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Association of Gastro-Esophageal Reflux Disease with Persistent Cough in Infants

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ABSTRACT

Gastroesophageal reflux disease (GERD) is widely recognized, alongside upper airway cough syndrome (also known as postnasal drip syndrome) and eosinophilic airway inflammation, as one of the predominant causes of chronic cough. Numerous global respiratory societies have published cough management guidelines that advocate for the assessment and treatment of GERD as a fundamental aspect of the diagnostic and therapeutic framework for addressing chronic cough. **Objectives:** To determine the association of gastroesophageal reflux disease with persistent cough in infants. **Methods:** This case-control study was conducted in the Department of Paediatric Medicine at The Children's Hospital and The Institute of Child Health, Lahore, from August 25, 2022, to February 25, 2023. This study was conducted on infants with complaints of persistent cough and healthy controls. These two groups underwent baseline assessment carried out by physicians and a diagnosis of GERD was made through a barium swallow test. The data were analyzed through SPSS version 25.0. Odds ratio (OR) was calculated to measure the association between persistent cough and GERD. **Results:** Among case patients, the mean age was 2.92±2.17 months, and 3.67±2.41 months among control patients. By comparing GERD between case and control groups, it was found that the percentage of GERD was 17.6% in case children and 5.9% control children. The difference was significant (p=0.033) and the risk ratio (OR=3.429). **Conclusions:** The presence of gastroesophageal reflux disease exhibited a notable correlation with the occurrence of chronic cough in the infant population.

INTRODUCTION

Gastroesophageal reflux involves the backward flow of stomach contents towards the esophagus, often leading to vomiting or regurgitation. This common occurrence, more noticeable after meals, can progress to GERD, causing discomfort and complications. For infants, regurgitation is a key symptom requiring effective management by caregivers and healthcare professionals. Understanding the transition from reflux to GERD is essential for developing effective treatment plans and relieving the condition's impact on individuals and families [1]. Infantile regurgitation, a common and typically harmless physiological process affecting about 70% to 85% of newborns in their first two months of life, tends to improve as infants grow [2]. Although persistent regurgitation beyond 90 days may lead to ongoing issues until around nine years old, it's important to note that in 95% of cases, gastroesophageal reflux resolves on its own by age one without major intervention. Concerning parents, most cases of infant regurgitation do not require aggressive treatment; instead, they often resolve as the child develops naturally [3, 4]. Gastroesophageal reflux (GER) and gastroesophageal reflux disease (GERD) can result in various symptoms and complications like weight loss, respiratory issues, and feeding difficulties. An anti-reflux barrier, formed by the crural diaphragm and lower esophageal sphincter (LES), is crucial in preventing gastric content from flowing back into the esophagus. The LES acts as a strong muscular barrier at the gastroesophageal junction, stopping reflux. This barrier, along with other elements, maintains the upper gastrointestinal tract's

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balance, preventing reflux-related disorders. Dysfunction in this system can lead to health complications [5]. The right crus of the diaphragm supports the lower esophageal sphincter(LES)to prevent gastroesophageal reflux. Failure in these mechanisms, compounded by delayed gastric emptying, can lead to reflux issues like GERD. Gastric emptying is affected by meal characteristics. Refluxate in the esophagus triggers clearance actions to prevent harmful effects. Primary and secondary peristalsis, along with the upper esophageal sphincter, aid in clearing refluxate. Understanding these processes is crucial for managing GERD and similar conditions effectively [6]. Following gastroesophageal reflux, primary peristalsis initiates movement through the esophagus in infants, while secondary peristalsis becomes dominant post-reflux to clear gastric acid, especially critical during sleep to prevent potential harm like apnea, mucosal damage, and bradycardia. Effective peristaltic activity is crucial to avoid adverse outcomes. Diagnosing infantile GERD involves a detailed medical history and physical examination since no single symptom or test definitively confirms the condition or predicts treatment response accurately [7, 8]. Studies in medical research and clinical observations of patients with a chronic cough show varying rates of gastroesophageal reflux disease prevalence, ranging from 5% to 41%. This indicates a significant difference in the frequency of this condition among individuals with persistent cough symptoms [9, 10]. GERD plays a significant role in chronic cough development, as supported by respiratory organizations emphasizing the importance of managing GERD for effective cough treatment. Studies using advanced monitoring methods confirm the link between cough episodes and reflux, strengthening the understanding of how GERD and cough interact. Integrated therapeutic approaches are crucial in clinical settings to address this relationship [11]. Diagnostic studies include endoscopy, barium studies, multi-channel intraluminal impedance and pH monitoring; the latter now being considered the most accurate method for evaluation of the association between cough and reflux [12,13].

Regrettably, there exists an exceedingly restricted amount of locally produced literature that pertains specifically to this particular topic of interest, which significantly hampers our understanding and analysis of the subject matter at hand.

This study aimed to provide valuable insights and contribute significantly to the field by examining and elucidating the intricate relationship that exists between gastroesophageal reflux disease (GERD) and persistent cough, thereby enhancing our overall comprehension of these interconnected medical issues.

METHODS

After taking approval from the hospital's Ethical Committee and written informed consent from parents, this case-control study was conducted in the Department of Paediatric Medicine, Children's Hospital, and The Institute of Child Health, Lahore, from August 25, 2022, to February 25, 2023, with CPSP Ref No. CPSP/REU/PED/2017-075-4516. A total of 136 infants were enrolled in this study after fulfilling the selection criteria (non-probability consecutive sampling). A sample size of 136(68 cases / 68 controls) was calculated by a 95% confidence level with 80% power of test and expected percentage of GERD as 22% in cases and 7% in controls. The sample size was calculated with the following formula.

$$n = \frac{\left[Z_{1-\alpha}\sqrt{2\bar{P}(1-\bar{P})} + Z_{1-\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)}\right]^2}{(P_1-P_2)^2}$$

The inclusion criteria were cases as infants of both genders exhibiting a persistent cough, per the operational definition and controls as infants of both genders who did not exhibit a persistent cough(after consent of guardian), while individuals presenting with any pre-existing diagnoses related to cough or abdominal discomfort, including but not limited to infections, asthma, or acute gastroenteritis and individuals with a documented history of abdominal surgical procedures and the guardian of the patient failing to provide consent were excluded from this study. The study included male and female infant cases with complaints of persistent cough and healthy controls. These two groups underwent baseline assessments carried out by physicians and a diagnosis of GERD was made through a barium swallow test that was interpreted by a radiologist. All data was recorded on a questionnaire. GERD was considered present if it was positive on the barium swallow test (when the contrast moves back in the esophagus). Persistent cough was defined as a cough that lasted more than 2 weeks. The data were subjected to analysis utilizing SPSS version 25.0. Qualitative variables, such as gender and results from the barium swallow examination, were represented in terms of frequencies and percentages, while the quantitative variable, namely age, was examined with its mean and standard deviations. The odds ratio (OR) was computed to evaluate the correlation between chronic cough and gastroesophageal reflux disease (GERD). An OR greater than 1 was deemed statistically significant. The data were stratified according to age and sex. Following stratification, the adjusted odds ratio (OR) was calculated, with an OR exceeding 1 considered significant, alongside a p-value of less than or equal to 0.05 being regarded as significant.

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RESULTS

A total of 136 patients (68 cases/68 controls) were included in this investigation and a comparison of gender distribution was observed. Among the case group, there were 37 (54.4%) male subjects and 31 (45.6%) female subjects, whereas within the control group, there were 35 (51.5%) male subjects and 33 (48.5%) female subjects (Table 1).

Table 1: Demographic Characteristics of Participants (n=106)

Gender	Cases	Controls	Total
Male	37 (54.4%)	35 (51.5%)	72 (52.9%)
Female	31 (45.6%)	33 (48.5%)	64 (47.1%)
Total	68 (100.0%)	68 (100.0%)	136 (100.0%)

In the case group, 45 (66.2%) of the subjects were categorized within the <6 months' age bracket, while 23 (33.8%) fell into the >6 months' category. In the control group, 43 (63.2%) were in the <6 months' age bracket, and 25 (36.8%) were in the >6 months' category. The mean age for the case group was 2.92±2.17 months, while for the control group, it was 3.67±2.41 months (Table 2).

Table 2: Comparison of Age Distribution Between Groups

Age Group	Cases	Controls	Total
<6 months	45 (66.2%)	43 (63.2%)	88 (64.7%)
>6 months	23 (33.8%)	25 (36.8%)	48 (35.3%)
Total	68 (100.0%)	68 (100.0%)	136 (100.0%)

It was determined that the incidence of GERD was 12 (17.6%) among the case group and 4 (5.9%) within the control group. This disparity was statistically significant (p=0.033), with an odds ratio of (OR=3.429) (Table 3).

Table 3: Association of GERD With Persistent Cough

GERD Status	Cases (n = 68)	Controls (n = 68)	Total (n = 136)	p-Value	Odds Ratio (OR)
Yes	12	4	16	0.033	3.429
No	56	64	120		
Total	68	68	136		

It was determined that the incidence of GERD was 4 (10.8%) in males and 8 (25.8%) in females among the case group. GERD incidence was 2 (5.7%) in males and 2 (15.6%) in females within the control group. This disparity was statistically insignificant (p=0.434), with an odds ratio of (OR=2.000) in males and was statistically significant (p=0.030), with an odds ratio of (OR=5.391) in females (Table 4).

Table 4: Association of GERD With Persistent Cough

Gender	GERD Status	Cases	Controls	Total	p-Value	Odds Ratio (OR)
Male	Yes	4	2	6	0.434	2.000
	No	33	33	66		
	Total	37	35	72		
Female	Yes	8	2	10	0.030	5.391
	No	23	31	54		
	Total	31	33	64		

It was determined that the incidence of GERD in the case group was 6 (13.3%) in the age group <6 months and 6 (26.08%) in the age group >6 months. Within the control group, GERD incidence was 3 (6.9%) in the age group <6 months and 1 (4%) in the age group >6 months. This disparity was statistically insignificant (p=0.325), with an odds ratio of (OR=2.051) in the age group <6 months and statistically significant (p=0.030), with an odds ratio of (OR=8.471) in the age group >6 months (Table 5).

Table 5: Association of GERD With Persistent Cough

Age Group	GERD	Cases	Controls	Total	p-Value	Odds Ratio (OR)
≤6 months	Yes	6	3	9	0.325	2.051
	No	39	40	79		
	Total	45	43	88		
>6 months	Yes	6	1	7	0.030	8.471
	No	17	24	41		
	Total	23	25	48		

DISCUSSION

Gastroesophageal reflux (GER) has been considered to be one of the factors of recurrent or persistent respiratory symptoms in every age group. Therefore, the common anti-reflux drugs are used in the treatment of many children with persistent cough, wheezing, or recurrent respiratory problems. Nevertheless, the connection is yet to be thoroughly studied because there is less opportunity to receive trustworthy research like endoscopy, barium investigations, and the more precise multi-channel intraluminal impedance in combination with pH monitoring [14]. Out of 136 patients included in this study, the case group had 54.4% males and 45.6% were females. The control group had 51.5% males and 48.5% females. Regarding the age distribution, 66.2% were <6 months of age in the case group, while 33.8% were >6 months of age. In the control group, 63.5% were <6 months of age, while 36.8% were >6 months of age. In our study, it was established that the prevalence of GER in the case group was 17.6% whereas the comparative analysis of the control group revealed a significantly lower prevalence rate of 5.9%. An Indian study by Jain *et al.* showed that 22% of kids with persistent coughing displayed GERD symptoms compared to only 7% in the control group. This highlights the need to consider GERD as a potential cause of pediatric respiratory problems [13]. Chang *et al.* studied factors causing persistent cough in infants and children with a history of cough lasting at least a month and normal chest X-rays. This study showed cough variant asthma as the main cause (32%), followed by sinusitis (23%) and GERD (15%). Therefore, identification of causes is crucial for

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guiding treatment and outcome [12]. Similarly, a Swiss study by Mallet MC *et al.*, revealed that asthma and asthma-like conditions were diagnosed in 132(36%) of 363 children, while upper respiratory cough syndrome in 48(13%) and GERD in 23(6%). It highlighted again that chronic cough is closely related to GERD [15]. Chen X had concluded that out of 85 children investigated for chronic cough 3(3.5%) had GERD [16]. A large pediatric study by Gan Y *et al.*, showed that 30% of children with chronic cough had acid reflux, and many others showed weakly acidic events [17]. A 2023 review in the Brazilian Journal of Otorhinolaryngology underscored non-acid reflux (detected by impedance pH monitoring) as a frequent contributor to cough in children [18]. In scenarios where gastric contents are neutralized after eating, reflux events with non-acidic pH may go undetected. By combining impedance with pH monitoring, reflux events can be categorized based on pH levels for a better understanding [19]. Its recent upsurge has therefore led to the finding of non-acid reflux, and thus the exhaustion experienced by the doctors when they find that acid suppression will go nowhere in yanking airway reflux [20]. In Pakistan, no large-scale cohorts linking infant GER with cough exist, and they often don't isolate cough outcomes, while international data show that cough is a common symptom of GER. Also, there is limited specific data using advanced diagnostic methods like 24-hour impedance pH monitoring in infants. Most local studies rely on basic imaging like barium swallow (in our case, due to limitations of resources) or symptom questionnaires, so Pakistan would benefit if large-scale cohort or case-control studies were carried out.

CONCLUSIONS

Gastroesophageal reflux disease exhibited a noteworthy and statistically significant correlation with the occurrence of persistent cough in the population of infants studied, suggesting a potential underlying pathophysiological relationship that warrants further investigation into the mechanisms by which this gastrointestinal disorder may contribute to respiratory symptoms in this vulnerable age group.

Authors Contribution

Conceptualization: SA,
Methodology: SJA, BZ
Formal analysis: AML, SJA, SJ,
Writing review and editing: SA, AML

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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