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Serum Magnesium Levels in Children with Acute Bronchial Asthma

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ABSTRACT

Background and Objective: Acute exacerbation of bronchial asthma is a very common presentation in the pediatric emergency department, thus being a major cause of morbidity in children. Intravenous magnesium sulfate is often used for the management of acute asthma. The actual association of serum magnesium levels with the severity of the disease has been explored in various studies but lacks concrete results, especially in Indian children. The aim of this study was to assess serum magnesium levels in children with acute bronchial asthma and determine the association between magnesium levels and various parameters in asthma.

Methods: This cross-sectional study was conducted in a tertiary care center in New Delhi in the year 2021-22. A total of 40 children aged 6-11 years presenting to the emergency department with acute exacerbation were included. Serum magnesium levels were determined in all patients who came to the emergency department with an acute exacerbation of bronchial asthma. The prevalence and association between hypomagnesemia and various disease and population variables were determined.

Findings: The prevalence of hypomagnesemia was 20% in the included patients. Lower magnesium levels were found to be associated with lower oxygen saturation on admission, longer duration of hospitalization, deranged pulmonary function tests, and the need for mechanical ventilation.

Conclusion: The results showed that hypomagnesemia was significantly associated with increased severity of bronchial asthma.

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Introduction

Bronchial asthma is one of the most common non-communicable diseases affecting approximately 339 million people globally. Around 6% of children and 3% of adults in India have asthma [1]. Bronchial asthma is a clinical condition characterized by a hyperresponsive airway to common provocative exposures such as allergens, tobacco smoke, air pollutants, viruses, and other irritants present in the environment. Pathologically represented by airway wall thickening, mucus gland hypertrophy, and smooth muscle contraction, it manifests as airflow obstruction and bronchoconstriction. Clinically, it is characterized by a reduced FEV/FVC ratio (Forced expiratory volume in 1 sec/Forced vital capacity) which normally is >0.7-0.8 in adults and >0.9 in children, and reversible airflow obstruction [2].

Acute asthma exacerbation is defined as an acute or subacute worsening of symptoms from the usual status of the patient such as inability to speak in sentences, preference to hunch forwards, increased respiratory and heart rates, and a dipping oxygen saturation. The severity of this is classified by many scores, one being the PASS (Pediatric Asthma Severity Score) which is assessed on PICU (Pediatric Intensive Care Unit) admission and is validated in certain studies [3]. Intravenous magnesium sulfate is a drug used commonly in the ICU for acute asthma management.

Magnesium is the fourth most common cation and third most common intracellular ion in the human body. Normal serum magnesium concentration is 1.5-2.3 mg/dl. Magnesium deficiency is manifested in multiple organ systems of the body characterized by anxiety, lethargy, musculoskeletal symptoms (tetany, carpopedal spasm), cardiovascular symptoms (arrhythmias, Torsade-de-pointes, coronary spasm), and nervous symptoms (tremor, vertigo, nystagmus, depression). Magnesium plays a crucial role in the respiratory system as well. Various studies prove the role of magnesium as a bronchodilator by inhibiting calcium influx, relaxing the smooth muscle airway, and inhibiting acetylcholine release from nerve endings [4-6]. The role of magnesium in asthma for symptom control, severity, and prevention of disease has been explored in many studies but there is no concrete conclusion, especially in children.

This study was conducted to find the role of serum magnesium in asthma in children and its correlation with acute exacerbation of asthma if it existed.

Methods

Study design and sampling

The cross-sectional study was conducted at the Department of Pediatrics in a tertiary care center in Delhi, India over a period of one year (2021-2022). It was a cross-sectional study performed on 40 children of 6 to 11 years of age presenting with acute exacerbation of bronchial asthma to the emergency department defined as per GINA 2020 guidelines [1]. Patients with known congenital renal magnesium wasting conditions such as Bartter and Gittelmann's syndrome were excluded. Patients who received magnesium in any form (intravenous, oral, or inhalational) in the last 24 hours and with surgical ileostomy and colostomy were also excluded from our study. 40 children were selected by simple randomization.

Data collection

Required data of all the participants was recorded using a predefined proforma. A detailed examination was done. Height was measured by a stadiometer and weight to the nearest 100 g by a standard weighing machine. Body Mass Index was calculated and expressed as age and sex-adjusted Z scores (Normal value of BMI taken -18.5-22.9). History of nasobronchial allergy mainly seen as allergic rhinobronchitis and skin allergy in the form of dermatographism, atopic dermatitis was duly noted. 5 ml of venous sample was drawn for estimation of serum magnesium levels using the Colorimetric method via commercially available kits on Vitros automated analyzer. The cut-off for hypomagnesemia was taken at 1.8 mg/dl (0.75mmol/L) [7]. Lung functions were tested by a trained lab technician under the supervision of the doctor using an ultrasonic technology-based spirometer, device as per ERS (European Respiratory Society) and ATS (American Thoracic

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Society) standards after stabilization of the patient. Severity of asthma was graded using the Pediatric Asthma severity score (Mild ≤7, Moderate 8-11, Severe≥12).Children were managed as per the protocols of the department based on GINA (Global Initiative for Asthma) guidelines.

Statistical analysis

All the collected data was systematically entered in Excel software and data analysis was done using software by IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. For all tests, a p-value of <0.05 was considered significant. Demographic details and baseline characteristics of all the patients were analyzed and then the occurrence of hypomagnesemia was correlated with various factors associated with the patients and the disease.

Results

A total of 40 children, aged between 6 and 11 years, participated in the study. The mean age of the patients was 6.7 years. There was a higher number of males as compared to females. Approximately 60% (24) of the children had a positive family history of bronchial asthma.

The severity of asthma was graded by PASS (Pediatric Asthma Severity Score) [8] at the time of presentation. None of the patients had a score ≤ 7, and 30 out of 40 (75%) had a score ≥12, making maximum patients fall in the severe category. Moreover, 62.5% of the asthmatics had no co-existing allergies. Among the patients presenting with acute exacerbation, 2 of them (5%) required mechanical ventilation and 14 of them (35%) had a previous history of hospitalization. A pulmonary function test was attempted on all patients after stabilization, only 13 of them could perform it and 4 (10%) of the cases had a deranged FEV/FVC **(Table 1).**

Among 40 cases, 32(80%) had a normal magnesium level and 8 (20%) had a magnesium level <1.7mg/dl. The mean level of magnesium was found to be lower in females (2.229±0.458mg/dl) as compared to males (2.288±0.602mg/dl) but this was statistically insignificant (p: 0.748).

The occurrence of hypomagnesemia patients was evenly distributed between rural and urban areas, as well as among individuals with or without a family history of asthma, and those with or without allergies. Exacerbations in the preceding 4 weeks did not influence the occurrence of hypomagnesemia, although the mean magnesium levels were lower in patients having exacerbation in the preceding 4 weeks (2.17±0.44 mg/dl), this difference was not statistically significant (p: 0.618). All the patients requiring mechanical ventilation had low magnesium levels and the mean levels of magnesium in those who required mechanical ventilation was 1.5±0.0 mg/dl against a mean level of 2.30±0.53 mg/dl in those who did not need mechanical ventilation and this was statistically significant (p-value: 0.04). At presentation, 7 among 8 cases (87.5%) with hypomagnesemia had a Spo2 of less than 90%. Thus, hypomagnesemia was more common in patients with lower Spo2 at presentation and this was statistically significant (p: 0.016). 7 (87.5%) cases with low magnesium levels had no history of previous hospital stay, thus the existence of previous hospital admissions did not influence magnesium levels in cases (p: 0.222). All cases of hypomagnesemia, constituting 100%, were associated with a Paediatric asthma severity score of ≥12, classifying them within the severe category. Additionally, among the 8 cases of hypomagnesemia, 3 displayed abnormalities in their pulmonary function tests. Thus, the reduction of FEV1/FVC values in the patient was significantly associated with the occurrence of hypomagnesemia (p: 0.015). Although most patients could not perform PFT, the results of PFT are difficult to be extrapolated. Most of the cases experienced a hospital stay lasting less than 20 days. Furthermore, there was a statistically significant difference in the duration of hospital stays between patients with low magnesium values and those with normal values. **(Table 2)**.

Discussion

The study was conducted by us in a tertiary care hospital in Delhi to see an association between

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hypomagnesemia and acute bronchial asthma. It was observed that all the patients who required mechanical ventilation had low magnesium levels (p-value: 0.03). This association was proven in other studies as well. In a meta-analysis done by Upala et al. [9], hypomagnesemia was associated with increased mortality in ICU patients. Also, patients with lower levels of magnesium were predisposed to increased length of ICU stay and increased need for mechanical ventilation. Another interesting observation in our study was that hypomagnesemia was more common in patients with lower Spo2 at presentation (p-value 0.01). While there are currently no available studies that have directly established a clear association between hypoxia and low magnesium levels in humans, an interesting study conducted by Torii et al sheds light on the significance of magnesium in regulating hypoxia [10]. Their research highlights that hypomagnesemia can potentially inhibit the activity of HIF-1α (Hypoxia-Inducible Factor-1α) in paraganglion cells located in the adrenal medulla and carotid body. Given that HIF-1α serves as a pivotal regulator of hypoxia, individuals with hypomagnesemia might be at risk of experiencing hypoxemia. There have been studies that explored the relevance of magnesium levels in critically sick patients. Safavi et al and Limaye et al conducted studies on critically ill patients and it was found that low magnesium levels were more profound in critically sick patients [11, 12]. The duration of hospital stay was significantly longer in those with hypomagnesemia in our study (p-value 0.04) which was similar to an observational study by Solanki et al. [13], which concluded that magnesium was an independent determinant for longer ICU stays and a higher APACHE 2 score in critically sick patients.

Table 1. Demographic details of participants

Sl. no	Variable	Subgroup	Number
1.	Age group	6-7 years	15 (37.5%)
		8-9 years	18 (45%)
		10-11 years	7 (17.5%)
2.	Gender	Male	26 (35%)
		Female	14 (65%)
3.	Area of residence	Rural	23 (57.5%)
		Urban	17 (42.5%)
4.	Family history of asthma	Yes	16 (40%)
		No	24 (60%)
5.	BMI (Body Mass Index)	Underweight (<18.5)	7 (17.5%)
		Normal (18.5-22.9)	16 (40%)
		Overweight (23-24.9)	7 (22.5%)
		Obese (>25)	10 (25%)
6.	PASS (Pediatric Asthma Severity Score)	Mild (≤7)	0
		Moderate (8-11)	10 (25%)
		Severe (≥12)	30 (75%)
7.	History of allergies	None	25 (62.5%)
		Skin	2 (5%)
		Naso-bronchial	8 (20%)
		Skin + naso-bronchial	5 (12.5%)
8.	Requirement of mechanical ventilation	Yes	2 (5%)
		No	38 (95%)
9.	Previous controller medication use	Yes	11 (27.5%)
		No	29 (72.5%)
10.	Previous history of hospitalization	Yes	14 (35%)
		No	26 (65%)
11.	FEV1/FVC	Normal	9 (22.5%)
		Deranged (<90%)	4 (10%)
		Could not be assessed	27 (67.5%)

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Table 2. Association of hypomagnesemia with the variables along with p-value (Chi-square test used for qualitative variables and paired t-test for quantitative)

No	Variable	Subgroup	Hypo-Magnesemia	Normal	P value
1.	Gender	Female	2 (25%)	12 (37.5%)	0.689
		Male	6 (75%)	20 (62.5%)	
2.	Age group	6-7	1 (12.5%)	14 (43.8%)	0.263
		8-9	5 (62.5%)	13 (40.6%)	
		10-11	2 (25%)	5 (15.6%)	
3.	Area of residence	Rural	4 (50%)	19 (59.4%)	0.702
		Urban	4 (50%)	13 (40.6%)	
4.	BMI (Body mass index)	Underweight (< 18.5)	1 (12.5%)	6 (18.8%)	0.221
		Normal (18.5 – 22.9)	3 (37.5%)	13 (40.6%)	
		Overweight (23 – 24.9)	0	7 (21.9%)	
		Obesity (>25)	4 (50%)	6 (18.8%)	
5.	Family history of asthma	No	4 (50%)	20 (62.5%)	0.690
		Yes	4 (50%)	12 (37.5%)	
6.	History of allergy	No	4 (50%)	21 (65.6%)	0.444
		Yes	4 (50%)	11 (34.4%)	
7.	Previous exacerbation in 4 weeks	No	7 (87.5%)	26 (81.2%)	0.618
		Yes	1 (12.5%)	6 (18.8%)	
8.	Need for mechanical ventilation	No	6 (75%)	32 (100%)	0.036
		Yes	2 (25%)	0	
9.	Use of controller medication	No	6 (75%)	23 (71.9%)	1.00
		Yes	2 (25%)	9 (28.1%)	
10.	School absenteeism	No	5 (62.5%)	20 (62.5%)	1.00
		Yes	3 (37.5%)	12 (37.5%)	
11.	Severity of symptoms	Asymptomatic	2 (25%)	10 (31.2%)	0.286
		Daytime symptoms	1 (12.5%)	13 (40.6%)	
		Day + night-time symptoms	3 (37.5%)	6 (18.8%)	
		Severe symptomatic	2 (25%)	3 (9.4%)	
12.	Oxygen saturation at presentation	<90%	7 (87.5%)	11 (34.4%)	0.016
		90 – 95%	0	17 (53.1%)	
		>95%	1 (12.5%)	4 (12.5%)	
13.	History of the previous hospitalization	No	7 (87.5%)	19 (59.4%)	0.222
		Yes	1 (12.5%)	13 (40.6%)	
14.	PASS (Pediatric asthma severity score)	Mild (≤7)	0	0	0.165
		Moderate (8-11)	0	10 (31.2%)	
		Severe (≥12)	8 (100%)	22 (68.8%)	
15.	FEV/FVC after treatment	Deranged	3 (37.5%)	1 (3.1%)	0.015
		Normal	1 (12.5%)	8 (25%)	
		Could not be assessed (CNBE)	4 (50%)	23 (71.9%)	
16.	PEFR (Peak expiratory flow rate)	250 – 300	1 (12.5%)	7 (21.9%)	0.196
		300 – 350	1 (12.5%)	2 (6.2%)	
		>350	1 (12.5%)	0	
		Could not be assessed	5 (62.5%)	23 (71.9%)	
17.	Duration of hospital stay (in days)	<5	3 (37.5%)	4 (12.5%)	0.049
		5-10	3 (37.5%)	25 (78.1%)	
		11-20	1 (12.5%)	3 (9.4%)	
		>20	1 (12.5%)	0	

We also correlated asthma exacerbations in the preceding 4 weeks with the occurrence of hypomagnesemia but out of 8 cases, only 1 had an exacerbation in the preceding 4 weeks, which was not significant. The majority of the patients (72.5%) were not on any regular prophylaxis and hypomagnesmia had no association with non-adherence to controller medication. Even those who

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were using preventive inhaler therapy were erratic in their dosage and use. This was also reflected in the fact that 14 (35%) had a history of previous hospitalizations for acute asthma. On analysis of PFT results, the reduction of FEV1/FVC value was significantly associated with the occurrence of hypomagnesemia (p-value 0.01). This was also observed in a case-control study by Kilic et al [14] where it was inferred that hypomagnesemia was more common in patients with lower FEV1 values.

On analysis of demographic factors, the male-to-female ratio in our study was 1.8:1, signifying a male preponderance in asthma. This was in concurrence with the study conducted by Trivedi et al., where bronchial asthma was found to be more common in boys until puberty which they attributed to the smaller size of airways and increased reactivity in pre-pubertal males [15]. It was noted that out of 40 cases, 16 (40%) had a positive family history of asthma. Atopic dermatitis was seen in 5% of patients. Familial predisposition to bronchial asthma has been described in other studies from India as well such as the cross-sectional study, conducted by Ganesh et al. in urban Puducherry which concluded that the prevalence of bronchial asthma was significantly higher in those with a positive family history and in children who had a house member who smoked [16]. Detailed anthropometric assessment revealed that 17 out of 40 (47.5%) cases were overweight or obese. This was in concordance with the Brazilian study by Leticia et al. which found that obese asthmatics had poor levels of control and a higher presence of rhinitis, family history, and positive skin test findings [17]. Also, in a systematic review conducted by William et al., it was seen that reduction of weight and improvement of BMI was associated with better asthma outcomes and a better quality of life in both children and adult populations [18].

Studies on hypomagnesemia in children presenting with an acute attack of asthma are few and with contrasting interpretations. In studies conducted by Falkner et al [19] and Kakish et al [20] a relationship between magnesium levels and asthma severity could not be established, whereas not serum magnesium levels but intracellular magnesium levels were found to be lower in patients presenting with severe asthma in studies conducted by Zervas et al [21] and Sedighi et al [22].

Despite the study's limitation in terms of sample size, it was able to identify several significant associations between hypomagnesemia and various parameters related to asthma. An especially noteworthy finding was the correlation between hypomagnesemia and hypoxia, marked by low oxygen saturation (SpO2). This association, which is likely being reported for the first time in this study, holds significant implications for the treatment of various respiratory conditions including asthma. Further research is imperative to substantiate the importance of this association and its potential impact on the management of respiratory illnesses.

Limitations

The small sample size and limited correlation with PFT were the main shortcomings of our study. However, due to significant associations, we suggest a case-control study to compare magnesium levels between two groups of healthy children and children with bronchial asthma. This might help in proving the role of serum magnesium levels in acute asthma.

Conclusions

To conclude, hypomagnesemia was associated with, lower oxygen saturation at presentation, deranged pulmonary function tests, a longer duration of hospital stay, and increased requirement of mechanical ventilation. The results of our study, particularly the hypoxemia, are expected to stimulate researchers to delve deeper into the relevance of hypomagnesemia and its association with hypoxia in future investigations.

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Ethical Considerations

The study was conducted after obtaining institutional ethical clearance (No.-IEC/MAMC/82/10/2020/No.136).

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Conflict of interest

There is no conflict of interest.

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