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Extraesophageal Associations of Gastroesophageal Reflux Disease in Children Without Neurologic Defects

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Background & Aims: The potential association between gastroesophageal reflux disease (GERD) and extraesophageal manifestations remains unknown in children without neurological defects. We conducted a large case-control study to examine the association between GERD and several upper and lower respiratory disorders in these children. **Methods:** We identified all patients between 2 and 18 years of age with GERD who were seen at Texas Children's Hospital between 1996 and 2000. Patients seen during the same time period without GERD were randomly selected as controls (4:1 ratio). Patients with mental retardation, cerebral palsy, or congenital esophageal anomalies were excluded. We compared the presence of several predefined upper and lower respiratory disorders in cases and controls. **Results:** We identified 1980 patients with GERD and 7920 controls without GERD. Cases and controls were without neurological deficits or congenital esophageal anomalies. Cases were older than controls (9.2 years ± 4.6 vs. 8.6 ± 4.9, $P < 0.0001$), and were more likely to be female (51.2% vs. 47.2%, $P = 0.0028$) and white (60.2% vs. 41.2%, $P < 0.0001$). Compared with controls in univariate analyses, cases with GERD had more sinusitis (4.2% vs. 1.4%, $P < 0.0001$), laryngitis (0.7% vs. 0.2%), asthma (13.2% vs. 6.8%, $P < 0.0001$), pneumonia (6.3% vs. 2.3%, $P < 0.0001$), and bronchiectasis (1.0% vs. 0.1%, $P < 0.0001$). However, otitis media was less common in cases than controls (2.1% vs. 4.6%, $P < 0.0001$). After adjusting for differences in age, gender, and ethnicity in the regression analyses, GERD remained a significant risk factor for sinusitis (adjusted odds ratio [OR], 2.3; 95% confidence intervals [CI], 1.7–3.2; $P < 0.0001$), laryngitis (OR, 2.6; CI, 1.2–5.6; $P = 0.0228$), asthma (OR, 1.9; CI, 1.6–2.3; $P < 0.0001$), pneumonia (OR, 2.3; CI, 1.8–2.9; $P < 0.0001$), and bronchiectasis (OR, 2.3; CI, 1.1–4.6; $P = 0.0193$). **Conclusions:** GERD in children without neurological defects is associated with a several-fold increase in the risk of sinusitis, laryngitis, asthma, pneumonia, and bronchiectasis. Further studies are needed to examine whether a cause-effect relationship exists between GERD and these disorders in children.

Gastroesophageal reflux disease (GERD) is a common condition that affects an estimated 10% of the U.S. adult population.[1,2] The manifestations of GERD range in severity from symptoms (e.g., heartburn, regurgitation) without gross damage to the esophagus to complicated GERD characterized by erosive esophagitis, esophageal strictures, and Barrett esophagus (BE).[3,4] In addition, GERD in adults has been associated with several extraesophageal manifestations, including pharyngitis, laryngitis, asthma, pulmonary fibrosis, and pulmonary aspiration syndromes such as bronchiectasis, lung abscesses, and recurrent pneumonia.[5,6]

Gastroesophageal reflux is often present in infants, although it is usually normal or "physiologic," spontaneously resolving by the second year of life.[7,8] Gastroesophageal reflux occurring in children older than 1.5–2 years is considered pathologic, or GERD.[9,10] Severe GERD during childhood has a few well-known risk factors: (1) neurologic disorders, such as spastic quadriplegia or cerebral palsy[11,12]; and (2) congenital malformation, such as esophageal atresia and tracheoesophageal fistula.[13,14] However, most children with GERD do not have these risk factors.

The clinical significance of the extraesophageal manifestations of GERD in children without neurologic defects remains unclear. Several investigators have estimated the prevalence of GERD in patients with sinusitis,[15] laryngitis,[16,17] or asthma.[18–22] These studies have derived their estimates from relatively small samples of children seen at referral centers. Most of these studies did not contain control populations for comparison. Moreover, they mostly studied the prevalence of

Abbreviations used in this paper: BE, Barrett esophagus; 95% CI, 95% confidence interval; CPT, Current Physician's Terminology; GERD, gastroesophageal reflux disease; ICD-9 CM, International Classification of Disease, Clinical Modification, ninth edition; OR, odds ratio; TCH, Texas Children's Hospital.

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GERD in children with 1 potential extraesophageal manifestation rather than analyzing the relationship between GERD and a spectrum of disorders. Finally, many of the children in these studies had 1 or more of the risk factors for severe GERD outlined above. As a result, there is a wide variation in the published estimates of GERD prevalence among patients with potential extraesophageal manifestations of GERD. Moreover, the prevalence of these disorders in children without neurologic defects or congenital esophageal anomalies remains unknown.

We used the computerized database at Texas Children's Hospital (TCH), one of the largest pediatric facilities in the United States, to conduct a case–control study to address this issue. We examined the association between GERD and several predefined potential extraesophageal manifestations of GERD in a large cohort of children without neurologic defects or esophageal congenital abnormalities.

Materials and Methods

Data Sources

TCH is the largest children's hospital in the United States. We used the administrative database at TCH, which contains medical diagnoses obtained at all inpatient and outpatient encounters; these diagnoses are coded according to the 9th revision of the International Classification of Disease, Clinical Modification (ICD-9 CM),[23] and the Current Physician's Terminology (CPT) codes.[24]

Study Population

Cases. We identified all patients at TCH with GERD (ICD-9 CM codes 530.81, 530.10, 530.11, 530.19, and 530.3) between October 1996 and October 2000. Only patients older than 2 years were included in the study. We excluded patients with cerebral palsy (ICD-9 CM codes 343.0 to 343.9, 344.0–344.9, and 348.0–348.9), mental retardation (ICD-9 CM codes 317.00–379.00), tracheoesophageal congenital anomalies (ICD-9 CM codes 530.84, 751.1, 750.5, and 750.7), or congenital esophageal stenosis (ICD-9 CM code 750.3).[19,20] For patients with multiple entries in the database, only the first was counted.

Controls. The same computerized data source (administrative database at TCH) that was used to identify cases was used to select controls. We applied the same exclusion criteria as those with cases; we excluded all patients with mental retardation, cerebral palsy, tracheoesophageal congenital anomalies, or congenital esophageal stenosis. From the remaining patients older than 2 years, 4 controls without GERD were randomly assigned for each case with GERD. The RANUNI procedure of SAS was used for random selection without replacement. Because disease-coding practices may change over time, cases and controls were matched on the year of first entry into the database.

Collected Information

For subjects (cases and controls) who satisfied the inclusion and exclusion criteria outlined above, we examined all medical diagnoses and medical and surgical procedures documented between 1996 and 2000. The presence of the following conditions was specifically sought: (A) potential risk factors: cystic fibrosis (ICD-9 CM codes 277, 277.00; cystic fibrosis that results in chronic pulmonary disease with increased intrathoracic pressure has been implicated as a cause of GERD[26]), scleroderma (ICD-9 CM code 710.1), and morbid obesity (ICD-9 CM codes 278, 278.00, 278.01); (B) upper respiratory disorders: sinusitis (ICD-9 CM codes 461.9, 473, 473.0, 473.2, 473.8, 473.9), laryngitis (ICD-9 CM codes 212.1, 464.0, 478.5), and otitis media (ICD-9 CM codes 381.00, 381.01, 381.10, 381.3, 381.4, 382.4, 382.9); (C) lower respiratory disorders: asthma (ICD-9 CM codes 493, 493.00, 493.01, 493.9, 493.90, 493.91), pneumonia (ICD-9 CM codes 482.1, 482.4, 482.41, 483, 483.0, 485, 486, 507, 507.0), and bronchiectasis with or without pulmonary collapse (ICD-9 CM codes 494, 515, 518.0); and (D) procedures: bronchoscopy, laryngoscopy, upper endoscopy with or without dilation, and sinus surgery.

To examine the degree of similarity between cases and controls in terms of comorbid illness and intensity of diagnostic work-up unrelated to the potential extraesophageal associations of GERD, we identified the occurrence of unspecified gastroenteritis (ICD-9 CM code 5589), pyrexia of unknown origin (ICD-9 CM code 7806), and follow-up examinations (ICD-9 CM codes V670 and V6759). We assumed that the last conditions/visits reflect the distribution of other relatively common disorders and the frequency of follow-up visits. We also examined the presence of acute upper respiratory infections (ICD-9 CM code 4659) as a control condition; we assumed that this respiratory condition was unrelated to GERD.

Data Analysis

Univariate analyses were used to test for differences between cases and controls with regard to demographic characteristics (age, sex, ethnicity), potential risk factors for GERD (cystic fibrosis, scleroderma, morbid obesity), upper respiratory tract disorders (sinusitis, otitis media, laryngitis), and lower respiratory tract disorders (asthma, pneumonia, bronchiectasis with or without pulmonary collapse). χ^2 tests were used for dichotomous variables, and unpaired t tests were used to compare continuous variables. Statistical analyses were performed using JMP IN statistical software (Duxbury Press, Wadsworth Publishing Co., Belmont, CA).

Results

Demographic Characteristics

Between October 1996 and October 2000, we identified GERD in 1980 children without neurologic defects or congenital esophageal anomalies. During the

same time, 7920 children without neurologic defects or congenital esophageal anomalies and without GERD were randomly assigned as controls. All cases and controls were older than 2 (and younger than 18) years. The average age of cases (9.16 years) was slightly greater than that of controls (8.64 years; $P < 0.0001$). There were significantly more girls (51% vs. 47%) and whites (60% vs. 41%) among cases than among controls.

Although the database does not contain information on the method used to diagnose GERD, 590 (30%) patients in the GERD group were documented to have undergone upper endoscopy during 1996–2000.

Risk Factors for GERD

Among the children with GERD, 399 (20.2%) were associated with either a potential risk factor (cystic fibrosis, morbid obesity, or scleroderma) or an upper or lower respiratory disorder. A significantly smaller proportion of controls, 1164 (14.7%), had any of these diagnoses ($P < 0.0001$). Of the potential risk factors for GERD, cystic fibrosis was reported in 50 patients in the case group (2.53%), which was approximately 3.5-fold more frequent than in controls (Table 1). Less frequently recorded in general, morbid obesity and systemic sclerosis were 3- and 2-fold more frequent, respectively, in cases than in controls.

Univariate Analyses

In univariate analyses, sinusitis and laryngitis were the 2 upper respiratory tract disorders significantly associated with GERD (Table 1). The prevalence of sinusitis or laryngitis was significantly increased among GERD patients compared with controls, and the unadjusted odds ratio (OR) for GERD was more than 3-fold greater among patients with these conditions. On the other hand, otitis media was inversely associated with GERD. All 3 lower respiratory disorders we examined were significantly increased among cases compared with controls ($P < 0.0001$). Asthma, pneumonia, and bronchiectasis with or without pulmonary collapse were 2, 3, and 6 times more frequent among cases than among controls. Similarly, the frequency of medical and surgical procedures related to respiratory disorders was greater among patients with GERD than among controls: laryngoscopy, 1.01% versus 0.24% ($P < 0.0001$); bronchoscopy, 1.31% versus 0.23% ($P < 0.0001$); sinus surgery, 0.86% versus 0.23% ($P < 0.0001$).

Cases and controls did not differ with respect to follow-up examinations or the occurrence of several other common disorders that were estimated to examine the similarity between cases and controls. These were unspecific gastroenteritis (OR, 1.14; 95% confidence interval [95% CI], 0.81–1.59), pyrexia of unknown origin (OR, 0.83; 95% CI, 0.60–1.15), follow-up examinations (OR, 1.31; 95% CI, 0.96–1.78), and acute upper respiratory infection (OR, 0.62; 95% CI, 0.36–1.06); all P values were >0.05.

Multivariate Analyses

We performed multivariable logistic regression analyses to control for the effects of differences in age,

Table 1. Univariate Comparisons of Children Older Than 2 Years With GERD and No Mental Retardation, Cerebral Palsy, Congenital Gastrointestinal Anomalies, or Esophageal Surgery (Cases) and Children Older Than 2 Years With No GERD and No Exclusion Criteria (Controls)

Variable	Cases (n = 1980)	Controls (n = 7920)	Odds ratio (95% CI)	*P*
Demographic features				
Age (*yr*) mean ± SD	9.16 (4.61)	8.64 (4.92)		<0.0001
Gender (male vs. female)	969 (48.94%)	4173 (52.69%)	0.86 (0.78–0.95)	0.0028
Race (white vs. other)	998 (60.23%)	3112 (41.18%)	1.91 (1.71–2.13)	<0.0001
Risk factors for GERD				
Cystic fibrosis	50 (2.53%)	59 (0.74%)	3.45 (2.36–5.05)	<0.0001
Morbid obesity	26 (1.31%)	56 (0.71%)	1.87 (1.17–2.98)	0.0078
Systemic sclerosis	4 (0.2%)	2 (0.06%)	8.01 (1.47–43.79)	0.0043
Upper respiratory tract disorders				
Sinusitis	83 (4.19%)	107 (1.35%)	3.19 (2.38–4.27)	<0.0001
Otitis media	41 (2.07%)	366 (4.62%)	0.44 (0.31–0.61)	<0.0001
Laryngitis	14 (0.71%)	15 (0.19%)	3.75 (1.81–7.79)	0.0001
Lower respiratory tract disorders				
Asthma	261 (13.18%)	535 (6.76%)	2.10 (1.79–2.45)	<0.0001
Pneumonia	124 (6.26%)	180 (2.27%)	2.87 (2.27–3.63)	<0.0001
Bronchiectasis with or without collapse	19 (0.96%)	19 (0.06%)	5.84 (3.20–10.68)	<0.0001
Medical/surgical procedures				
Laryngoscopy	20 (1.01%)	19 (0.24%)	4.24 (2.26–7.97)	<0.0001
Bronchoscopy	26 (1.31%)	18 (0.23%)	5.84 (3.20–10.68)	<0.0001
Sinus surgery	17 (0.86%)	18 (0.23%)	3.80 (1.96–7.39)	<0.0001

NOTE. Cases and controls were identified at Texas Children's Hospital, Houston, TX, 1996 through 2000.

sex, and ethnicity on the observed associations between GERD and potential risk factors (cystic fibrosis, morbid obesity, systemic sclerosis) or potential complications (upper and lower respiratory tract disorders). GERD served as the outcome variable in all the regression models. Covariates in separate models included either potential risk factors or complications of GERD. The results of these regression models are presented in Table 2. In general, the associations observed in the univariate analyses (Table 1) remained significant in the regression analyses. Modest increases in the risk of GERD were seen with older age (48% increase per 10 years), female sex (15% increase compared with male), and white race (58% increase compared with nonwhites). After controlling for older age and the concomitant presence of respiratory conditions, the adjusted ORs calculated for upper and lower respiratory tract disorders remained significantly elevated, except for otitis media, which remained inversely associated with GERD.

Because cystic fibrosis is a known risk factor for sinusitis, pneumonia, bronchiectasis, and pulmonary collapse, the regression analysis was repeated among cases and controls without cystic fibrosis (97% of the total study population). The calculated ORs were similar to those described in Tables 1 and 2.

Discussion

This is by far the largest study to evaluate the association between GERD and respiratory disorders in children without neurologic defects or congenital esophageal anomalies. The results have shown the frequency of sinusitis, laryngitis, asthma, pneumonia, and bronchiectasis to be 2–6-fold higher among children with GERD than among controls. The risk of having these conditions in children with GERD remained significantly elevated after controlling for age, sex, and ethnicity.

Approximately one third (34.6%) of children with GERD in the present study had either a potential risk factor (cystic fibrosis, morbid obesity, scleroderma) or an upper or lower respiratory tract disorder. The other two thirds of children with GERD were otherwise normal. This finding is in general agreement with previously published studies.[9]

Our results corroborate previous experimental, clinical, and therapeutic studies that indicate a pathophysiologic role for GERD in several extraesophageal diseases.[15–22,25–29] Several uncontrolled clinical studies have investigated this relationship in children. For example, one study reported that 19 (63%) of 30 children with chronic sinus disease had GERD as determined by 24-hour pH probe. In 15 (79%) of these 19 patients, sinus symptoms improved after treatment of GERD.[15] In another retrospective study of 155 children undergoing laryngoscopy and bronchoscopy, GERD as defined by upper gastrointestinal contrast series, pH probe, gastric scintiscan, or esophageal biopsy was found in 130 patients (84%). Of those patients, 90% had a laryngotracheal abnormality.[16] Several case series examined the prevalence of GERD in patients with asthma.[19–22] Abnormal acid reflux was noted in 24 patients (63%) on prolonged pH monitoring and or scintiscanning in 38 infants and children referred to a pulmonary clinic for

Table 2. Estimated Associations Between GERD and Demographic Features, Potential Risk Factors, and Several Extraesophageal Complications Involving the Upper and Lower Respiratory Tracts

	Parameter estimate	Adjusted odds ratio	95% CI	*P*
Demographic features				
Older age (per 10 years)	0.014	1.48	1.15–1.90	0.0018
Gender (men vs. women)	−0.16	0.85	0.77–0.95	0.0022
Ethnicity (white vs. other)	0.46	1.58	1.43–1.75	<0.0001
Risk factors[a]				
Cystic fibrosis	1.06	2.89	1.97–4.25	<0.0001
Morbid obesity	0.64	1.90	1.17–3.02	0.0074
Systemic sclerosis	1.91	6.74	1.30–48.92	0.0286
Upper respiratory disorder[a]				
Otitis media	−0.92	0.40	0.28–0.55	<0.0001
Sinusitis	0.85	2.34	1.72–3.19	<0.0001
Laryngitis	0.96	2.62	1.20–5.64	0.0228
Lower respiratory disorder[a]				
Asthma	0.66	1.93	1.63–2.28	<0.0001
Pneumonia	0.82	2.28	1.77–2.93	<0.0001
Bronchiectasis with or without collapse	0.74	2.28	1.14–4.57	0.0193

NOTE. Data are results of multivariate logistic regression analysis in 1980 children with GERD and 7920 controls without GERD diagnosed between 1996 and 2000 at Texas Children's Hospital.
[a]Age, gender, and ethnicity adjusted.

severe respiratory symptoms, including cough, wheezing, and recurrent pneumonia.[20] Another series reported gastroesophageal reflux in 27 (75%) of 36 children with uncontrolled asthma using 24-hour esophageal pHmetry.[22] In another series, esophageal manometry revealed abnormalities in 60% of 52 asthmatics and 14% of 28 healthy volunteers ($P < 0.01$).[29] Higher prevalence of GERD was reported in patients with nocturnal asthma, with one case series reporting high reflux scores on esophageal pHmetry in 16 (64%) of 25 patients.[18] Finally, a double-blind cross-over placebo-controlled study examined 4-week treatment with ranitidine 300 mg as a single evening dose in 37 children and adolescents with asthma. A modest 30% reduction of nocturnal asthma symptoms was reported.[28]

In uncontrolled studies involving small numbers of patients, previous investigators reported a high prevalence of GERD among patients with otitis media.[30,31] Both disorders are relatively common in children and therefore may be diagnosed concomitantly. For a positive association to be demonstrated, an appropriate control group (without GERD) is needed for valid estimation of risk. In the present case–control study, a significant inverse relationship between GERD and otitis media was observed. These results cast doubt on the role of GERD as a risk factor for otitis media. However, there is no mechanism known to us by which GERD may protect against otitis media. Further studies are needed to confirm this finding.

It is important to point out the potential limitations of our study design. First, some of the patients included in the present analysis may have received part of their medical care outside TCH. The medical care documented in the database may not represent all relevant health information pertaining to an individual patient. However, this is likely to affect cases and controls to similar degrees, leaving the calculated ORs relatively unchanged. Second, we are unable to determine the method of diagnosis for any of the medical conditions or to ascertain whether all patients were studied for GERD or for its potential risk factors or complications. However, one third of all patients with GERD were documented to have undergone endoscopy during the study period. GERD is often diagnosed based on symptoms; this information is not captured by the database. An unknown number of controls may have had undocumented GERD. As a result of this bias, the adjusted ORs reported here might be an underestimate of the true risk. On the other hand, GERD may be particularly sought among patients with respiratory disorders more than those without these disorders. This bias will overestimate the calculated ORs. To minimize the influence of this potential bias on our analysis, we examined the patients' entire records over a period of up to 5 years (1996–2000). We assumed that in most patients with respiratory disorders, the association between GERD and these disorders would become apparent, even if both diagnoses were not established at the same time. Finally, because this is a hospital-based case–control study, the prevalence of respiratory disorders such as pneumonia and asthma are much higher in the control group than would be expected in the general population. For these reasons, our analysis probably provides conservative estimates of the magnitude of the associations between GERD and various extraesophageal conditions.

The present study also has several strengths. First, all patients in the study population were older than 2 years to avoid inclusion of patients with the more common and largely self-limiting "physiologic" reflux of infants. Second, the case–control study design was essential for studying the comorbid occurrence of these complications among children with GERD. Some of the potential extraesophageal complications, such as asthma, are relatively common among pediatric patients and thus likely to coexist with GERD by chance. Controls in this study were selected randomly from the same data source and were matched on the year of appearance in the database to avoid differences that may result from temporal changes in disease coding practices. We used 2 unrelated diagnoses as surrogate measures of comorbid illnesses (pyrexia of unknown origin and unspecified gastroenteritis), follow-up visits, and a respiratory condition less likely to be related to GERD (acute upper respiratory infection) as a "control" condition. The frequency of these conditions and follow-up visits did not differ between cases and controls. The absence of significant differences in the proportion of cases and controls with these conditions is reassuring as to the similarity between cases and controls, except for GERD and its potential association. Third, the sample size is much greater than in previous studies. Therefore, the calculated estimates tended to be precise, as reflected by the relatively narrow 95% CIs. Finally, all diagnoses in the database were established before and unrelated to our study. Because diagnoses were established in the course of usual care, they were likely to be clinically relevant. This also avoids the potential for interviewer and recall bias inherent in studies that define diagnoses using patient interviews.

In summary, this is the first case–control study to confirm a significant statistical association between GERD and several important respiratory disorders (sinusitis, laryngitis, asthma, pneumonia, bronchiectasis) in

children without neurologic defects or congenital esophageal anomalies. However, further studies are needed to examine whether a cause–effect relationship exists between GERD and these potential extraesophageal disorders.

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