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A Study of Iron Deficiency Anemia in Children with Bronchial Asthma

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Introduction

Asthma is a heterogenous disease, usually characterized by chronic airway inflammation. It is defined by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary overtime and in intensity, together with variable expiratory airflow limitation[1]. According to Global Initiative for Asthma (GINA 2019), acute asthma is characterized by worsening of symptoms and lung function from patient's usual status. Asthma is one of the most commonly encountered diseases in clinical practice. The true burden of asthma in India is unknown. Indian asthmatics have a high frequency of reported exacerbations leading to substantial limitations of daily activities, lung function impairment, reduced quality of life and an adverse socioeconomic burden. Asthma insights and management was conducted in 9 countries in the Asia pacific region (AP-AIM study) including India in 2011. According to the study, asthmatics reported 8.4 exacerbations per year, each lasting a mean of 4days. Nearly in India, 78% of asthmatics reported missing work/ school due to their asthma in the year 2018. Productivity of asthmatics fell from 70% to 35% on the day with worst symptoms of asthma[1]. Symptoms and airflow limitation may resolve spontaneously or in response to medication and may sometimes be absent for weeks or months at a time. Some patients experience episodic exacerbations of asthma that may be life threatening and carry a significant burden to them and the community. Airway hyper responsiveness and chronic airway inflammation usually persist, even when symptoms are absent or lung function is normal, but may normalize with treatment.[1,2,3,4] Bronchial asthma is a major cause of morbidity and mortality among the pediatrics age group. Male: Female ratio of asthma in children is2:1, but in adults the ratio is 1:1. The prevalence of asthma has been increasing rapidly in westernized and industrialized countries[1,2,3,4]. Anemia associated with acute infection occurs more commonly in children than adults. Iron deficiency exerts adverse effect on immune response and alters the

metabolism and growth of pathogens[6,7,8]. Anemia was suggested to be a risk factor in exacerbation of asthmatic attack because Hemoglobin facilitates oxygen and carbon dioxide transport, carries and inactivates nitric oxide and act as buffer. Hemoglobin in blood is mainly responsible for stabilizing the oxygen pressure in blood and tissues[8,9]. It has already been reported that low Hemoglobin impairs tissue oxygenation and acts as an independent risk factor developing LRTI in children. Since anemia has been shown to be a risk factor for LRTI, this descriptive study aims to assess the incidence of iron deficiency anemia in asthmatic pediatric patients in supporting the clinical findings at Department of Pediatrics, Grant Medical College and Sir JJ Group of Hospitals Mumbai, Maharashtra, India and is planned to determine serum iron level in children of bronchial asthma[8,9].

Aims and Objectives

- To study serum iron profile in children with bronchial asthma.
- To study the association of iron deficiency anemia in children with bronchial asthma.

Materials and Methods

- **Study and Location:** The study was carried out in the Department of Pediatrics, Grant Medical College and Sir JJ Group of Hospitals Mumbai, Maharashtra**.**
- **Study Type:** Comparative descriptive cross-sectional study.
- **Study Duration:** The study was conducted from January 2018 to Dec 2019 (18 months).
- **Selection of Cases:** All pediatric cases in the age group of 2 years to 12 years, those attending OPD or admitted in ward during January 2018 to December 2019 with following inclusive and exclusive criteria were included in this study.
- **Sample Size:** A sample size of 100 was selected.
- **Inclusion Criteria:** 1. Patients in the age

group of 2 to 12 years of age with already diagnosed as asthma on treatment. 2. Recurrent episodic respiratory symptoms of cough, wheeze and chest tightness induced by precipitating factors characteristic of asthma. 3. PFT indicating airway obstruction (between 6-12 years of age group) or air trapping present on body plethysmography. 4. More than 3 episodes of wheezing attack were present in 1 year with family history and atopic features (atopic eczema / dermatitis, allergic rhinitis). 5. Cough persisting for more than 2 weeks with good response to bronchodilator. 6. Symptoms that improve with administration of bronchodilator or a 12% or greater increase in FEV1 after bronchodilator administration.

- **Exclusion Criteria:** 1. Children less than 2 years and more than 12 years of age. 2. Cases with possible causes of wheezes other than asthma as children with congenital malformation of the chest wall, reflex disease, congenital heart disease, possible immune deficiency evidence of bacterial infection, parasitic infestations and wheezes at first time were excluded from study. 3. Those with family history suggested hemolytic anemia as G6PD deficiency and thalassemia were excluded. 4. Cases with severe systemic illness, protein energy malnutrition > grade 3/4 according to IAP, cystic fibrosis, TB, lung abscess, pleural effusion, malignancies. 5. Patient already on iron therapy for 30 days and anemia other than iron deficiency anemia, and received blood transfusion recently. 6. Children with history of low birth weight or prematurity were also excluded.

Method

Diagnosed asthmatics based on GINA guidelines 2019 /pulmonary function test earlier who were followed up on OPD and those who required

inpatient care were included. Detailed history was taken with complete clinical examination. The group was divided in to two categories according to their hemoglobin status - asthma patients with anemia and without anemia. Peripheral blood smear, red blood indices, serum iron studies were studied in all subjects.

Statistical Analysis: Result of 61 asthma cases with anemias were analyzed and compared with 39 cases of asthma patients without anemia using the IBM statistical packages for social sciences, SPSS software version 22. Results of continuous measurements was measured as frequency mean and standard deviation (SD). Results of categorical measurements are presented as number (%) Chi square test and Mann Whitney U test was used to compare the different type of measurements. 2. p-value greater than 0.05 were considered statistically insignificant. 3. p-values less than 0.05 were considered statistically significant. 4. And p-values less than 0.01 were considered statistically highly significant.

Results

In the present study 61 cases of asthma patients with anemia were compared to 39 cases of asthma patients without anemia. Two groups were matched with age and gender as shown listed in table 1. Mean age of the study population was 5.94±2.99 years. Majority of the study participants were in the age group of 2-5 years (42%) followed by 5-8 years (29%), 8-10 years (15%) and 10-12 years (14%). Male: female ratio in study group was 1.9:1.

The common presenting symptoms in both groups (asthma patients with anemia and without anemia) were listed in table 2. The most common symptoms were cough, breathlessness, wheeze, fever, chest tightness, throat pain, chest pain and poor weight gain. Respiratory symptoms were seen in higher number of children in asthma patients with anemia than without anemia. However statistically significant association was not established for any symptoms.

In current study as shown in table 3 asthma patients with anemia had highest number of recurrent admissions 47 (77.0%). The mean duration of hospital stays among asthma patients with anemia compared to patients without anemia was 3.07±2.08 vs 0.54±1.33 days. There was a statistically significant difference seen (p value=0.04 and 0.00 respectively) with respect to history of recurrent admission and duration of hospital stay.

In this study as seen in table 4 Hemoglobin level was studied and anemia was diagnosed as per cut-off values of WHO criteria (age wise). Study group was divided into asthma patient with anemia and without anemia according to hemoglobin values. Anemia was also graded into mild (10-10.9g/dl) moderate (7- 9.9g/dl) and severe (<7g/dl).

Based on severity classification of asthma, the study group was divided into intermittent asthma (28%) mild persistent asthma (37%) moderate persistent asthma (22%) and severe persistent asthma (13%) as listed in table 5. Severity of asthma correlated with anemia. It was found that majority of the study participants with severe persistent asthma had severe anemia 9 (69.23%) and those with moderate persistent asthma had moderate anemia 15 (68.18%) while the ones with intermittent and mild persistent asthma had normal hemoglobin levels 20 (71.43%) and 18 (48.65%) respectively. This association was statistically significant.

As seen in table 6 pallor was absent highest among asthma patients without anemia as compared with asthma patient with anemia (84.6% vs 19.6%) Mild pallor was seen highest among asthma patient with anemia as compared to without anemia (19.6% vs 15.3%). Moderate pallor (24.5%) and severe pallor (36.0%) were present only among asthma patients with anemia. However, there was no statistical significance among both study groups (p=0.05). Nail changes were also examined in study groups and graded as no changes, pale, platynychia and koilonychia Normal nail was seen highest among asthma

patients without anemia 35 (89.7%) as compared to with anemia 7 (11.4%) as was pale nail, more among asthma patients with anemia 14 (22.9%) as compared to without anemia 4(10.2%). Platynychia was present only in anemia group and absent in without anemia 22 (36.0% vs 0%) as was koilonychia18 (29.5 % vs 0 %). The difference however had no statistical significance (p=0.23)

The mean hemoglobin (7.93±1.66) g/dl, Hematocrit (26.06±5.89), Mean corpuscular volume (62.42±9.31) fl, Serum iron (51.48±29.92) mcg/dl, Serum ferritin (26.28±20.72) ng/ml and Transferrin Saturation (17.5±10.19) was significantly lower in study participants with asthma with anemia. It was also found that majority of the study participants with severe persistent asthma had severe anemia 9 (69.23%) as listed in table 7

Peripheral blood smear examination was studied in all study groups to look for presence of microcytic hypochromic anemia as shown in fig 1. Microcytic hypochromic anemia was present among asthma patients with anemia 54 (88.52%) as compared to those without anemia 4 (10.26%). However, there was a statistically significant difference among study groups.

Table 1: Distribution of study participants according to demographics

		Groups (n)		Total (n=100)	p
		Asthma patients without Anemia (n=39)	Asthma patients with Anemia (n=61)		
Age Groups	≥2Y-<5years	11(28.2%)	31(50.8%)	42	0.10
	≥5-<8years	16(41.0%)	13(21.3%)	29	
	≥8-<10years	6(15.3%)	9(14.7%)	15	
	≥10-≤12 Years	6(15.3%)	8(13.1%)	14	
Gender	Male	24(61.5%)	42(68.8%)	66	0.29
	Female	15(38.4%)	19(31.1%)	34	
Chi square test; *Statistically significant, p<0.05					

Table 2: Distribution of study participants according to presenting complaints

Presenting complaints		Groups (%)		Total(n=100)	P
		Asthma patients without Anemia (n=39)	Asthma patients With Anemia(n=61)		
Fever	No	9(23.0%)	8(13.1%)	17	0.15
	Yes	30(76.9%)	53(86.6%)	83	
Cough	No	0(0%)	0(0%)	0	-
	Yes	39(100%)	61(100%)	100(100%)	
Breathlessness	No	12(30.7%)	12(19.6%)	24	0.37
	Yes	27(69.2%)	49(80.3%)	76(76%)	
Wheeze	No	10(25.6%)	11(18.0%)	21	0.71
	Yes	29(74.5%)	50(81.9%)	79(79%)	
Chest Tightness	No	33(84.6%)	57(93.3%)	90	0.24
	Yes	6(15.3%)	4(6.5%)	10	
Chest pain	No	38(97.4%)	61(100%)	99	0.39
	Yes	1(2.5%)	0(0%)	1	
Weight Gain	No	39(100%)	60(98.3%)	99	1.00
	Yes	0(0%)	1(2.5%)	1	
Throat Pain	No	37(94.8%)	61(100%)	98	0.20
	Yes	2(5.1%)	0(0%)	2	
Chi square test; *Statistically significant, p<0.05					

Table 3: Distribution of study participants according to past history of admission.

			Groups		Total (n=100)	P
			Asthma patients without Anemia (n=39)	Asthma patients with Anemia (n=61)		
Past history	History of recurrent admission (%)	No	33(84.6%)	14(22.9%)	47	0.04*
		Yes	6(15.3%)	47(77.0%)	53	
	Duration of hospital stay (Mean±Std. Deviation)		0.54±1.33	3.07±2.08	2.80±2.20	0.00#*

Chi-square test; #Mann Whitney U test*Statistically significant, p<0.05

Table 4: Hemoglobin level in both the groups

		Groups (%)		Total (n=100)	P
		Asthma patients Without Anemia(n=39)	Asthma patients with Anemia (n=61)		
Hemogobin levels	Normal	39	0	39	0.00*
	Mild	0	12(19.6%)	12	
	Moderate	0	31(50.8%)	31	
	Severe	0	18(29.5%)	18	

Chi-square test *Statistically significant, p<0.05

Table 5: Hemoglobin level in different types of asthma

		Diagnosis [n(%)]				Total (%) (n=100)	p
		Intermittent Asthma	Mild Persistent Asthma	Moderate Persistent Asthma	Severe Persistent Asthma		
Anemia types	Normal	20(71.43%)	18(48.65%)	1(4.55%)	0(0%)	39	0.00*
	Mild	5(17.86%)	6(16.22%)	1(4.55%)	0(0%)	12	
	Moderate	2(7.14%)	10(27.03%)	15(68.18%)	4(30.77%)	31	
	Severe	1(3.57%)	3(8.11%)	5(22.73%)	9(69.23%)	18	
	Total	28(100%)	37(100%)	22(100%)	13(100%)	100	

Chi-square test *Statistically significant, p<0.05

Table 6: Distribution of study participants according general examination and head to toe examination.

			Groups (%)		Total(n=100)	P
			Asthma patients without Anaemia (n=39)	Asthma patients with Anaemia (n=61)		
General examination	Pallor	No	33(84.6%)	12(19.6%)	45	0.05
		Mild	6(15.3%)	12(19.6%)	18	
		Moderate	0(0%)	15(24.5%)	15	
		Severe	0(0%)	22(36.0%)	22	
Nail changes	Normal		35(89.7%)	7(11.4%)	42	0.23
	Pale		4(10.2%)	14(22.9%)	18	
	Platynychia		0(0%)	22(36.0%)	22	
	Koilonychia		0(0%)	18(29.5%)	18	

Chi-square test; # Mann Whitney U test*Statistically significant, p<0.05

Table 7: Comparison of laboratory investigation of the study participants

		Groups		Total (n=100)	P
		Asthma patients without Anemia(n=39)	Asthma patients with Anemia (n=61)		
CBC indices (Mean ± Std. Deviation)	Hemoglobin	12.55±1.39	7.93±1.66	9.73±2.75	0.04*
	Platelet	357820.51±124590.46	420426.23±174020.35	396010± 158913.45	0.00*
	PCV	32.28±4.87	26.06±5.89	28.49±6.28	0.05*
	RBC	3.76±0.64	3.05±0.73	3.33±0.77	0.02*
	MCV	73.07±5.24	62.42±9.31	66.58±9.5	0.00*
	MCH	24.56±4.43	21.31±5.83	22.58±5.54	0.00*
	MCHC	33.05±4.03	26.73±6.07	29.2±6.18	0.00*
	RDW	14.35±3.2	19.05±6.01	17.22±5.58	0.00*
	MentzerIndex	14.9±3.21	19.49±4.28	17.7±4.49	0.00*
Serum Iron Studies (Mean±Std. Deviation)	SerumIron	91.87±27.51	51.48±29.92	67.23±35	0.00*
	SerumFerritin	62.9±24.79	26.28±20.72	40.56±28.61	0.00*
	Transferrin Saturation	30.4±9.5	17.5±10.19	22.53±11.73	0.00*
	TIBC	303.69±48.9	391.34±66.53	357.16±73.8	0.00*
Peripheral blood smear examination [Microcytic Hypochromic/ Marked Anisopoikilocytosis/ Target Cells] [n(%)]	Absent	35(89.74%)	7(11.48%)	42(42%)	0.00#*
	Present	4(10.26%)	54(88.52%)	58(58%)	
	Total	39(100%)	61(100%)	100(100%)	

Mann Whitney U test; #Chi-square test, *Statistically significant, p<0.05
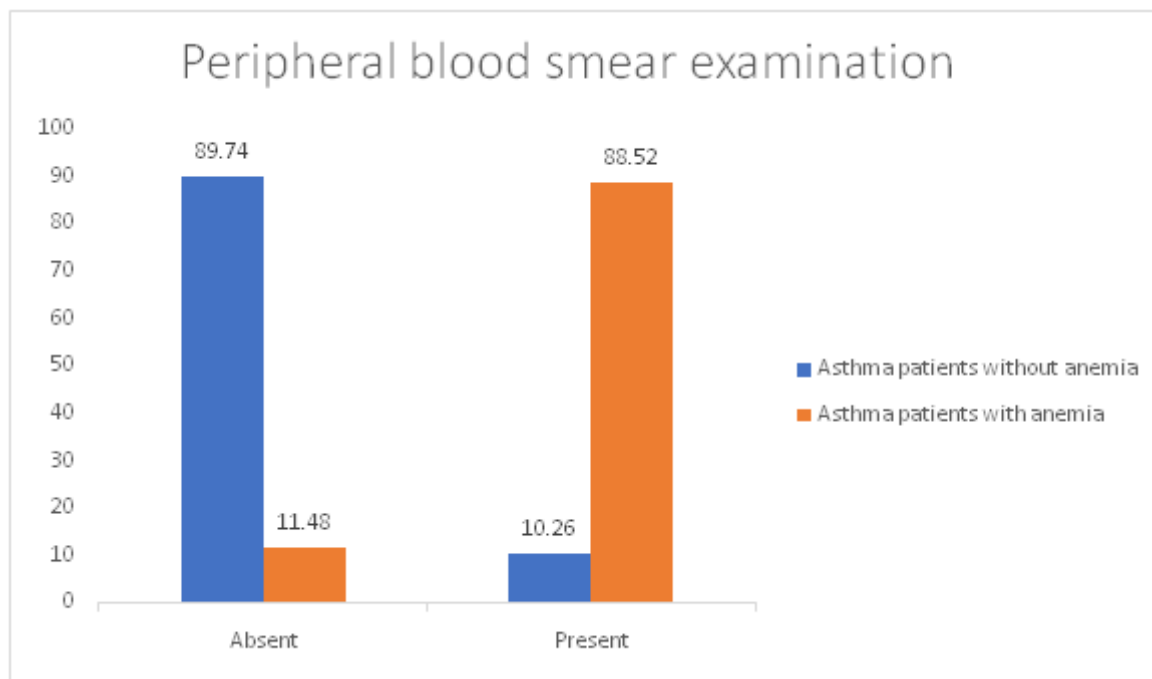

Figure 1: Comparison of peripheral blood smear examination amongst asthma patients with and without anemia.

Discussion

Incidence of bronchial asthma has increased worldwide. 90% of children are diagnosed by the age of 5 year. Childhood asthma is the most common cause of childhood emergency department visits, hospitalizations and missed school days[1,5,10,11,12]. It has a tremendous negative impact through increased asthma exacerbations, hospital admission, absence from school, and high healthcare cost.

Mean age of the study population was 5.94±2.99 years. Among the study participants, 66% were male and 34% were females. Based on severity classification of asthma, correlated with asthma study group was divided into intermittent asthma (28%), mild persistent asthma (37%), moderate persistent asthma (22%) and severe persistent asthma (13%). In current study, asthma patients with anaemia (n=61) had highest number of recurrent admissions 47 (77.0%). And also there was a statistically significant difference seen (p value=0.04 and 0.00 respectively) with respect to history of recurrent admission and duration of hospital stay. The mean haemoglobin (7.93±1.66)g/dl, Hematocrit (26.06±5.89), Mean corpuscular volume (62.42±9.31) fl, Serum iron (51.48±29.92)mcg/dl, Serum ferritin (26.28±20.72)ng/ml and Transferrin Saturation (17.5±10.19) was significantly lower in study participants with asthma with anaemia. It was also found that majority of the study participants with severe persistent asthma had severe anaemia 9 (69.23%). Association of anemia with asthmatic children was found in other reports. Ramakrishnan K. et al 2010[12] suggested that anemia is possible risk factor of asthma. They found that incidence of asthma in Indian anemic children was 74% compared to 33% of non- anemic controls with predominance of IDA (85 % of anemic asthmatics). Eissa SA et al 2016[11] found children with IDA has more risk of asthma (66 %) compared to non-asthmatics (24 %).Also in the study conducted by Fida et al 2008- 2009[5], suggest that the prevalence of IDA in asthmatic patients was 19.70%.In conclusion, IDA needs to be considered as a risk factor in asthmatic patients. Also a similar study conducted by Wagdy et.al. 2017[10] shows that iron deficiency anaemia is more prevalent in asthmatic children compared to healthy controls. Asthmatic children have a risk of iron deficiency even when they are not anaemic. Red cell counts and iron deficiency increases with severity of asthma.

Conclusion

Present study investigated iron deficiency anemia, complete blood count indices, serum iron studies in children with bronchial asthma. We found asthmatic children have higher risk of iron deficiency anemia even when they are not clinically anemic on examination. Iron deficiency anemia correlated with severity of asthma attack and may be considered as a risk factor for development of asthmatic attacks in children. Screening followed by treatment of asthmatic children for iron deficiency anemia may be helpful in holistic management of asthma children. Timing of treatment needs further investigations. Supplementing infants with iron might prove to be a safe and effective strategy for reducing the risk of asthma, but further studies to determine the causality needs to be done. Introduction of iron rich food in diet during infancy is also important in preventing asthma and allergies.

Recommendation

Introduction of iron rich food in diet during infancy is important in preventing asthma and allergies.

Limitations

Some limitations in our study are small sample size, which nearly covers one phenotype "non - atopic type" which occurs in preschool age. Larger studies are required to cover all pediatric ages and all asthmatic phenotype including atopic phenotype and also to include asthmatic children who are in quiescent

"controlled" to allow comparison with those in exacerbation "acute attack". Other markers of iron state, serum transferrin receptor (sTfR) which is a measure of tissue iron need and as TfR-F index, which estimates total body iron correlated better with pulmonary function than serum ferritin but ferritin correlated better as protective against asthma at certain threshold (7). Another limitation is the lack of data on oral iron supplements and other supplements in study population.

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