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Association of gastroesophageal reflux disease in children with bronchial asthma

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ABSTRACT

BACKGROUND AND OBJECTIVES: Gastroesophageal reflux disease (GERD) and asthma are often linked, with GERD potentially triggering or worsening asthma symptoms. This study aimed to determine the association between gastroesophageal reflux disease and bronchial asthma in children.

METHODOLOGY: This case-control study was conducted at the Pediatric Medicine Department, Ibn-e-Siena Hospital, Multan, over a 6-month period. Children aged 3–12 years presenting to the pediatric outpatient department were consecutively enrolled. Cases were children diagnosed with bronchial asthma based on spirometry (FEV1/FVC <90% and FEV1 < 0% adjusted for age, gender, and height), while controls were children without respiratory symptoms and with normal spirometry. All participants underwent an upper gastrointestinal (GI) barium study, and gastroesophageal reflux disease (GERD) was diagnosed based on reflux esophagitis, hiatal hernia, or impaired gastric motility. Data were analyzed using SPSS version 23, and logistic regression was used to assess the association between GERD and asthma.

RESULTS: The study included 63 cases and 63 controls, with a mean age of 7.01 ± 2.1 years and equal gender distribution. GERD prevalence was higher in cases (78.1% vs. 21.9%, p < 0.001). Asthmatic children had significantly lower BMI (16.0 ± 0.9 vs. 16.6 ± 0.9, p = 0.001). Logistic regression revealed GERD as an independent risk factor for asthma (OR: 4.9, 95% CI: 1.9–12.8, p=0.001), while higher BMI had a protective effect (OR: 0.55, 95% CI: 0.4–0.8, p=0.006).

CONCLUSION: GERD is significantly associated with bronchial asthma in children, while higher BMI appears protective. Managing GERD may play a role in asthma management.

KEYWORDS: Asthma, Gastroesophageal reflux, Children, Body mass index.

INTRODUCTION

The passage of stomach particles into the esophagus, accompanied by clinical features and/or consequences that may be extra-esophageal or esophageal, is known as gastroesophageal reflux disease (GERD)[1]. Males are more likely than females to have GERD in children[2]. Because of the gastro-esophageal junction's immaturity, which diminishes during the first year of life, it may manifest physiologically even before that time[3]. Children who are obese and have neurological disorders, congenital heart diseases, gastrointestinal system abnormalities, and congenital diaphragmatic hernias are more likely to develop GERD[4]. Exclusive breastfeeding, however, is a preventive measure against GERD[5]. Asthma is the most extensively studied respiratory complication of GERD in children and it is primarily caused by vagal mechanisms, neurogenic inflammation, acid microaspiration, and increased bronchial responsiveness[6].

According to clinical research, up to 80% of children with asthma have GERD, although over half of them do not exhibit any symptoms[7]. There is evidence from numerous studies that GERD and asthma are interrelated[8]. A total of 90 controls (without bronchial asthma) and 45 cases (with bronchial asthma) were enrolled by Ricra R et al. GERD was significantly more common in cases (33.33%) than in controls (11.11%) (p = 0.002)[9]. Using a barium esophagogram, Mays EE et al. conducted a similar study in adults and found that 13 of 28 (46%) asthmatics reported reflux symptoms, compared with 23 of 468 (5%) normal control patients[10].

The objective of our study was to determine an association between GERD and bronchial asthma in children presenting at our local setting. The study results will provide local evidence for pediatricians working in our setup regarding any connection between the two conditions. If they are found to be significantly associated, in the future, all patients with

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chronic cough or asthma will be aggressively investigated for GERD. Timely treatment with proton pump inhibitors in such patients might also improve asthma symptoms. Identifying GERD in children with asthma will help in optimizing management strategies and reducing hospitalizations due to asthma exacerbations. We hypothesized that the prevalence of gastroesophageal reflux disease is higher in children with bronchial asthma than in healthy controls.

METHODOLOGY

This case-control study was conducted at the Department of Pediatric Medicine, Ibn-e-Siena Hospital, Multan, over a period of 6 months from 1st November 2023 to 30th April 2024 after approval from the institutional ethics review committee (ERC approval number: C-70-1021-01, dated: 15th October 2023). Children aged 3–12 years, male or female, presenting to the pediatric outpatient department were consecutively approached. Children diagnosed with bronchial asthma, i.e., FEV1/FVC ratio < 90% and FEV1 < 80% adjusted for age, gender, and height on spirometry, were taken as cases. Children without any respiratory symptoms and normal spirometry were taken as controls. All participants were selected after their parents provided informed consent. Children with developmental delays and congenital heart diseases were excluded from the study.

A minimum sample size of 126 children (63 cases and 63 controls) was calculated using the OpenEpi online software, based on a case-control study formula with a case frequency of 33.33% and a control frequency of 11.11%[9]. Power of the study 80% and the confidence level is 95%. Data was analyzed through SPSS version 23. Normality of numerical data was assessed through the Shapiro-Wilk test. Age, illness duration, and BMI are presented as means and standard deviations. Gender, family history of atopy and GERD (yes/no) are presented as frequency and percentages.

Baseline data, including age, gender, duration of illness (years), BMI (kg/m2), and family history of atopy (yes/no), were recorded. Body mass index was calculated using the formula: weight (kg)/height (m2). Weight was measured on a weighing scale, and height was measured on a stadiometer. All the children underwent an upper GI barium study from the radiology department as per hospital protocol. All the barium studies were reported by a consultant radiologist, and any one or more findings of (i) reflux esophagitis, (ii) hiatal hernia, (iii) impaired gastric motility were labelled as GERD positive. Children with GERD-positive were put on standard treatment.

The association between GERD and bronchial asthma is assessed using logistic regression. Univariate analysis was run for significant factors. Factors with a p-value ≤ 0.20 were entered into multivariable regression analysis. Independent factors associated with asthma were assessed at a < 0.05 significance level. For logistic regression, we used the Wald test to assess the significance of individual predictors and the Likelihood Ratio Test (LRT) to compare model fit at the multivariable level. Odds ratios with 95% confidence intervals are reported.

RESULTS

The mean age of the enrolled patients was 7.01 ± 2.1 years. There was equal representation of male (49.2%) and female (50.8%) children in the study. The mean BMI of the participants was 16.3 ± 0.9 kg/m2, and the duration of asthma in cases was 3.2 ± 1.6 years. Family history of atopy was positive in 46.8% (n=59) of participants, and gastroesophageal reflux disease was present in 25.4% (n=32). Children with asthma (cases) were significantly younger (6.6 ± 1.9 vs. 7.4 ± 2.2 years, p-value 0.02) than the children without asthma (controls). The mean BMI of cases was significantly less than that of the controls (16.0 ± 0.9 vs. 16.6 ± 0.9 kg/m2, p-value 0.001). The prevalence of GERD was significantly higher in cases than in controls (78.1% vs. 21.9%, p-value < 0.001) (Table-I).

Table-I: Characteristics of children with bronchial asthma and healthy controls (n=126).

Characteristics	Overall (n=126)	Cases (n=63)	Controls (n=63)	P-Value*
Age (years)	7.01 ± 2.1	6.6 ± 1.9	7.4 ± 2.2	0.020
Gender Male Female	 62 (49.2) 64 (50.8)	 29 (46.8) 34 (53.1)	 33 (53.2) 30 (46.9)	 0.476
BMI (kg/m2)	16.3 ± 0.9	16.0 ± 0.9	16.6 ± 0.9	0.001
Duration of Asthma (n=63)	3.2 ± 1.6	3.2 ± 1.6	-	---
Family h/o Atopy Yes No	 59 (46.8) 67 (53.2)	 29 (49.2) 34 (50.7)	 30 (50.8) 33 (49.3)	 0.858
Gastro-esophageal Reflux Disease Yes No	 32 (25.4) 94 (74.6)	 25 (78.1) 38 (40.4)	 7 (21.9) 56 (59.6)	 < 0.001

***Chi-square test for categorical comparison and t-test for numerical comparison.**

Table-II: Univariate analysis of Association of GERD with bronchial asthma in children (n=126).

Predictors*		B	SE	Wald	df	OR (95% CI)	P-value
GERD	Yes	1.6	0.47	12.1	1	5.3 (2.1 – 13.4)	< 0.001
Age Group	3 – 7 years	0.67	0.37	3.3	1	1.9 (0.9 – 4.0)	0.070
Gender	Female	0.25	0.36	0.51	1	1.3 (0.6 – 2.6)	0.476
BMI (kg/m2)		0.64	0.21	9.2	1	0.53 (0.4 – 0.8)	0.002
Family h/o atopy	Yes	0.06	0.36	0.03	1	0.9 (0.5 – 1.9)	0.858

GERD: gastroesophageal reflux disease * Reference category is 'No' for GERD and Family h/o atopy, '8-12 years' for age, and 'Male' for Gender.

Compared to children without asthma, asthmatic children had 5.3 (95% CI: 2.1 – 13.4, p-value < 0.001) odds of having gastroesophageal reflux disease, 1.9 (95% CI: 0.9 – 4.0, p-value 0.070) odds of younger age (3-7 years), 1.3 (95% CI: 0.6 – 2.6, p-value 0.476) odds of being male, BMI odds of 0.53 (95% CI: 0.35–0.80, p-value 0.002) and 0.9 (0.5 – 1.9, p-value 0.858) odds of positive family history of atopy (Table-II).

Multivariable analysis indicated two independent factors associated with bronchial asthma: gastroesophageal reflux disease (OR: 4.9, 95% CI: 1.9 – 12.8, p-value 0.001) and BMI ,having a protective effect on the development of bronchial asthma (OR 0.55, 95% CI: 0.4 – 0.8, p-value 0.006) (Table-III).

Table-III: Multivariate analysis of Association of GERD with bronchial asthma in children (n=126).

Factors		B	SE	Wald	df	OR (95% CI)	P-value
GERD	Yes	1.6	0.49	10.6	1	4.9 (1.9 – 12.8)	0.001
BMI (kg/m2)		-0.60	0.22	7.60	1	0.55 (0.4 – 0.8)	0.006

GERD: gastroesophageal reflux disease.

DISCUSSION

Our study showed that the prevalence of GERD was significantly higher in asthmatic children compared to healthy controls. Three hypothesized etiologies raised bronchial responsiveness, micro-aspirations of acidic stomach contents into the upper airways, and enhanced vagal tone can account for bronchoconstriction produced by acid reflux [11]. Other authors have proposed the "reflux theory," involved directly, and the "reflex theory," involved indirectly, as explanations for the association between gastroesophageal reflux and asthma [12,13].

A total of 1,612,361 patients across various age groups were included in 32 relevant investigations conducted in 14 countries, according to Mallah N et al. Overall, there was little correlation between GERD and asthma exacerbation (OR = 1.27; 95% CI 1.18–1.35). However, compared to adults, children with GERD had a greater chance of experiencing an asthma attack [14]. In a recent study, Lupu VV et al enrolled 56 children with asthma admitted to a local center of pediatric gastroenterology. They observed that 39 patients (69.64%) had GERD, determined on 24-hour continuous oesophageal PH monitoring. The presence of asthma increased the risk of GERD by 2.86 times [15]. These findings are comparable to our results.

Numerous factors, such as coughing and breathing difficulty, increased lung inflation, diaphragm contractions, and an increased pressure gradient across the lower esophageal sphincter (LES), have been documented to contribute to the aggravation of GERD in asthmatic individuals [16]. Various asthma drugs, such as corticosteroids, β-agonists, and theophylline, may exacerbate reflux [1].

From Italy, Cantarutti A et al reported that 1652/86,381 (1.9%) children were experiencing GERD in the first 12 months of life, of which 53% were treated with acid-suppressive medications. Compared with controls, children with GERD were at increased risk of clinical asthma (HR: 1.40, 95% CI 1.15–1.70) [17].

On the other hand, Tanner N et al. evaluated 127 children with severe asthma who underwent pH testing and bronchoscopy. When comparing individuals with and without acid reflux, there were no differences in asthma management or in measurements of airway inflammation or remodelling. They concluded that gastroesophageal reflux was not a significant comorbidity in children with severe asthma [18].

Ghaemi MR et al. conducted a cross-sectional study of patients aged 6 to 18 years with asthma. 25% of patients had reflux. Reflux and the severity of asthma did not significantly correlate (P=0.06) [19]. According to the study by Arul et al, this finding can be elaborated by the fact that GERD symptoms can occur without actual findings on endoscopy and that there is no correlation between the severity of these symptoms and endoscopic findings [20].

According to a systematic analysis by Thakkar K et al, asthmatic patients had a higher frequency of GERD (22.0%) than controls (4.8%) [21]. Likewise, another study conducted by Havemann B et al. revealed a statistically significant correlation between GERD and asthma characteristics, with a cumulative OR of 5.5 (95% CI: 1.9-15.8) [22].

Recent research on tissue biomarkers and esophageal functions in individuals with asthma and related GERD has shown that impairments in neuronal sensory perception and esophageal motility play a significant role in connecting the two conditions. Since both neutrophilic and eosinophilic type 2 inflammatory alterations have been reported, the characterisation of the underlying inflammatory substrate has produced contradictory findings [23].

Our study had some limitations. The study's external validity may have been impacted by its single-center design. Other factors, such as the use of bronchodilators for asthma in patients with GERD diagnoses whose usage has been demonstrated to raise the chances of developing asthma in GERD patients were not assessed [24]. Moreover, our study did not assess the relationship between asthma severity and a high prevalence of GERD or the effect of GERD treatment on asthma patients.

CONCLUSION

Our study concluded that GERD is strongly associated with bronchial asthma in the pediatric population. Management strategies should be focused on treating both clinical conditions simultaneously. Ongoing research is crucial to further elucidate the pathophysiological mechanisms underlying these associations and optimize treatment approaches.

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Seemab Saleem: Substantial contributions to the conception ,design and the acquisition of data for the work.
Saba Wamiq : Interpretation ,Drafting the work and reviewing it critically for important intellectual content.
Rabeea Saadat: Analysis and interpretation of data.
Saima Manzoor: Final approval of the version to be published.