subject ***(Ramakrishnan and Harish, 2006).***

AIM OF THE STUDY

Was to evaluate the role of iron deficiency anemia as a risk factor for lower respiratory tract infections in children.

Acute Lower Respiratory Tract Infections

Acute respiratory tract infection (ARTI) is a major cause of morbidity and mortality worldwide, particularly in children ***(O'Grady et al., 2010)***. An estimated 1.9 million children die from ARTI every year, with 70% of the mortality occurring in Africa and Southeast Asia ***(Williams et al., 2002)***. Most respiratory tract infections are caused by viruses ***(Khor et al., 2012)***.

According to the World Health Organization (WHO), the death rate from bronchiolitis is greatest in Egypt at 31 deaths per 1 million people; by comparison, the death rate from bronchiolitis in the United States is 0.8 per 1 million people ***(WHO, 2010).***

Pneumonia is a forgotten killer of children leads to 11% of infant mortality in Egypt, the challenges can be conducted as follows: Firstly, lack of knowledge of risk factors and prevention measures at the family level with much worse situation among families with low living conditions. Secondly, low public attention and recognition of the disease and its seriousness. Lastly, vaccination against pneumonia is not included in Egypt National Mandatory Immunization program ***(WHO, 2010)***

A. General anatomy of LRT:

LRT is usually divided into two segments.

I. The Respiratory Airways: This includes the trachea, bronchi, and bronchioles.

II. The Lungs: This includes alveolar ducts, alveolar sacs, and the alveoli ***(Gonlugur et al., 2005)***.

The alveoli are lined with two types of cells, the Type 1 and Type 2 pneumocyte. The Type 1 pneumocyte is a very large thin cell stretched over a very large area. This cell can not replicate and is susceptible to a

large number of toxic insults. Type 1 pneumocytes are responsible for gas exchanges occurring in the alveoli ***(Meenakshi et al., 2004)***.

B. Defense mechanisms of airway

Particles from 2 um to 0.2 um (like most bacteria and all viruses) can go all the way down inside the alveoli avoiding the defenses of the upper respiratory tract and the mucociliary elevator ***(Meenakshi et al., 2004)***.

The following defense mechanisms in the alveoli protect the parenchymal cells from invasion by microorganisms.

- Alveolar macrophages (the most important)
- Complement components
- Alveolar lining fluid containing surfactant, phospholipids, neutral lipids, IgG, IgE, IgA, secretory IgA, certain complement components, that maybe important in activation of alveolar macrophages
- B cells, T cells, and Null cells that can elicit a localized immune response to infection
- Lymphoid tissue associated with the lungs ***(Gonlugur et al., 2005)***

C. Defense mechanisms during infection.

During pulmonary infection, neutrophils migrate out of the pulmonary capillaries and into the air spaces. After phagocytosis, neutrophils kill ingested microbes with reactive oxygen species (e.g., hypochlorite), antimicrobial proteins (e.g., bactericidal permeability-inducing protein and lactoferrin), and degradative enzymes (e.g., elastase) (figure, 1) ***(Mizgerd, 2008).***

Adhesion molecules induced on lung cells provide traction and signaling information to neutrophils ***(Mizgerd, 2002).*** Chemokines from lung cells stimulate chemotaxis and influence the directional motility of

neutrophils. Colony-stimulating factors signal neutrophil production and release from hematopoietic tissues ***(Christopher and Link, 2007).***

D. Invaders mechanisms used to avoid the normal defense mechanisms of the lung.

To kill the microorganism in the alveoli it must be phagocytized by the alveolar macrophage. If these microbes can avoid phagocytosis or survive once phagocytized they can survive in the lung. Microorganisms have developed a number of ways to avoid phagocytosis. Once phagocytized certain organisms can survive in the phagocyte ***(Gonlugur et al., 2005)***.

Mechanisms used to avoid phagocytosis:

- Capsule production. (Streptococcus pneumoniae, Hemophiles influenza, Bacillus anthracis, Neisseria meningitidis, Klebsiella pneumoniae)
- Toxin production. These toxins could include cytotoxins, leukocidins, and exotoxins (examples; Staphylococcus aureus produces leukocidins and cytotoxins. Pseudomonas aeruginosa produces exotoxin A which destroys cells much like the diphtheria toxin does.)
- Being too large to phagocytize. Parasites and fungi are often too large for the phagocyte to engulf.
- Replication inside cells. Viruses and Chlamydia sp. are obligate intracellular organisms that replicate inside the cells of the lung avoiding the phagocyte.
- Mimicry. Some organisms produce surface proteins which are very similar to host proteins or acquire host proteins and appear to the phagocyte as self. Some bacteria produce proteins that cause host