Gastroesophageal Reflux and Respiratory Diseases in Children

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74.1 Introduction

Gastroesophageal reflux (GER) is the backflow of gastric contents towards the esophagus, and this may be accompanied by regurgitation/vomiting. GER can be seen in children of all ages without any diseases [1]. In the pediatric age group, GER is most common in infancy, especially between 1 and 4 months. GER, which is a physiological entity in newborns and infants, gradually decreases in the first year of life [2].

GER has been associated with a variety of respiratory symptoms and disorders in the pediatric age group. When GER causes troublesome symptoms and complications, it is referred to as gastroesophageal reflux disease (GERD). The main classical symptoms of pathologic pediatric GER (GERD) are vomiting, retching, dysphagia, wheezing, choking attacks, and a delay in growth [3]. In routine clinical practice, antireflux measures/treatments to prevent delayed recovery and mucosal edema that may be caused by GER/GERD before and after airway surgeries is almost a general rule practiced by clinicians [4, 5].

GERD-related symptoms can be gastrointestinal, neurobehavioral, and respiratory origin. It has been suggested that GERD is associated with common symptoms such as heartburn and chest pain in the pediatric age group, as well as respiratory problems such as cough, stridor, wheezing, and pneumonia [4]. It is seen that the scientific evidence on the relationship between respiratory diseases and GERD has intensified in the last 30 years [3]. In a study conducted by Junqueira and Penna, the results of nasopharyngeal pH measurement in children with chronic respiratory

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problems had lowered (acidic) compared to the children in the control group. However, no data/theory has been provided on the pathophysiological mechanism that may be the cause of this finding [6].

It is also seen that clinicians' search for solutions to airway problems that may be associated with GERD is reflected more frequently in their daily practice. One study found that GERD diagnoses in infants increased more than threefold between 2000 and 2005 [2]. To reduce airway problems that may be associated with gastric acid content, clinicians are increasingly prescribing acid suppressant drugs such as proton pump inhibitors (PPIs), and PPIs are among the most prescribed drug classes today [4, 7].

Various theories have been proposed regarding the relationship between GER and the development of airway problems [3, 4]. First, in 1892, Osler suggested that these two entities may interact. Accordingly, GER may play a role in the development of a reactive airway disease, as well as reactive airway diseases such as asthma and the antiasthmatic drugs may cause GER to exacerbate [8]. Another proposed mechanism in the development of gastroesophageal reflux-mediated airway problems is the microaspiration of the gastric contents that are refluxed into the mouth and are then aspirated into the lower airway tract. This can cause irritation, inflammation, and spasms in the affected airway part. However it is very challenging to prove the aspiration that occurs in this way [9, 10]. Rosen et al. studied bacterial microflora of gastric, bronchoalveolar lavage, and oropharyngeal fluids in 116 children aged 1 to 18. In this study, it was reported that the bacterial composition of the gastric and lung fluid was much more alike than the oropharyngeal flora. These results support the idea that full column GER can alter the bacterial microflora of the lungs. This result also suggested that there was direct communication between the stomach and the lower respiratory tract, independent of the oropharynx. This study is important because it supports reflux as a valid mechanism for the development of lung disease in GERD patients. Considering these data, it suggests that a patient's lung bacterial profile may serve as a future biomarker of reflux-associated lung disease [11].

The laryngotracheoalveolar system develops by dissociating from the embryogenic origin common with the gastrointestinal tract. Not only do these two systems (aerodigestive systems) intersect luminal anatomy, but neurons, receptors, and reflexes are also interconnected [12]. It is highly possible that these interconnections are involved in irritative bronchospasm associated with GER. GER may play an important inflammatory cofactor role during the development of airway disorders [13]. Another proposed mechanism that derives from this knowledge postulated that activation of proximal airway receptors in children by gastroesophageal reflux-related materials such as acid and pepsin can increase airway resistance and may lead to the development of reactive airway disease [14].

Considering all these proposed mechanisms, GER/GERD can theoretically cause airway obstruction in the following four main ways and so trigger or exacerbate the development of different airway diseases:

1. Mucus oversecretion as a result of inflammation and/or reflexive stimulation.

2. Intraluminal mucosal edema caused by chemical/inflammatory mediators or stimulation of neural pathways.
3. Direct obstruction by aspirated refluxate material.
4. Bronchospasm as a result of peribronchial muscle spasm caused by local irritation and/or reflex pathways.

It should also be kept in mind that airway diseases themselves can increase GER through similar ways and interactions and cause GERD development. Therefore, treatment success can be increased by considering both airway disease and reflux when necessary [13–19].

74.2 GER Evaluation in Children with Respiratory Disorders

The most child-friendly and simplest method in evaluating GER is questionnaires. However, there is no validated and reliable questionnaire that is universally used in the evaluation of pediatric GER [20, 21]. In addition, as we learn from studies in adults, the correlation between GER/GERD questionnaires and investigations such as endoscopy and pH monitoring is quite weak [22].

Physical examination and flexible endoscopic examination, which are frequently used in otolaryngology practice, are of very limited value in detecting GER in the pediatric age group [23]. No classical physical examination findings specific to gastroesophageal reflux have been identified in the pediatric population. Posterior glottic erythema, posterior glottic edema, laryngomalacia, and subglottic stenosis have been reported as the most common flexible endoscopic examination findings in pediatric patients with GERD [20, 24, 25].

The barium swallow test can be used in the evaluation of accompanying swallowing disorder, aspiration, and anatomical structural problems, but its usefulness in detecting GERD is very limited [26]. Ultrasound is advantageous in that it is noninvasive, but it has limitations in terms of experience and subjective aspects of the performer. It is not useful in detecting GERD, except to show structural problems. Scintigraphy may be useful in detecting pulmonary aspiration, but its use in daily routine practice for this purpose is rare [27]. Upper gastrointestinal endoscopy has the advantages of direct examination of the esophageal lumen, detecting hernia and performing biopsy when necessary but is inadequate in detecting GER. Endoscopy and biopsy are the gold standard in the diagnosis of eosinophilic esophagitis, which is an important diagnostic dilemma for the pediatric age group [28]. Manometry is valuable in detecting mechanisms that may be the underlying cause of GER, not GER itself [29]. The two most valuable contemporary investigations used in the diagnosis of GERD are esophageal pH monitorization test (pHmetry), which can detect acidic liquid reflux, and impedance tests that can detect both liquid and gas acidic/nonacidic reflux. [27] The pHmetry with double-electrode probe has been the most commonly used test evaluating of otolaryngologic/respiratory manifestations of GER [30]. However, impedance is the method of choice in evaluating the response of children receiving antacid therapy and respiratory tract problems that may be

associated with persistent non-acid reflux. Therefore, impedance is currently the recommended clinical test tool for use in research [31]. Although impedance is a valuable test in detecting reflux episodes and their types, its routine application and advantages in evaluating airway problems with GERD in children are controversial because of the heterogeneity of the studies, technical differences, diversity in the parameters evaluated, and the insufficiency of normative data [32]. Studies which have more common and homogeneous inclusion criteria, analyzed parameters, baseline, and prospective symptom features are needed to draw precise and clinically useful conclusions.

The results of the Bilitec test, which can detect esophageal reflux of bile content, are still insufficient [33]. Investigations analyzing samples taken from airway secretions can also be used in the diagnosis of reflux-related airway disorders. The sensitivity and specificity of detecting fat-laden macrophages or their index is quite low [34]. Instead, it has been reported that pepsin screening has higher sensitivity and specificity in bronchial secretion samples. It has been reported that acid detection in oropharyngeal secretions, which are cheaper, easier, and less invasive than these aforementioned tests, may be useful in detecting acid reflux in infants [32].

It has been suggested that a genetic variant may be effective in the development of GERD, especially in its severe or chronic forms. Hu et al. investigated inheritance pattern of patients with GERD and mapped the genetic locus for severe pediatric GERD to identify a gene for GERD. Their study reported that the severe pediatric GERD gene matches chromosome 13q14. Such studies may provide new diagnostic and treatment strategies for GERD in the future [35].

74.3 GERD and Respiratory Symptoms/Disorders

The relationship between GERD and respiratory problems and diseases has been an interesting area of research in recent decades. It has been suggested that GERD may be an important cause of the symptoms in a substantial proportion of children with persistent respiratory problems. There have been increased awareness of GERD as a cause of pediatric respiratory problems and data in the literature showing an increased incidence of GERD in children with a certain type of respiratory tract disorders [36, 37]. GERD could be a causative etiologic factor in reactive airway diseases, recurrent croup, chronic bronchitis, apnea, chronic cough, and subglottic stenosis [38]. However, there are limitations to the documentation and evidence for this relationship in the pediatric age group. One of the most important issue in reflux-related airway pathologies is the inadequacy of normative data belonging to different age, gender, and ethnic groups [7, 32]. Radiological tests, which are less invasive in the evaluation of pediatric GER, are generally performed in the postprandial period, but have limited value in the diagnosis of GERD due to the high prevalence of GER in the postprandial period [4, 27].

In their study Wenzl et al. suggested that there is a strong relationship between GER and respiratory symptoms [39]. However, it has been stated that there is a strong correlation between respiratory problems and reflux occurring in nonacidic

type rather than acidic and impedancemetry test should be performed to determine this. The cutoff values for impedancemetry test have not yet been determined to distinguish normal children from GERD patients [4, 40]. Rosen et al. evaluated reflux using multi-canal intraluminal impedance in 28 children with chronic respiratory disease with a mean age of 6.5 years. In their study, they found a stronger correlation between chronic airway symptoms and non-acid reflux episodes compared to acid reflux episodes. They concluded that chronic respiratory manifestations such as coughing and wheezing are correlated with GERD in their pediatric patients group. They also reported that the closer the gastric reflux content to the proximal levels of the esophagus, the more respiratory symptoms increased [11].

Jein et al. evaluated children with persistent and/or recurrent respiratory problems between 3 months and 3 years with a median age of 14 months for GER by performing upper gastrointestinal endoscopy, biopsy, gastroesophageal scintigraphy, and 24 h esophageal pH monitoring tests. The results of this study suggest that GER may be a possible causal contributing factor in children with recurrent and persistent respiratory problems [41].

Yellon et al. reported significant relationship between presence of histologic esophagitis and chronic cough in children suspicious for GER-related symptoms [28]. In addition, during the cough associated with airway disease and GERD, the intra-abdominal pressure increases and this triggers GER and thus a vicious circle may occur. It was found that the thoracoabdominal expiratory pressure level increased in rats with partial airway obstruction [42].

GERD is considered to be a contributing factor for croup, but this relationship has not been clearly established yet. Waki et al. performed scintiscan, barium swallow, esophagoscopy, and pHmetry tests on 32 children with recurrent croup and reported that they detected GERD in 15 children (47%). In another study in which pharyngeal and esophageal pH monitoring was used simultaneously, Contencin and Narcy reported that GERD was detected in all eight children with recurrent croup [43, 44].

GERD can cause stridor, which has been called pseudolaryngomalacia by some authors because of similar symptoms [45]. Intermittent stridor occurring only during GER attacks has been demonstrated by intraesophageal pH measurements in infants [46]. Reflux associated with GER in young children may not be directly related to airway involvement but may also be associated with agitation caused by pain caused by acidic reflux [47].

Pediatric subglottic stenosis may develop as a result of many different reasons such as infection, trauma, congenital, autoimmune diseases, and sometimes a cause may not be documented [48]. GERD is one of the factors included in this etiological spectrum. However, the evidence on this subject has mostly derived from experimental animal studies. In a study conducted in canines, subglottic stenosis created experimentally significantly aggravated after gastric content application [49]. Gaynor reported ulceration and necrosis in histopathological evaluation after exposing rabbit tracheas to synthetic gastric content for periods of 1–4 h [50]. In another canine study, Koufman reported that when pepsin with acid was applied to the area of subglottic mucosal trauma, recovery was better than the group applied saline with

acid [5]. In an experimental pig model study, Yellon et al. evaluated the effects of short-term contact of gastric content with healthy subglottic mucosa by reverse transcriptase polymerase chain reaction and histologically. The direct effects of this interaction on intact subglottic mucosa were ulceration, basal epithelial hyperplasia, and downregulation of epidermal growth factor receptor messenger RNA production [51]. Based on limited information, no benefit has been reported in performing diagnostic GERD tests or administering GERD therapy in subglottic stenosis surgery. However, many surgeons use GERD treatment very aggressively during the management of subglottic stenosis [4, 7, 13].

Studies of GERD as a factor that triggers or aggravates pediatric asthma have increased over the past decades. In experimental studies, it has been shown that bronchial spasm increases with increasing intraesophageal pH level by a vagal pathway [1–4]. In some epidemiological studies, the prevalence of GERD in pediatric asthma patients has been reported to be at least 50% [3, 7, 8]. GERD is more common in pediatric patients with asthma with nocturnal exacerbations and more severe asthma. It has been reported that severity of asthma symptoms decreases after pharmacotherapeutic treatment. Patients in the pediatric age group with a higher chance of responding to antireflux therapy are those with classic reflux symptoms such as heartburn and regurgitation, and those with nocturnal and non-allergic asthma [3, 8]. Particular attention should be given to nocturnal control of reflux in children with asthma who are scheduled for antireflux therapy. Children with severe asthma or symptoms that are difficult to control may require steroid use. It should not be forgotten that reflux will worsen asthma in this patient group. Conservative and medical measures should be initiated before steroid therapy in these patients [8, 10].

Further prospective clinical studies are needed to establish a definite cause-and-effect relationship between GERD and these respiratory symptoms/disorders and to determine how effective antireflux treatment methods are in controlling such respiratory problems.

74.4 GERD and Apnea

Although the exact mechanism of GERD-induced apnea is not known, some theories have been proposed. One possible mechanism is that gastric content reaching the respiratory tract (glottis, subglottis, tracheobronchial system) causes laryngospasm. The other is reflex-mediated neural mechanisms, which were mentioned earlier in this section [36, 39]. With the use of intraesophageal pH probe technology, clinicians have had the opportunity to show that there may be an association between cyanotic apnea episodes and GER (acid reflux type) in infants. In a study evaluating 1400 babies with apneic episodes, Kahn et al. reported that they detected excessive acid reflux in about half of the babies [52]. Afterward, different studies were carried out using pH probe and polysomnography to support the temporal relationship between apnea or hypoxemia and reflux. However, on the other hand, it is seen that studies showing the opposite of these findings and rejecting the mentioned significant relationship between reflux and apnea are presented to the

literature [53]. These types of studies have various technical difficulties and handicaps. In addition, apnea occurs as a result of infants' response to a number of different neurosensory stimuli. Although it is thought that reflux is a possible stimulus in the formation of apnea, it is very difficult to prove the exact mechanism. Data from some experimental studies have reported that an increase in intraesophageal acidity may cause apnea in some susceptible subjects [54, 55]. In different studies focusing on reflux as the cause of infantile apnea, there are studies reporting the results of conservative approaches, medical treatment, and fundoplication as reflux treatment. Considering that infantile apnea resolves spontaneously in many cases, it is necessary to be very careful when choosing such modalities. Nevertheless, it is necessary not to avoid performing antireflux therapy to some infants with apnea episodes [56]. The history taken from the family/caregiver is very important in making this decision. The main features of apnea that may be associated with GERD and increase the chance of benefiting from antireflux therapy occur when the baby is awake, in the supine position, and about the first hour after feeding. In addition, the presence of tension in the baby's body, bending, redness and bruising, respiratory effort, and nutrient presence in the mouth and/or nose in the history of the baby should be especially questioned [53–56]. In apnea, which may be associated with GER, it is very difficult to decide which babies need further tests, which babies can be followed up at home, and which babies should be given antireflux therapy. Proper positioning, increasing the consistency of the food, and reducing the volume given during feeding should primarily be the preferred methods and are often effective and sufficient [56–58].

74.5 Treatment of GER-Related Respiratory Symptoms/ Disorders

There are studies reporting that respiratory symptoms associated with GER can be significantly improved with antireflux therapy [59]. Jein et al. reported that in most of the children with persistent respiratory complaints, they found significant improvement after 3–6 months after antireflux treatment (frequent and low volume feeding with viscous foods, upright positioning, prokinetic and H2 blocker drugs) [3, 4]. However, it has been stated that this treatment may change the bacterial content of the gastrointestinal and respiratory systems' microbial environment. Therefore, antireflux medications (especially PPIs) used to reduce respiratory symptoms can worsen the problem. It has been reported that prolonged gastric acid suppression in adults may cause impaired nutrient absorption and pneumonia. It can be thought that suppression of gastric content, which also has antibacterial properties, may cause similar problems in children [2, 7, 10]. Rosen et al. in their study found that the gastric contents of children under acid suppression had higher concentrations of acid-sensitive bacteria, which may play a role in some upper airway infections and pneumonia, compared to children not under acid suppression. Gastric acid suppression drugs alter the gastric bacterial profile which can also affect the airway microbiome via high level GER. [11]

74.6 Conclusion

The complexity of interactions between the upper gastrointestinal tract and the airway still contains many unknowns to be explained. Although it is considered as a high probability that GER/GERD is associated with airway symptoms and disorders in pediatric patients in clinical practice, the scientific evidence of this relationship is not strong enough yet. Knowledge on the current literature consists largely of the results of studies with significant methodological deficiencies such as insufficient diagnostic workup for GER, biased patients selection/population, and limited statistical analysis. Studies to understand and elucidate these problems will allow children with morbidity due to respiratory diseases to be managed optimally. Understanding and preventing airway problems caused by GER/GERD means capturing one of the pieces to the advantage of winning this challenging game of chess.

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