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Role of Iron Deficiency Anaemia as A Risk Factor for Wheeze Associated Respiratory Tract Infection in Children

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Introduction: Acute lower respiratory tract infections form a major portion of early childhood illnesses and infections. Iron deficiency anemia is an independent risk factor for lower respiratory tract infections (LRTI), however may also play an important role in wheeze associated respiratory tract infections. Wheezing is common in children with cumulative prevalence of almost 50% by the age of 6 yrs. **Objective:** To assess the role of iron deficiency anemia as a risk factor for wheeze associated respiratory tract infection in children. **Methods**: This case control study was conducted at Department of Pediatrics, Rajshahi Medical College Hospital, Rajshahi, Bangladesh from January to June 2022. Total 60 patients from both groups were included in our study. Among children six months to five years and having ≥2 episodes of wheeze associated respiratory tract infections. The clinical presentation and laboratory profile were recorded on a predesignated proforma. Iron deficiency anemia was diagnosed by hemoglobin <11.0 gm%, serum ferritin<12 ng/ml and RDW>15%. The statistical analysis was done using SPSS, Version 21. **Results**: A total of 60 children were enrolled in the study, of which 30 were cases and 30 were matched controls. Majority of subjects in both groups were male (n=19;63.3%), with male to female ratio of 1.6:1. On clinical evaluation of the cases, pallor was observed in 17 (56.7%) cases, mild to moderate respiratory distress was observed in 8 (26.7%), chest in drawing in 7 (23.3%), audible wheeze on inspiration in 3 (10%), presence of rhonchi in 2 (6.7%), hyper resonant note on

percussion in 6.7% and bilateral wheeze in 27 (90%) cases. Proportion of cases with iron deficiency anemia were higher among cases (33.3%) as compared to controls (23.3%) but the difference between two groups was not significant statistically (p=0.373) despite having higher risk (OR=1.49;95% CI=0.62-3.59). Mean monocyte, eosinophil and absolute eosinophil count was found to be significantly higher in cases as compared to controls (p<0.05). **Conclusion:** The present study does not suggest a possible linkage between iron deficiency anemia and wheeze associated respiratory infection, however its role as causative factor needs to be explored through long-term prospective and intervention studies on a large population.

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INTRODUCTION

Acute lower respiratory tract infections form a major portion of early childhood illnesses and infections. Acute lower respiratory tract infection (ALRTI) is characterized by inflammation of respiratory airways below the larynx till lung parenchyma [1]. Amongst them, pneumonia is the major killer accounting for 18% of under 5 year children mortality every year, according to World Health Organization (WHO) [2]. It is a chronic inflammatory condition of the lung airways resulting in episodic airflow obstruction [3]. Anemia associated with acute infections occurs more commonly in children than in adults. About 61.9% of children belonging to the age group <5 years are suffering from anemia. Population studies have shown that approximately one in three children has at least one episode of wheezing prior to their third birthday, and the cumulative prevalence of wheeze is almost 50% at the age of six years [4]. Despite its high prevalence, there is a lack of evidence regarding the pathophysiology and treatment of the first episode of wheeze [5]. Iron deficiency exerts adverse effects on immune response and alters the metabolism and growth of pathogens. It has already been reported that low hemoglobin and impaired tissue oxygenation acts as an independent risk factor for developing lower respiratory tract infections (LRTI) in children [6]. Anemia is defined as a hemoglobin level of less than 11 g/dl for age groups <5 yrs and that less than 12g/dl for up to 12 yrs of age [7]. WHO estimates that in 2001, iron deficiency anemia (IDA) resulted in 273,000 deaths: 45% in Southeast Asia [8]. A Global Action Plan for Prevention and Control of Pneumonia (GAPP) has been devised by WHO with the goal to reduce pneumonia-associated early childhood deaths to as few as 3 per 1000 live births every year by 2025 [9]. Iron deficiency exerts adverse effects on immune response and alters the metabolism and growth of pathogens. It acts as an independent risk factor for developing lower respiratory tract infections (LRTI) in children [10]. Iron deficiency thus may play an important role in wheeze associated respiratory tract infection. Iron has a crucial role in functioning of iron proteins such as hepcidin, lactoferrin, haptoglobin, and transferrin. These proteins help in building up the innate immunity [10,11]. Thus, in cases of iron deficiency there is an inadequate immune response and an increased risk of acquiring infection particularly in children.

MATERIAL AND METHODS

This case control study was conducted at the Department of Pediatrics, Rajshahi Medical College Hospital, Rajshahi, Bangladesh from January to June 2022. Total 60 patients from both groups were included in our study. Children in the age group six months to five years and having two or more

episodes of wheeze associated respiratory tract infections, reporting to the pediatrics department were enrolled as cases and healthy children of the same age group as controls. Children with co-morbidities like pre-existing pulmonary, cardiac or any other systemic illness and congenital anomalies were excluded from study.

The clinical presentation of the patients was recorded after taking a detailed history from parents. Clinical signs and laboratory investigations were recorded on a predesignated proforma. Healthy controls were selected from the pediatric OPD and well-baby clinic after taking consent from parents. Ethical clearance was obtained from the institutional ethical committee. A sample size of 30 children was selected for each group of cases and control. Venous blood was collected from each participant for complete hemogram, peripheral blood smear and iron studies. Iron deficiency was diagnosed by hemoglobin value <11.0 gm%, serum ferritin <12 ng/ml and RDW>15%. The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 Statistical Analysis Software.

RESULTS

Total 30 children in each group were enrolled in the study. Majority of subjects in both the groups were males (n=19; 63.3%). Male to female ratio of study subjects was 1.63:1. Mean age of cases was 2.49±0.88 years (range 0.6–4.0 years) whereas in control was 2.62±0.83 years (range 1–4.5 years). There was no significant difference between two groups with respect to gestational age at delivery, mode of delivery, need of NICU admission and use of drugs in neonatal period (p>0.05). Both the groups were matched for anthropometric parameters and immunization status. The demographic characteristics of study population are shown in table 1. Table-2 shows that, the clinical evaluation of the cases, pallor was observed in 17 (56.7%) cases, mild to moderate respiratory distress was observed in 8 (26.7%), chest indrawing in 7 (23.3%), audible wheeze on inspiration in 3 (10%), presence of rhonchi in 2 (6.7%), hyper resonant note on percussion in 6.7% and bilateral wheeze in 27 (90%) cases. The hematological parameters were similar in two groups, except for difference in monocyte and eosinophil counts and absolute eosinophil count. Mean monocyte, eosinophil and absolute eosinophil count was found to be significantly higher in cases as compared to controls (p<0.05). Though proportion of cases with iron deficiency anaemia was higher among cases (33.3%) as compared to controls (23.3%) yet the difference between two groups was not significant statistically (p=0.373) as seen in table 3 & fig -2. The peripheral blood smear was evaluated and microcytic, hypochromic blood picture was slightly higher in cases, but statistically, there was no significant difference between two groups (p>0.05). The comparison of blood picture is shown in table 4.

Table 1: Demographic Characteristics of cases and controls (N=60)

Characteristic	Cases (n=30) N(%)	Controls (n=30) N (%)	p-value
Gender			
Male	19(63.3)	19 (63.3)	0.840
Female	11 (36.7)	11(36.7)	
Mean Age± SD	2.49±0.88	2.62±0.83	
(range) in years	(0.6-4.0)	(1-4.5)	
Place of living			0.840
Rural	13 (43.3)	12 (40)	
Urban	17 (56.7)	18 (60)	

Table 2: Comparison of hematological parameters in study population (N=60)

SN	Features	Cases (n=30)		Controls (n=30)		
		Mean	SD	Mean	SD	p
1.	Hb (g%)	10.52	1.67	10.47	1.57	0.888
2.	TLC (‘000)	10.1	3.4	9.6	3.0	0.436
3.	Polymorphs (%)	46.16	13.02	48.84	11.04	0.270
4.	Lymphocytes (%)	40.34	12.71	42.60	9.38	0.314
5.	Monocytes (%)	2.98	2.00	2.16	1.15	0.014
6.	Eosinophils (%)	4.82	4.52	2.74	2.13	0.004
7.	Absolute eosinophil count	621.58	298.46	444.40	176.52	<0.001
8.	RDW (%)	15.05	1.72	14.67	1.59	0.251
9.	TIBC (µg/dl)	350.50	59.38	340.16	49.21	0.345
10.	S. Iron (µg/dl)	94.48	40.22	101.12	32.98	0.369
11.	S.transferrin saturation (%)	32.43	15.00	34.24	11.94	0.505
12.	S. Ferritin (ng/ml)	29.94	22.42	34.42	18.79	0.281

Table 3: Comparison of iron deficiency anemia in study population (N=60)

Iron Deficiency Anaemia	Cases (n=30) N(%)	Controls (n=30) N (%)	p value
Absent	20 (66.7)	23 (76.7)	0.373
Present	10 (33.3)	7 (23.3)	
χ^2=0.794 (df=1); OR=1.49; 95% CI=0.62-3.59)			

Table 4: Comparison of blood picture in study population (N=60)

PBS	Cases (n=30) N(%)	Controls (n=30) N (%)
Microcytic Hypochromic	12(40)	10(33.3)
Microcytic hypochromic picture with leucocytosis	1(3.3)	0(0.0)
Microcytic hypochromic with eosinophilia	2(6.7)	0(0.0)
Normocytic Normochromic	15(50)	20(66.7)
χ^2=5.074 (df=3); p=0.166		

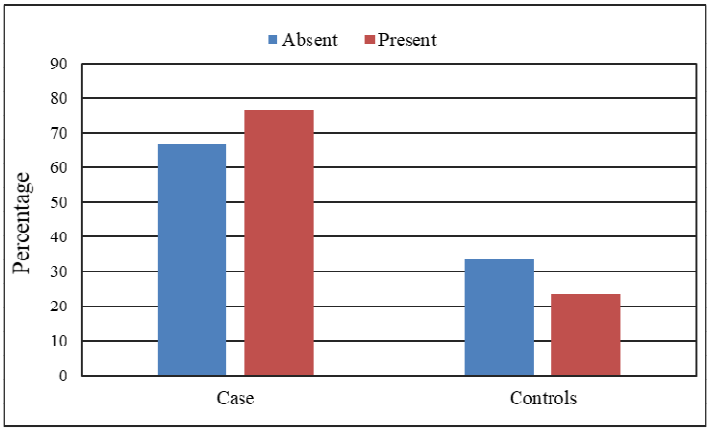

Fig-2: Comparison of indices of iron deficiency anemia in study population.

DISCUSSION

Iron deficiency is a leading risk factor for anemia in children. About 150 million episodes of childhood pneumonia are reported every year worldwide [8,9,10]. Every year globally 0.9 million children die due to pneumonia and out of which 80% children are under the age of 5 years [10]. A hemoglobin level of <11 g/dl, an MCV of <75fl and a serum ferritin level of <30 ng/ml was taken as a criterion to diagnose iron deficiency anemia [11]. In communities subsisting on plant-based diets, inadequate dietary intake of iron with particular reference to bioavailable iron accounts for the problem of IDA. Infectious illnesses are known to contribute to various nutritional deficiencies through their physiologic and metabolic effects. Among preschool children living in underprivileged communities in developing countries, respiratory infectious diseases and IDA are often coexistent and have complex, mutually adverse interactions leaving severe functional consequences. A total of 30 children in each group were enrolled in the study. Majority of subjects in both the groups were males (n=19; 63.3%). Male to female ratio of study subjects was 1.63:1. Mean age of cases was 2.49±0.88 years (range 0.6 - 4.0 years) whereas in control was 2.62±0.83 years (range 1- 4.5 years). There was no significant difference between two groups with respect to gestational age at delivery, mode of delivery, need of NICU admission and use of drugs in neonatal period (p>0.05). Both the groups were matched for anthropometric parameters and immunization status. In present study, there were more number of boys 19(63.3%) having wheeze associated respiratory infection and were in agreement with the observations made by several researchers, [10] who showed higher prevalence of male in different subsets of children suffering from respiratory tract infections including those categorized as wheeze-associated infections. The mean age of patients was 2.49±0.88 years with maximum age of 4 years, thus indicating higher prevalence of wheeze- associated respiratory illnesses among younger age groups. The acute illness may also affect the hematological parameters. A prospective study done on children with acute respiratory infections, a significant drop in hemoglobin concentration by days 9 to 14 post mild viral illness was seen [12]. On clinical evaluation of the cases, pallor was observed in 17 (56.7%) cases, mild to moderate respiratory distress was observed in 8 (26.7%), chest retractions in 7 (23.3%), audible wheeze on inspiration in 3 (10%), presence of rhonchi in 2 (6.7%), hyper resonant note on percussion in 6.7% and bilateral wheeze in 27 (90%) cases. Serum iron and transferrin saturation fell significantly, whereas erythrocyte protoporphyrin and serum ferritin increased significantly. Most of the changes in iron

parameters persisted for two or three weeks after the appearance of fever, and some measures may have even become abnormal during the incubation period of viral illness. Thus, as infection or inflammation can influence iron status, it is always very challenging to exclude iron deficiency anemia in the context of concomitant inflammation [13]. The hematological parameters were similar in two groups, except for differences in monocyte and eosinophil counts and absolute eosinophil count. Mean monocyte, eosinophil and absolute eosinophil count was found to be significantly higher in cases as compared to controls ($p<0.05$). Though proportion of cases with iron deficiency anemia was higher among cases (33.3%) as compared to controls (23.3%) yet the difference between two groups was not significant statistically ($p=0.373$). In the present study, taking hemoglobin levels as the criteria for detecting anemia, the majority 56.6% were found to be anemic and among these 43.4% were found to be having iron deficiency. Thus, in present study the prevalence of iron deficiency anemia itself is lower than that reported in general (67-77%) [14] which might be due to usage of a strict criteria of combination of serum ferritin<12 ng/ml and RDW>15%. As aforementioned, the combined criteria are more specific and rules out the chance of higher prevalence of IDA [15]. Prevalence of iron deficiency anemia as per our criteria in present study was 32% in cases and 24% in control group, however, the difference was not significant statistically though children with iron deficiency anemia were at a higher risk of wheeze associated respiratory diseases (OR=1.49; 95% CI 0.62-3.59). This finding is in agreement with the observations of workers such as Ramakrishnan and Borade et al [16], who reported higher prevalence of asthma among anemic children as compared to non-anaemic children and also indicated a significant association between iron-deficiency anemia and respiratory illness. On evaluating the hematological profile for differential counts of the children in case group to that of control group, no statistically significant difference was observed between two groups except of mean monocyte, eosinophil and absolute eosinophil count to be higher in cases as compared to controls and may indicate the presence of an atopic etiology in wheeze- associated infections. Hence timely measures should be taken through education of community masses regarding prevention of iron deficiency. Earlier recognition and timely intervention will help decrease the various complications associated with it. The limitation of this study is small sample size and duration. In order to get more reliable data, it is recommended to perform more studies but with a bigger sample size.

CONCLUSION

In conclusion, the study does not suggest a possible linkage between iron deficiency anemia and wheeze associated respiratory infection. However, investigation of a link is a step forward in direction of further studies specifically targeted to review the role of iron deficiency anemia as a cause of wheeze associated respiratory infection. It is essential that possibility of such linkage should be explored further in long-term prospective intervention studies on a larger population to establish the iron deficiency anemia as a cause of wheeze associated respiratory infection.

Conflict of interests: None.

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