Anemia as a risk factor for lower respiratory tract infection in children of 6 months to 5 years of age

Dhruv Vashishth[1], Girdhari Lal Sharma[2], Rupesh Masand[3]

From [1]Junior Resident, [2]Assistant Professor, [3]Professor and Head, Department of Pediatrics, National Institute of Medical Sciences and Research, Jaipur, Rajasthan, India

Correspondence to: Dr. Girdhari Lal Sharma, 10A Raghu Vihar Maharani Farm, Jaipur – 302 018, Rajasthan, India. E-mail: dr.gls25@gmail.com

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ABSTRACT

Objective: To determine whether anemia is a risk factor for acute lower respiratory tract infections (ALRTI) in children aging 6 months–5 years. **Materials and Methods:** Observational case–control study was performed in 540 children in the age group of 6 months–5 years who attended the outpatient and inpatient unit of the department of pediatrics of a tertiary care hospital of Jaipur, during the period from January 2017 to June 2018. 270 cases hospitalized for LRTI who fulfilled the inclusion criteria and 270 healthy age and sex matched controls without any respiratory problems attending outpatient department of the department of pediatrics. Children with congenital anomalies, protein energy malnutrition, tuberculosis, congenital heart defects, HIV, and malignancies were excluded from the study. After a detailed history and anthropometric measurements, complete blood count, C-reactive protein, peripheral blood film examination, reticulocyte count, chest skiagram, Mantoux test were done. Iron profile and detailed anemic investigations are done if hemoglobin level was below 11 g/dl as per the WHO criteria. The sentence in abstract can be framed like this. The norms considered for ALRTI were also considered as per defined by the WHO criteria. **Results:** Male preponderance was observed (55.2%) in the study group. Most of the children were <2 years of age (59.6%). On auscultation, crepitations were a major finding (64.8%). Out of 270; 240 (88.9%) patients were diagnosed as pneumonia and rest 30 (11.1%) cases as bronchiolitis. Anemic patients were found to be 3.7 times more susceptible to ALRTI in this study (p=0.01). Iron deficiency anemia (IDA) was found in 63.7% of total anemic cases in the study group. In the study group, the mean serum iron level 26.3±7.9 mcg/dl in the anemic cases and 29.11±8.95 mcg/dl in the non-anemic cases. It was observed that with an increase in the severity of anemia among the cases, a concomitant increase in the severity of pneumonia was also observed (p=0.04). **Conclusion:** Early detection, preventive measures, and aggressive treatment with proper nutrition and medication of anemia; especially, IDA in all children are helpful for prevention of ALRTI.

Key words: *Anemia, Risk factor, Respiratory tract infection*

Anemia is defined as a reduction of hemoglobin (Hb) concentration or red blood cell (RBC) volume below the range of values occurring in healthy persons [1]. It is a major global nutritional problem of immense public health significance, affecting people of all ages, sex, and economic group [2]. The prevalence of anemia varies between 44% and 74% in developing nations which is significantly higher than the developed world [3].

Acute lower respiratory tract infections (ALRTI) refer to all infections of the lungs and the airways below the level of larynx [4]. Approximately 150 million episodes of childhood pneumonia are reported every year from the world, and there are about 3 million deaths each year due to pneumonia, in 0–5 year age group. Of these deaths, 90–95% of deaths are in the developing countries [5].

Approximately over 59% of children in the age group of 6 months–5 years are anemic in Rajasthan [6]. ALRTI along with anemia occurs more commonly in these children than in adults. Iron deficiency anemia (IDA) occurs more commonly in the age group of 6 months–3 years which is the same period as when repeated LRTI occur [2]. However, irrespective of etiology of anemia, the relationship between the low level of Hb and ALRTI has not been fully evaluated. This study was conducted to assess the association of anemia as a risk factor for developing ALRTI in pre-school children.

MATERIALS AND METHODS

This observational case–control study was performed in 540 children in the age group of 6 months–5 years who attended the outpatient and inpatient unit of the department of pediatrics of a tertiary care teaching hospital of Jaipur, during the period from January 2017 to June 2018. The study was conducted after getting the approval of the ethical committee of the institution, and written consent was taken from parents or guardians before enrollment of the child in the study. 270 cases hospitalized for

LRTI and 270 healthy age- and sex-matched controls without any respiratory problems attending outpatient department of the department of pediatrics.

The sample size of 270 allocated in each group was calculated considering the incidence of anemia as 60% [7] among the case as well as a control group. With the power of 90%, the following formula was used $n = 4\frac{pq}{e^2}$ where n is the desired sample size, p is peak incidence, q is quotient, and e is margin for error which was taken as 5%. The minimum sample size required came out to be 266 for each group.

All children in the age group 6 months–5 years of either sex with the clinical diagnosis of ALRTI, (i.e. cough and/or difficult breathing, with or without fever, fast breathing [according to the age of the child] or lower chest wall in-drawing or at least one other danger sign), were included in the study. Patients having any of the following conditions were excluded from the study: Protein-energy malnutrition (PEM) ≥Grade III as per Indian Academy of Pediatrics (IAP) Classification, tuberculosis (any clinical evidence±Mantoux test positive cases), congenital cardiac/lung parenchymal lesions/chest wall malformations, bronchial asthma, immunodeficiency disorders, for example, HIV infection, lung abscess, and chronic diseases, for example, diabetes mellitus, hepatitis, liver failure, and children who are already on oral or injectable antibiotics/iron therapy, children <6 months or >5 years of age, and parents/guardians not providing consent for the study.

A detailed history was taken and clinical examination including all relevant anthropometric measurement was performed and recorded in a pre-tested pro forma. The following laboratory tests were done in all children: Complete blood count, C-reactive protein (CRP), peripheral blood film (PBF) examination, reticulocyte count, chest skiagram, tuberculin skin test, iron level, ferritin levels, and total iron binding capacity (TIBC) if Hb level was <11 g/dl. The norms considered for ALRTI was defined as per the WHO criteria, i.e., presence of fever, cough with fast breathing of >60/min in <2 months and >50/min in 2–12 month of age and >40/min in 12 month–5 years of age, the duration of illness being <30 days. Pneumonia was further classified into pneumonia, severe pneumonia per the WHO criteria for assessing the severity of pneumonia; and anemia was considered to be, 11 g%/dl as per the WHO criteria.

A trained phlebotomist drew blood from the antecubital vein of each child. Sterile, disposable syringes and needles, and proper tubes were used, and the blood samples were sent to the clinical laboratory for relevant investigations. Every child could not be assessed for all the kind of anemia, so iron profile was done for all anemic patients and other tests were implemented on patients with either with clinical signs or if PBF, or any other investigation if suggests so.

Hb level was estimated in the blood samples using an automatic blood cell counter. The cutoff point for low Hb level was 11g/dl [8]; meeting the definition of anemia as Hb level being −2 standard deviations (SDs) below the mean for age, as fixed by the WHO [9]. Iron level and TIBC were measured using the ferrozine method without deproteinization. Reference ranges were 37–145 μg/dl for iron level, and 228–428μg/dl for TIBC [9]. As for ferritin, the electrochemiluminescence "ECLIA" was used with a cutoff point of 20 μg/l. The transferrin was measured by immunoturbidimetry assay with 200–360 mg/dl reference ranges [9]. The transferrin saturation through the formula: IRON level/TIBC X 100 (normal values: 20–50%). CRP was considered positive if >0.3 mg/dl. The diagnosis of IDA was diagnosed in the control group when a low ferritin level was found with high TIBC [10]. PBF would be analyzed under the microscope. Other blood investigations were done on the basis of PBF and were sent to a laboratory for the screen of either hemolytic anemia or megaloblastic anemia, or anemia of any other cause.

Numerical variables were reported in terms of mean and SD. Categorical variables were reported in terms of numbers and percentages. Association of each of the categorical variable with response variable was assessed by Chi-square test, and the strength of their association was computed by unadjusted odds ratio. Variables showing statistically significant association in univariate analysis with the outcome variable up to p=0.5 were considered as a risk factor. Only those variables were subjected to multivariate analysis. Logistic regression technique was used to find the risk factor for ALRTI. In multivariate analysis, variables showing p<0.05 were considered to be statistically significant. The data collected were analyzed using SPSS Version 16.

RESULTS

A total of 270 cases and 270 healthy controls were included in this study. Maximum patients were <2 years of age in both case (59.6%) and control group (63.3%) (p=0.37) as shown in Table 1. Male preponderance (55.20%) was seen in the case and female preponderance (51.90%) in the control group.

The mean Hb level in anemic cases was 9.1±1.99 g/dl (median −8.55, range: 4.8–10.4 g/dl) while it was 10.42±1.57 g/dl (median −9.30, range: 6.3–10.8 g/dl) in the control group. Statistically, the difference was significant (t=14.94, p=0.001). Table 2 depicts the frequency of anemia in cases and controls. Among the case group, anemia (77.8%) was prevalent while in the control group non-anemic (74.4%) subjects dominated. Non-IDA consisted of megaloblastic anemia and hemolytic anemia which was observed in 15.9% cases with ALRTI.

All markers except serum ferritin were suggestive of IDA in study subjects as shown in Table 3.

All patients of Group A were subjected for a chest radiograph. Patients were either diagnosed with pneumonia (88.9%) or bronchiolitis (11.1%). Table 4 correlates the severity of pneumonia with the severity of anemia. A significant correlation was observed between increasing severity of anemia and pneumonia in study subjects belong to Group A.

DISCUSSION

Of 270 patients from age 6 months to 5 years with ALRTI registered as cases, the majority (59.6%) were between 6 and

24 months of age which was comparable with other studies [11-13]. This denotes that ALRTI is most common in the age group of <2 years. A higher incidence of ALRTI in lower age group can be due to various physiological and anatomical factors in infants such as they are compulsive nose breathers having a larger tongue relative to the oral cavity, smaller airway, and poor elasticity of alveoli. During this period, children especially in rural areas and in urban slums continue to breastfeed, and complementary feeding is usually improper and inadequate, thus leading to anemia.

Of the 270 cases with ALRTI, 240 (88.9%) patients were diagnosed as pneumonia and rest 30 (11.1%) cases as bronchiolitis on the basis of radiological findings on chest X-ray. A study done by Rijal *et al.* [13] showed similar results with pneumonia in 83.6% and bronchiolitis in 16.4%. In contrast, Malla *et al.* [11] observed an approximately equal number of bronchopneumonia and bronchiolitis (51.4 vs. 48.6%). The reason for higher incidence of bronchiolitis in the study of Malla *et al.* [11] is due to the inclusion of study subjects <6 months of age and bronchiolitis has a higher incidence in this age group.

In this study, IDA was most common type of anemia. It was observed in 172 (63.7%) out of all subjects of Group A and 63 (23.3%) subjects of controls. Hussain *et al.* [12] observed that deficiency of iron was found in 78.9% of anemic patients. Mourad, *et al.* [14] observed that the percentage of IDA in 48 anemic patients was 75% and that in 22 anemic controls wer 68.75%. Association of Vitamin B12 and folate deficiency with ALRTI was also exclusively observed in cases (15.9%) and controls (2.2%).

In multivariate linear regression analysis, among the laboratory parameters, TIBC, serum iron, and serum transferrin saturation percentage were statistically significant predictors of iron deficiency in ALRTI cases. In this study, serum ferritin levels were significantly higher in cases (103.46±92.83 pg) as compared to healthy controls (38.40±86.57 pg). This may be due to the fact that as an acute phase reactant, serum ferritin level is raised in infections whereas the other parameters indicating IDA are unaffected. This was similarly observed by Hussain *et al.* [12] As it is quite difficult to ascertain the serum ferritin status during inflammation or infection, serum tranferrin saturation percentage has been considered for the diagnosis of IDA in this study. The WHO recommends the use of serum transferrin saturation percentage for the diagnosis of IDA in addition to Hb levels and serum iron. Recent studies give suggestions towards the measurement of the levels of hepcidin, which is an iron regulatory peptide for the differentiation of inflammatory anemia and IDA. This could not be attempted due to financial and logistic constraints faced while conducting this study. In this study, it was observed that with an increase in the severity of anemia among the cases, a concomitant increase in the severity of pneumonia was also observed. However, this finding was not reflected in previous studies.

Table 1: Age (months) category wise comparison of groups

Age (in weeks)	Case n (%)	Control n (%)	Total	p value
6–24	161 (59.6)	171 (63.3)	332 (61.5)	0.65
24–42	54 (20.0)	51 (18.9)	105 (19.4)	
>42	55 (20.4)	48 (17.8)	103 (19.1)	
Total	270 (100)	270 (100)	270 (100)	

Table 2: Frequency of anemia among our patients and controls

Anemia	Patients n (%)	Controls n (%)	p value	OR	95% CI
Non- anemic	60 (22.2)	201 (74.4)	0.001*	3.17	0.06–0.14
Anemic	210 (77.8)	69 (25.6)			
IDA	167 (61.8)	63 (23.3)			
Non IDA	43 (15.9)	6 (2.2)			

*Significant difference, OR: Odds ratio, CI: Confidence interval

Table 3: Iron profile in iron deficient cases and control group

Iron Profile	IDA patients (n=169)		IDA controls (n=63)		t-test	p value
	Mean±SD	Median (range)	Mean±SD	Median (range)		
Serum iron (µg/dl)	26.3±7.9	29 (20–36)	29.11±8.95	33 (20–59)	6.43	0.001*
Serum ferritin (µg/l)	103.46±92.83	92 (6.8–301)	38.0±27.70	27 (10–99)	5.65	0.01*
TIBC (µg/dl)	483.05±71.25	492 (312–612)	464.77±61.02	476 (312–563)	3.26	0.07
Transferrin saturation (%)	6.72±1.36	6.62(2.84–10.25)	6.69±1.35	6.59(3.73–10.57)	1.3#	0.86

#Mann–Whitney U-test *significant difference, SD: Standard deviation, IDA: Iron deficiency anemia, TIBC: Total iron binding capacity

Table 4: Comparison of the severity of pneumonia and anemia

Cases	Severity of anemia			Total	χ^2	p value
Severity of pneumonia	Absent	Moderate	Severe		4.33	0.04
Moderate	51	114	57	222		
Severe	9	18	21	48		
Total	60	132	78	270		

In this study, an odds ratio of 3.78 with anemia as a risk factor for ALRTI was observed. Other studies [11,15-17] have also suggested anemia as a definite predisposing factor for ALRTI in children. However, anemia was considered as a likely risk factor in the meta-analysis conducted by Broor *et al.* [18] A hypothesis can be stated regarding the role of decreased Hb for an increase in ALRTI in children. Hb not only facilitates oxygen and carbon dioxide transport but it also carries and inactivates nitric oxide (NO) and also acts as a buffer of blood by the Haldane effect. Due to this, the function of alveolar macrophages is hampered as they obtain iron mainly through RBC or plasma pool. The role of Hb as a tissue oxygen buffer is very important, as it is mainly responsible for stabilizing the oxygen pressure in the tissues.

Among preschool children living in developing countries, ALRTI and IDA often exist hand in hand as increased concentrations of iron have been quantified many times in the secretions of the pulmonary cells. This theory supports a disruption in iron homeostasis of the lower respiratory tract. The common source of iron in the lungs is serum iron, which is derived from the erythrocytes that are catabolized, and the iron that is absorbed by the cells. ALRTI exaggerates the production of iron deficient Hb cells by blocking the release of iron from the storage pools itself. On the other hand, researchers have argued that any decrease in the supply of iron to body tissue cells is a determining factor for reduced immunity [19]. The effect of IDA on decreased immunity and a significant increase in susceptibility towards infections is well established. Changes in iron status during commonly occurring acute infections in children are not well understood because infection or inflammation can influence iron status.

The strengths of the study were that the sample size was adequate and with considerable power. Serum transferrin saturation percentage, which is unaffected in infections, was considered as the diagnostic parameter indicating IDA in this study. The limitations were that it was a hospital-based study; hence, the results may not be representative of the entire adjoining rural pediatric population. It is important to consider that malnutrition (IAP-PEM grade 1 and 2), poor sanitary conditions, overcrowding, and environmental factors which may also contribute toward etiology of ALRTI have not been included as a part of this study. More such studies at the community level are the need of the hour.

CONCLUSION

We conclude that anemia of any cause, especially IDA, is still a major problem in community and anemia is a risk factor for chest infections, including pneumonia.

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