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Hypomagnesemia in children with bronchial asthma

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Abstract

Introduction: Magnesium is the second most abundant intracellular cation and is involved in protein folding, intracellular signaling and enzyme catalysis. It has been shown that magnesium deficiency exacerbates airway hyperresponsiveness. Several studies had shown that magnesium level has no effect on asthma, but some have shown contributory effect. Considering these facts, we planned a study to estimate serum magnesium level in newly diagnosed asthmatics and in non-asthmatic children aged 5 to 11 years of age and to determine the relationship of serum magnesium level with severity of asthma lung function, frequency of asthma exacerbations

Methods: A case control study was conducted from January 2017 to June 2018 at IMCH, Govt. Medical college, Kozhikode. A total of 80 children aged 5 to 12 years newly diagnosed with bronchial asthma were included in the study. Age and sex matched non asthmatic children who attended outpatient unit were taken as controls. Venous samples were obtained from both cases and controls to do serum magnesium level. Serum magnesium level is compared with different variables of asthma. Normal serum magnesium level was taken as 1.6 to 2.3 mg/dl.GINA 2015 guidelines were used to assess the frequency and severity of asthma. Lung function was assessed by peak flo meter.

Results and discussion: Mean age was 6.89 (SD 1.445) years. equal number of males and females were there in the study. Normal serum magnesium level was found in 87.5% of cases, with a mean of 2 (SD 0.44) mg/dl. 12.5 % of cases had hypomagnesemia ranging from 0.9 to 1.6 mg/dl. In control group 6.3% had hypomagnesemia. Chi square value is 3.730 with p value of 0.155. relationship of hypomagnesemia with age, sex, weight, height, frequency of symptoms, severity of asthma, anemia, and lung function were evaluated. Significant relationship was found between magnesium level and frequency of symptoms (p value = .026), severity of asthma (p value = .024). No significant relation was found between magnesium level and age (p value = 0.959), gender (p value =0.176), lung function (p value = 0.144), weight (p value =0.091), height (p value =0.894) ,anemia (p value=0.116)

Conclusions: An association with hypomagnesemia and frequency of exacerbations and severity of asthma was found in children with hypomagnesemia. There

found to be no significant difference in serum magnesium levels between asthmatic and non asthmatic children. There is no statistically significant association with hypomagnesaemia and lung function in children with bronchial asthma.

Keywords: Asthma, Children, Serum Magnesium, Exacerbations, Kerala, India

Introduction

Bronchial asthma is a chronic inflammatory disease of the airways resulting in episodic airway obstruction. It affects about 1-18% of the population in different countries. It is one of the leading causes of childhood morbidity worldwide. Asthma is a heterogenous disease. It is defined by history of respiratory symptoms such as wheeze, shortness of breath chest tightness, cough that vary over time and intensity, together with variable expiratory airflow limitation. These variations are often triggered by factors such as exercise, allergen, or irritant exposure, change in weather or viral respiratory infections [1]

Magnesium is the fourth most abundant cation in the body and the second most common intracellular cation. Since magnesium intervenes calcium transport mechanism and intracellular phosphorylation reactions, it constitutes an important determinant of the contraction and relaxation of the bronchial smooth muscle.[2]

Hypomagnesemia has been suggested to be associated with increased incidence of wheeze, airway hyper reactivity and impairment of lung function. Mechanism of action of magnesium on respiratory airways is multiple and includes bronchodilation, anticholinergic effect and stabilization of mast cells. Magnesium plays a crucial role in the regulation of bronchial smooth muscles and hyper responsiveness [3]

Studies in adult patients have shown that low serum magnesium levels are associated with an increased risk of asthma attacks and subsequent hospitalizations compared to the risk in patients with normal magnesium levels. Studies in children have reported significantly lower magnesium levels in children with acute bronchial asthma than non-asthmatic children.[4]

High magnesium intake is associated with better lung function and less risk of bronchial hyperactivity and wheezing [5] In clinical trials, children with bronchial asthma were reported to have remarkable improvement in short term pulmonary function when given high doses of intravenous magnesium sulphate for moderate to severe asthmatic exacerbation. Nevertheless, meta-analyses and systemic reviews of intravenous magnesium sulphate for treating acute asthma have shown benefit in children with acute asthma[6]

In this setting we planned this case control study aiming to compare serum magnesium level in newly diagnosed asthmatics and non-asthmatic children aged 5 to 11 years of age and to determine the relationship of serum magnesium level with severity of asthma, frequency of exacerbations, and lung function.

Although there have been substantial studies on the relationship of blood magnesium level and bronchial asthma, there have been few studies in pediatric patients. In India there are not many studies assessing serum magnesium level in asthmatic and non-asthmatic children and to determine its relationship with severity of asthma. Present study done to evaluate the levels of serum magnesium in patients with bronchial asthma and the possible significance of hypomagnesemia in them.

Methodology

Study Design: Case Control Study

Study Setting: Department of Pediatrics, Institute of Maternal & Child Health, Government Medical College, Kozhikode.

Study Period: The study was conducted for a period of 1 ½ years from January 2017 to june 2018

Sampling Technique: Convenient sampling

Sample Size: Sample size was calculated by the formula

$N = (Z\alpha + Z\beta)\ 2\ (\ SD) \times 2\ /d^2$

$Z\alpha = 1.96$

$Z\beta = 0.84$

Standard deviation = 0.33

d= 0.15

The estimated sample size is 77 each in cases and control

Study Population: Cases

Inclusion Criteria

The children with newly diagnosed asthma aged 5 to 11 years admitted in wards or attending the asthma clinic of IMCH, Government Medical College, Kozhikode, Kerala, India

Exclusion Criteria

1. Children with asthma who are less than 5 years of age
2. Those who are known to be suffering from other comorbid conditions.
3. Those who are taking calcium antagonists, diuretics, digoxin, laxatives , vitamin D ,multivitamin drops.
4. Children already on treatment for asthma with preventers.

Control

Inclusion Criteria

Otherwise normal children who attended the casualty or outpatient department of IMCH, Government Medical College, Kozhikode

Exclusion Criteria

Children taking calcium, vitamin D, or multivitamins

Data Collection Methods and Tools

Children with asthma attending the asthma clinic at IMCH, Govt. Medical College, Kozhikode were included in this study.80 consecutive asthmatic children diagnosed clinically , were given detailed questionnaires regarding asthma. Baseline height weight and clinical examination were recorded. Cases attending the asthma clinic had a profile of investigations already done which included complete blood count, serum IgE levels and chest x ray. After ensuring that the children were not started on preventers, consent was obtained from parents and 1ml of venous blood is drawn for estimation of serum magnesium level.

Controls were selected only after all 80 cases were selected. Age and sex matched controls were taken. All the controls had attended either the emergency department or the pediatric outpatient department of government medical college Kozhikode. blood samples were drawn only when the child was being pricked for another purpose for eg investigations for the illness for which they were brought to the hospital, clotting time estimation for history of unknown bite. Consent was taken from the parents for the inclusion in the study.

Serum magnesium is measured by chemiluminescence method. Normal value is taken as 1.6 – 2.3 mg/dl

Lung function is measured by PEFR. The PEFR is determined using Wright's peak flow meter(Ferraris Medical Ltd,Edmonton,London,UK).The peak flow rate is measured with subject standing. The mouthpiece of the meter is placed in the subject's mouth, and lips are sealed around the mouthpiece. Take a deep breath. In one breath, blow out as hard and quickly as possible. PEFR measurements can be accurately performed by

most patients older than 5 years. Each subject is asked to perform the test three times, and the highest of the three reading is used as the recorded value of PEFR.Value is compared with normal values for height

EU flow meter			Length (cm)	Mini-Wright flow meter		
50%	75%	Predicted		Predicted	75%	50%
43	65	87	85	84	63	31
47	71	95	90	96	72	36
52	78	104	95	110	82	41
57	86	115	100	126	94	47
63	95	127	105	143	107	53
70	105	141	110	163	122	61
78	117	157	115	185	138	69
87	130	174	120	208	156	78
96	144	192	125	231	173	86
106	159	212	130	256	192	96
116	174	233	135	281	210	105
127	190	254	140	305	228	114
138	207	276	145	330	247	123
149	224	299	150	355	266	133
161	242	323	155	379	284	142
173	259	346	160	402	301	150

Values are shown for the European Union (EU) flow meter as well as the standard Mini-Wright flow meter. The predicted peak flow rates as well as the values that represent 75% and 50% of predicted are shown.

Figure 1: Peak Expiratory Flow Rates

Severity of asthma is assessed according to GINA guidelines

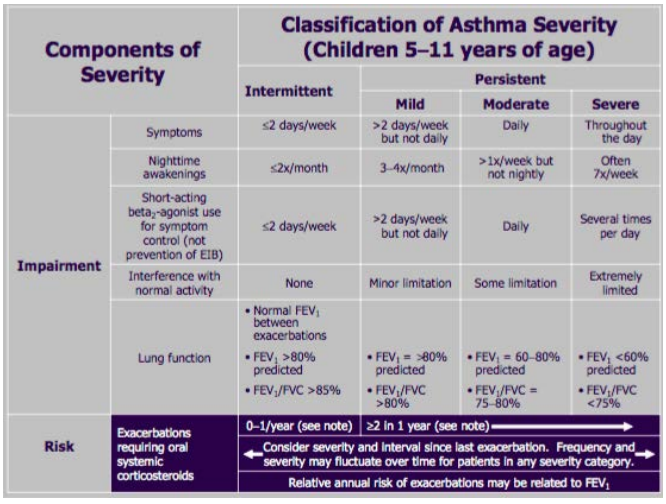

Figure 2: classification of asthma severity (GINA guidelines 2015)

Statistical Analysis

The collected data were entered in Microsoft Excel and analyzed using PASW Statistics software.

Analysis and Results

A total of 80 asthmatic children and 80 controls were entered into the study. There are 40 (50%) males and 40 (50%) females.

Table 1: Distribution of cases and controls according to sex

Sex	Case	Control	Total
Male	40 (50%)	40 (50%)	80 (50%)
Female	40 (50%)	40 (50%)	80 (50%)
Total	80 (100%)	80 (100%)	160 (100%)

Chi square value is 0.006 with p value of 0.936.

Mean age of population is 6.89 with SD of 1. 445. Details are as in figure.3

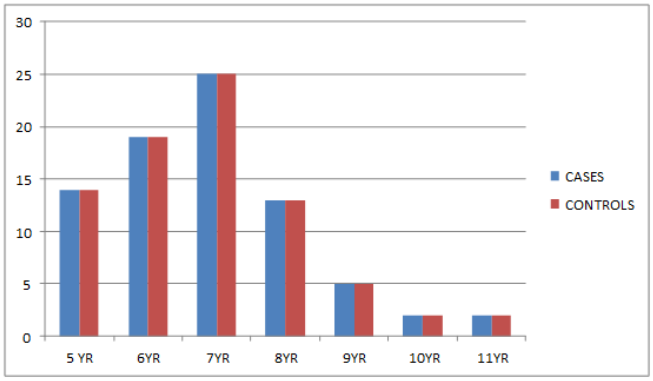

Figure 3: Age distribution of cases and controls.

Table 2: Frequency of night symptoms

Frequency of night symptoms	Case	Total
1	2 (2.5%)	2
2	11 (11%)	11
3	40 (50%)	40
4	27 (33.8%)	27
Total	80	80

1=Severe, 2 = Moderate, 3 = Mild, 4 = Intermittent. (GINA guidelines)

Out of 80 cases, 2 children had night symptoms in all days. Eleven children had more than 1 episode per week.40 children had less than 3-4 episode per

month.27 children had less than or equal to 2 episodes in 1 month

Table 3: Frequency of day symptoms

Frequency of day symptoms	Case	Total
1	4 (5%)	4
2	10 (12.5%)	10
3	40 (50%)	40
4	26 (26%)	26
Total	80	80

1=severe, 2=moderate, 3=mild, 4=intermittent

Table 4: Frequency of life threatening episodes

Life threatening episodes	Cases	Total
Present	5 (6.3%)	5
Absent	75 (93.8%)	75
Total	80	80

In 80 cases ,5 children had life threatening episodes.

Table 5: Distribution of severity of asthma

Severity of asthma	Cases	Total
Intermittent asthma	26(32.5%)	26
Mild persistent asthma	43 (53.8%)	43
Moderate persistent asthma	10 (12.5%)	10
Severe persistent asthma	1 (1.3%)	1
Total	80	80

In 80 cases, 23 children had intermittent asthma.43 children had mild persistent asthma.10 children had moderate persistent asthma.1 child had severe persistent asthma

Table 6: Distribution of cases according to PEFR

PEFR	Cases	Total
Low	47 (58.8%)	47
Normal	33 (41.3%)	33
Total	80	80

of 80 cases , 47 children had low PEFR than predicted.33 children had normal PEFR.

Table 7: Serum magnesium level in cases and controls

Serum magnesium	Case	Control	Total
< 1.6 mg/dl	10 (12.5%)	5 (6.3%)	15 (9.4%)
1.6 – 2.3 mg/dl	70 (87.5%)	73(91.3%)	143(89.4%)
>2.3 mg/dl	0	2 (2.5%)	2 (1.3%)
Total	80	80	160

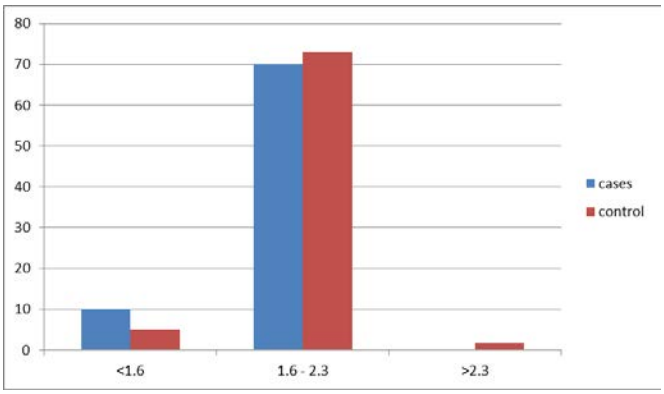

Figure 4: Serum magnesium level in cases and controls

In this study, serum magnesium value between 1.6 and 2.3 mg/dl was considered normal and any value below 1.6mg/dl was considered as hypomagnesemia. Using this cut off value, 10 cases were found to have hypomagnesemia. Their serum magnesium ranges from 0.9 to 1.6 mg/dl. Rest of cases 70 children had normal magnesium level. In control, 5 children were found to have hypomagnesemia. Their serum magnesium ranges from 1.2 to 1.6 mg/dl.

Chi square value is 3.730 with p value of 0.155. Serum magnesium levels in asthmatic children are not significantly different from those of a control group.

Table 8: Modified table of serum magnesium in cases and controls

Serum magnesium	Case – control		Total
	Case	Control	
Low	10 (12.5%)	5 (6.3%)	15 (9.4%)
Normal	70 (87.5%)	75 (93.8%)	145(90.6%)
Total	80	80	160

For obtaining odds ratio, table is modified by merging normal and high magnesium level to normal magnesium level.

Chi square value is 1.839 with p value 0.175. Odds ratio is 2.143 with 95% confidence interval ranging from 0.698 to 6.58

Out of 40 male children, 3 had hypomagnesemia. Out of 40 female children 7 had hypomagnesemia. Out of 10 hypomagnesemia children 7 are females and 3 are males. Even though number appears significant, there is no statistically significant relationship with hypomagnesemia and gender of children.

Table 9: Serum magnesium and frequency of symptoms

Frequency of symptoms	Hypomagnesemia (n = 10)	Normomagnesemia (n= 70)	P value
1	2(50%)	2	
2	0	10	.026
3	7(17%)	33	
4	1(3.8%)	25	

Hypomagnesemia is related to frequency of symptoms with p value <.05

Table 10 : Serum magnesium and severity of asthma

Severity of asthma	hypomagnesemia	Normomagnesemia	P value
Intermittent	1(3.8%)	25(96.2%)	
Mild persistent	7(16.3%)	36(83.7%)	
Moderate persistent	1(10%)	9(90%)	0.024
Severe persistent	1(100%)	0	

Severity of asthma shows significant relationship with hypomagnesemia

Table 11: Serum magnesium and PEFR

PEFR	Hypomagnesemia	Normomagnesemia	P value
Low	8 (17%)	39(83%)	.144
Normal	2 (6.1%)	31(93.9%)	

Out of 10 hypomagnesemia children ,8 children had low PEFR. But it is not statistically significant comparing to normal magnesium group.

Discussion

Magnesium is an intracellular cation. Serum magnesium level may appear normal in in spite of decreased body store. The estimation of magnesium level in red blood cells will be more correlating of body store. In this study serum magnesium is measured because test to estimate magnesium level in red blood cells is not available in our institution.

Hypomagnesemia is the most common under diagnosed electrolyte disturbance in medical practice. Its prevalence in hospitalized patients ranges from 4.6 to 47 %[7]. In a previous study by Rolla et al the prevalence of hypomagnesemia in asthma found to have 11%.[8]

It is not clear whether magnesium deficiency plays a role in asthma but magnesium sulphate has therapeutic role in asthma management.[9]

Fedoseev et al reported hypomagnesaemia in patients with bronchial asthma. But in our study serum magnesium levels in asthmatic children is not significantly different from those of control group[10]. Majority of the cases about 87.5% in this study were found to have normal magnesium level.10 % of cases have hypomagnesemia. The low prevalence of hypomagnesemia in our study is similar to other previous studies.[11] De valk et al reported no significant difference in magnesium level in asthamtics compared to control which is similar to this study.[12]

We studied in stable asthmatic patients. It is thought that redistribution of magnesium mainly takes place during acute exacerbation. hypomagnesemia may present during exacerbations.[13]

Another study by Dominguez et al showed hypomagnesemia in asthmatic patients[2]. Our low prevalence of hypomagnesemia may be due to our diet which consist of rice as staple food which is rich in magnesium. [14]

Magnesium status is usually determined by serum levels. Serum magnesium tend to reflect variations in intake but not total body stores. Many studies measured intracellular content of magnesium .Normal serum magnesium will not exclude hypomagnesaemia in cells.[15]

The age of population in this study is from 5 to 11 years. Most of the studies are in adult population. Serum magnesium level varies with age. The difference in age range of cases from varies studies may explain conflicting results.

Several studies have proved that hypomagnesemia in asthma is associated with increased incidence of wheeze, impairment of lung function and severity of asthma. In this study found to significant relationship of serum magnesium and severity of asthma with p value less than .05. O.S.B. Alamode et al reported that hypomagnesemia is related severity of asthma.[16]Emelyanov et al found a correlation between airway hyperreactivity and low magnesium level in asthmatics compared to normal subjects.[10]Das et al in their study proved hypomagnesemia in asthma is associated with severity of asthma with p value of .025[17]. These findings are similar to our study which has shown significant association with severe asthma.

In this study serum magnesium level is significantly associated with frequency of exacerbations. It may be due to increased bronchial hyperreactivity due to hypomagnesemia. Several mechanisms have been put forward like increased production of acetyl choline in cholinergic nerve endings[18],increased histamine release from mast cells. [19]

In this study hypomagnesemia is not related to lung function. Lung function measured only by PEFR. Sein et al done a study to determine relationship of intracellular magnesium level and lung function and asthma control in children with chronic bronchial asthma. It showed no significant difference in intracellular magnesium levels in uncontrolled and controlled asthmatic patients and no association with lung function.[20]

There has been no previous study done to see any relationship of hypomagnesemia with undernutrition, stunting, anemia in asthmatics. In this study these variables are studied. we found no statistically significant relationship between hypomagnesemia and undernutrition, stunting, anemia in children with asthma.

To conclude we found no evidence for the existence of decreased magnesium level in children with bronchial asthma.

Conclusion

1. In this study we found that there is no significant difference in serum magnesium levels between asthmatic and non asthmatic children.
2. In this study we found that in those children having hypomagnesemia, there is statistically significant association with hypomagnesemia and frequency of exacerbations and severity of asthma.
3. In this study there is no statistically significant association with hypomagnesemia and lung function in children with bronchial asthma.

Limitations

1. In this study serum magnesium was measured. Serum magnesium level will be normal even when total body store of magnesium is depleted. It is recommended to measure intracellular magnesium.
2. Small sample size
3. Dietic history not enquired. The children magnesium rich diet might have explained why there is no significant difference in the level of magnesium between cohorts.
4. For lung function PEFR alone was measured.

Suggestions

1. Further studies with large number of children are required
2. Intracellular magnesium is to be measured

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