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Bronchiectasis in Chronic Pulmonary Aspiration: Risk Factors and Clinical Implications

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Summary. Introduction: Bronchiectasis is a well-known sequela of chronic pulmonary aspiration (CPA) that can result in significant respiratory morbidity and death. However, its true prevalence is unknown because diagnosis requires high resolution computed tomography which is not routinely utilized in this population. This study describes the prevalence, time course for development, and risk factors for bronchiectasis in children with CPA. Materials and Methods: Using a cross-sectional design, medical records were reviewed for all patients with swallow study or airway endoscopy-confirmed aspiration in our airway center over a 21 month period. All patients underwent rigid and flexible bronchoscopy, and high resolution chest computed tomography. Prevalence, distribution, and risk factors for bronchiectasis were identified. Results: One hundred subjects age 6 months to 19 years were identified. Overall, 66% had bronchiectasis, including 51% of those less than 2 years old. The youngest was 8 months old. Severe neurological impairment (OR 9.45, $P < 0.004$) and history of gastroesophageal reflux (OR 3.36, $P = 0.036$) were identified as risk factors. Clinical history, exam, and other co-morbidities did not predict bronchiectasis. Sixteen subjects with bronchiectasis had repeat chest computed tomography with 44% demonstrating improvement or resolution. Discussion: Bronchiectasis is highly prevalent in children with CPA and its presence in young children demonstrates that it can develop rapidly. Early identification of bronchiectasis, along with interventions aimed at preventing further airway damage, may minimize morbidity and mortality in patients with CPA. **Pediatr Pulmonol. 2012; 47:447–452.** © 2011 Wiley Periodicals, Inc.

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INTRODUCTION

Bronchiectasis is the abnormal dilatation of bronchi and bronchioles that results from damage to the airways caused by infection and inflammation.[1,2] It can lead to considerable morbidity including chronic cough, recurrent infections, and impaired lung function.[3] When bronchiectasis develops during childhood it may become irreversible and lead to chronic disease into adulthood with increased risk for mortality due to respiratory failure.[2,4]

The current gold standard for diagnosis of bronchiectasis is high resolution chest CT (HRCT). HRCT is a radiographic technique ideally suited to evaluate diffuse lung diseases and the images obtained are representative of those found on histopathology.[5] HRCT uses limited sampling which allows radiation doses to be minimized and current protocols deliver doses equivalent to 6 weeks of ambient radiation exposure.[6]

Chronic pulmonary aspiration (CPA) is a well-known cause of bronchiectasis in children, but several recent reviews of non-cystic fibrosis bronchiectasis implicate CPA as the cause in only 2–18% of cases.[7–11] Because HRCT is not routinely utilized in the evaluation and

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management of children with CPA, this cause of bronchiectasis may be underrepresented in these studies.

Chronic pulmonary aspiration is characterized by the recurrent spillage of food, regurgitated material due to gastro-esophageal reflux, and/or oral secretions into the subglottic airways.[12] Causes include dysfunctional swallowing, impaired airway protective responses, and abnormal anatomical connections between the airway and gastrointestinal tract. CPA is the leading cause of death in children with severe neurological disorders.[13–15] Clinical symptoms are non-specific, including chronic cough, wheezing, and recurrent pneumonia.[12,16] When these symptoms are caused by other conditions, however, bronchiectasis is not an expected finding.[17]

Video fluoroscopic swallowing studies (VSS) and fiberoptic-endoscopic evaluation of swallowing (FEES) are part of the diagnostic evaluation for CPA.[18,19] In addition, flexible bronchoscopy with bronchoalveolar lavage (BAL) can be performed to obtain lower respiratory secretions for culture and cytological analysis, and aid in the identification of anatomical abnormalities. Rigid bronchoscopy is the preferred method for evaluation of suspected laryngeal cleft or tracheoesophageal fistula (TEF).[20]

The prevalence of bronchiectasis in children with CPA has not been well described nor is it clear if the presence of bronchiectasis is related to the mechanism of aspiration, the material aspirated, or other clinical correlates (such as: gender, prematurity, tracheostomy status, ventilator dependence, or severe neurological disease). The aim of this study is to describe the prevalence, distribution, and time course for the development of bronchiectasis in children with CPA. We compare the symptoms, physical exam findings, and lower airway inflammatory markers of those with and without bronchiectasis and attempt to identify predictors of its presence. We also investigate the role of CPA etiology and co-morbidities as possible risk factors for the development of bronchiectasis.

MATERIALS AND METHODS

Study Population

The study was approved by the Institutional Review Board and a waiver of informed consent was granted. The study population was selected from our Aerodigestive and Sleep Center. This program is a tertiary referral program in which children with multi-system disease receive coordinated multi-disciplinary evaluation and treatment for airway reconstruction, chronic aspiration, and feeding disorders. Approximately 100 new pediatric patients are evaluated annually, many of whom are suspected of having CPA as a part of their clinical spectrum. Medical records were reviewed for all new patients diagnosed with CPA after evaluation in this center between July 2006 and March 2009.

Diagnostic Evaluation

All patients underwent rigid and flexible bronchoscopy, HRCT of the chest, and at least one swallowing study at the time of their initial evaluation. The diagnosis of CPA was made if the swallowing study (VSS or FEES) demonstrated aspiration, or if either a laryngeal cleft (excluding type I cleft) or TEF was identified on endoscopic examination. Chest HRCT was performed using controlled ventilation techniques with thin (1 mm) images obtained at intervals of 10 mm during a controlled inspiratory breath hold and then again at 20 mm intervals in exhalation. Images were reviewed for the presence and location of bronchiectasis as specified by the radiographic definition described in the Fleischner Society lexicon.[21] Patient characteristics including co-morbid conditions are described in Table 1. Their presenting symptoms and physical exam findings were recorded. BAL fluid analysis was reviewed to identify markers of airway inflammation and infection (defined as $>10^6$ colonies/ml of a single organism on bacterial culture). When available, results of esophageal impedance studies and any follow-up HRCT scans were also reviewed.

Statistical Analysis

Summary statistics were used to describe the age at identification of bronchiectasis and the extent and anatomical distribution of bronchiectasis when present. The frequency of respiratory symptoms, physical exam findings, and co-morbid conditions were compared between those with and without bronchiectasis using Chi-square or Fisher's exact tests (depending on sample size). Age and mean percent neutrophils and lipid laden macrophages were compared using the Kruskal–Wallis non-parametric test. The proportions of subjects with airway infection were compared using a Chi-Square test. Potential risk factors for the

TABLE 1— Patient Characteristics

Age (mean in months)	6 month–19 year (49)
Gender (M, F)	56, 44
VSS positive for aspiration (%)	62
FEES positive for aspiration (%)	51
Laryngotracheoesophageal cleft or TEF (%)	12
Premature birth (%)	53
Severe neurological impairment (%)	30
Tracheostomy status (%)	50
Ventilator dependence (%)	9
Reported history of GER (%)	80
History of prior fundoplication (%)	56

development of bronchiectasis within this population of children with CPA were evaluated by logistic regression. The initial model included: age, gender, history of GER, positive esophageal impedance study, history of gastric fundoplication, prematurity (<37 weeks gestation), airway anatomical abnormalities, severe neurological impairment, tracheostomy status, and ventilator dependence. All statistical tests were performed using SAS 9.2 (The SAS Institute Inc. Cary, NC). Values of $P < 0.05$ were considered statistically significant.

RESULTS

One-hundred children met the inclusion criteria for this study. Their demographics, diagnostic evaluation results, and clinical characteristics are described in Table 1. Bronchiectasis was identified in 66% of subjects at the time of initial evaluation. A representative example of the HRCT findings is shown in Figure 1. The prevalence was similar in subjects younger than 2 years (51%), with the youngest subject only 8 months old. Overall, bronchiectasis occurred bilaterally in 48% and was isolated to a single lobe in only 14% of cases. The most commonly affected lobes were the left lower lobe (52%), right lower lobe (50%), and right upper lobe (43%). Involvement of the lingula (4%), left upper lobe (13%), and right middle lobe (11%) was less frequent.

Table 2 compares patient characteristics, frequency of respiratory symptoms, physical exam findings, results of BAL fluid analysis, and co-morbid conditions between subjects with and without bronchiectasis. There was a modest difference in age, but no significant differences were identified between the groups with respect to symptom history (chronic cough, wheezing, chest congestion, recurrent pneumonia), physical exam (crackles, wheezing, clubbing), or BAL analysis (bacterial infection, neutrophil percentage, percent of lipid laden macrophages). Notably, 72% of these children with CPA had fewer than 5% of macrophages stained positive for lipid.

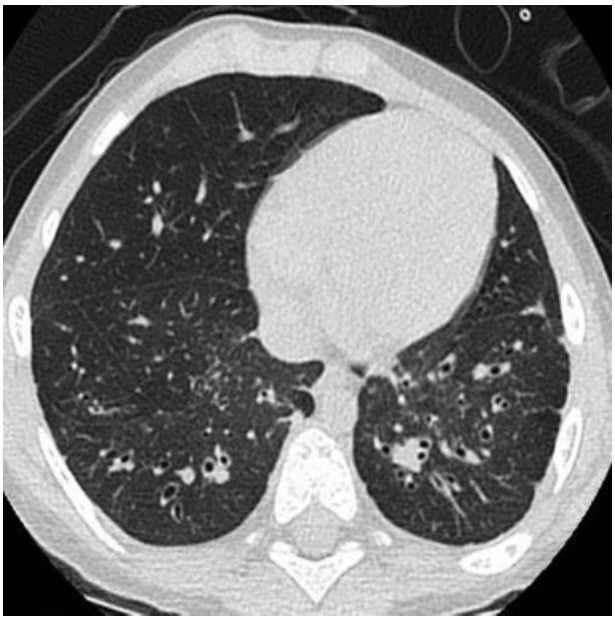

Fig. 1. High-resolution Chest CT demonstrating diffuse bronchiectasis. There are numerous dilated and thickened bronchi that exceed the diameter of their corresponding blood vessels. The bronchiectatic airways are most abundant in the posterior segments of the lower lobes.

Logistic regression analysis identified severe neurological impairment and parental report of prior history of GER as the only significant predictors for the presence of bronchiectasis with odds ratios of 9.45 (95% CI 2.05–43.6) and 3.36 (95% CI 1.08–10.43), respectively. Bronchiectasis was present in 93% of the 30 subjects who had severe neurological impairment. There was no statistically significant association between the presence of bronchiectasis and any of the other covariates, which were removed from the final model.

Sixteen subjects with bronchiectasis on their initial HRCT scan had a subsequent scan performed. Bronchiectasis was reported as improved or resolved in seven (44%), stable in six (38%), and progressed in three (18%). In the three patients who had disease progression, one was later found to have immunodeficiency secondary to impaired T-cell function, one was found to have a large paraesophageal hernia with pooling of gastric fluid in the distal esophagus, and one had severe neurological impairment and persistent aspiration of saliva despite treatment.

DISCUSSION

The prevalence of bronchiectasis in children with CPA in our study was high and was seen in children as young as 8 months of age suggesting that airway remodeling begins early in response to repeated aspiration events. The occult development of progressive lung disease in this population is concerning, since bronchiectasis has the potential to develop into a lifelong chronic disease with considerable morbidity and mortality.[1,2] In our clinical practice, the finding of bronchiectasis increases our urgency to intervene to prevent further aspiration, even when the interventions are surgical or require major lifestyle changes. A known diagnosis of bronchiectasis may lower the threshold for initiating antibiotic therapy, extend the duration of antibiotics, and lead to institution of regular airway clearance.[2,22,23]

The high prevalence of bronchiectasis in CPA and its rarity in the general population support a potential role for HRCT in the diagnostic evaluation of CPA. The sensitivity of swallowing studies varies, and abnormal

TABLE 2— Comparison of History, Physical Exam, BAL Analysis, and Co-Morbid Conditions Between Children With and Without Bronchiectasis

	Bronchiectasis	No bronchiectasis	*P*-value
History of chronic cough (%)	70.3	63.6	NS[1]
History of wheezing (%)	36.5	45.5	NS[1]
History of chest congestion (%)	51.6	39.4	NS[1]
History of recurrent pneumonia	55.4	48.5	NS[1]
Crackles on physical exam (%)	15.9	9.1	NS[2]
Wheezing on physical exam (%)	3.2	9.1	NS[2]
Clubbing (%)	3.2	3.0	NS[2]
Bacterial infection by BAL culture (%)	32.8	29.4	NS[1]
BAL neutrophils (% of WBC)	43.8	45.0	NS[3]
BAL LLM (% of macrophages)	4.9	4.1	NS[3]
Age (mean in months)	53.8	40.5	0.04[3]
Gender (% male/% female)	59/41	50/50	NS[1]
Preterm birth (%)	53.2	60.6	NS[1]
Severe neurological impairment (%)	42.4	5.9	<0.004[1]
Status tracheostomy (%)	56.1	39.4	0.12[1]
Ventilator dependent (%)	7.6	12.1	NS[1]
Parent reported history of GER (%)	89.4	65.6	0.036[1]
GER based on impedance study (%)	31.1	24.1	NS[1]
History of prior fundoplication (%)	57.6	52.9	NS[1]

LLM, lipid laden macrophages; NS, non-significant.
[1]Chi-square;
[2]Fisher's exact test;
[3]Kruskal–Wallis non-parametric test.

swallowing function with vestibular penetration of food material is frequently identified in the absence of visualized spillage into the subglottic airway. Results are often reported as indeterminate or ''at risk for aspiration.'' In this subset of patients, where the suspicion of CPA is high, the presence or absence of bronchiectasis may substantially improve the positive and negative predictive value of VSS and FEES. Further study is needed to formally evaluate the diagnostic value of HRCT in this population.

This study suggests that respiratory symptoms, physical exam findings, and much of the clinical history do not predict which children with CPA have developed bronchiectasis. Bronchiectasis was not related to co-morbidities such as prematurity, tracheostomy, or ventilator dependence. Not surprisingly, severe neurological impairment was an independent predictor for the presence of bronchiectasis. Impaired airway protective responses, prolonged time in the recumbent position, and reduced airway clearance mechanisms associated with compromised chest mechanics likely contribute to this finding.[24] Since the estimated mortality rate is 33% by age 20 years in this population, with aspiration pneumonia (21%) and other respiratory complications (40%) implicated as the leading causes of death, early identification, and treatment of bronchiectasis may significantly impact mortality.[13,15]

We expected that the role of GER as a risk factor for bronchiectasis would be difficult to ascertain in a retrospective design and sought to evaluate this by various approaches. Regardless, our results are difficult to interpret. While presenting with a reported history of GER was associated with a threefold increase in the prevalence of bronchiectasis, there was no correlation found with positive results on esophageal impedance monitoring at the time of evaluation, nor was there any apparent protective effect of previous gastric fundoplication. It is possible that the bronchiectasis found on HRCT, in some instances, developed prior to the performance of a fundoplication. Additionally, as suggested by others, the finding of GER on esophageal impedance likely demonstrates opportunities to aspirate rather than proof of aspiration itself; which limits this tool in the assessment of CPA.[25] Overall, lung injury is the outcome of greatest concern in children with CPA. Given that the severity of aspiration is difficult to quantify and most clinical indicators (aside from CNS impairment) are not predictive, HRCT could be more readily utilized in the evaluation of CPA to identify which patients have developed significant lung injury.

Only one quarter of our population of children with CPA had lipid laden macrophages on BAL fluid in excess of 5%. There are several potential explanations for this finding. First, the majority of the diagnostic evaluations were performed on patients referred from other centers and occurred at a time when the patients were considered to be at their baseline health. Many patients already had their feeding modified due to known

dysphagia. It is therefore quite likely that some of these children were ''aspirators'' whose oral intake restrictions helped prevent them from aspirating significantly in the days or weeks that preceded their evaluation. This is further supported by the lack of association between BAL markers of infection or inflammation, and the presence of bronchiectasis. Additionally, these findings may reflect an inherent limitation in the ability of lipid laden macrophages to reliably identify children with chronic aspiration.[19,26–30]

A striking result was the finding, even in this challenging patient population, that bronchiectasis can improve. At our center, therapeutic interventions are individually tailored for each patient and often include feeding modification, airway clearance therapy, gastric fundoplication, and therapies aimed at reducing the volume of salivary gland secretions. Although only 16 of the children in our study had chest HRCT repeated, 81% had stable or improved bronchiectasis. Most of these children had repeat HRCT performed due to incomplete resolution of coughing and wheezing despite interventions to manage their aspiration. There was uncertainty as to whether these symptoms were due to ongoing aspiration or other underlying pulmonary disease. Given the diagnostic challenges in CPA, including the limited sensitivity of any single evaluation, HRCT may serve a useful role in ongoing management.

There are several limitations to the study. The retrospective design limits definitive insight into the relationship between the duration and severity of aspiration and the development of bronchiectasis. Due to the variable and sporadic nature of CPA, this would be difficult to establish even in a prospective clinical study. This study was not designed to compare treatment outcomes (which were variable and individually tailored) in this population. While the chart reviews captured some outcome data regarding improvement or progression of bronchiectasis, in those patients who had follow-up HRCT scans, the decision to do so was driven by clinical symptoms rather than formal methodological follow-up, thereby limiting the conclusions that can be drawn.

This study demonstrates that CPA frequently results in bronchiectasis even at a very early age. It occurs at an alarming rate in patients with severe neurological impairment and may also be more common in those with GER. Because early identification of bronchiectasis due to CPA may alter treatment, and improvement or resolution is achievable, HRCT should be strongly considered in this population. In particular, the results of this study support consideration of chest HRCT for[1] the child in whom chronic aspiration is highly suspected on clinical grounds, but VSS and FEES are inconclusive;[2] the child in whom the diagnosis of chronic aspiration has been established, but therapeutic interventions have been unsuccessful, and ongoing symptoms may be due to bronchiectasis rather than ongoing aspiration; and[3] as a marker of disease severity in children being considered for laryngo-tracheal separation. Given the poor ability of clinical history, symptoms, or physical exam findings to predict bronchiectasis, coupled with the difficulty at times in establishing which children are aspirating significantly, HRCT may also serve an important role in the routine evaluation and follow-up of children suspected of having CPA. Prospective studies are needed to determine whether early identification of bronchiectasis alters prognosis in CPA, which treatment modalities are most effective for the treatment of CPA, and to better define the role of HRCT as a clinical and research outcome measure in this population.

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REFERENCES

1. Barker AF. Bronchiectasis. New Engl J Med 2002;346:1383–1393.
2. O'Donnell AE. Bronchiectasis. Chest 2008;134:815–823.
3. Martinez-Garcia MA, Soler-Cataluna JJ, Perpina-Tordera M, Romain-Sanchez P, Soriano J. Factors associated with lung function decline in adult patients with stable non-cystic fibrosis bronchiectasis. Chest 2007;132:1565–1572.
4. Onen ZP, Gulbay BE, Sen E, Yildiz OA, Saryal S, Acican T, Karabiyikoglu G. Analysis of the factors related to mortality in patients with bronchiectasis. Respir Med 2007;101:1390–1397.
5. Kang EY, Miller RR, Muller NL. Bronchiectasis: comparison of preoperative thin-section CT and pathologic findings in resected specimens. Radiology 1995;195:649–654.
6. Loeve M, Lequin MH, de Bruijne M, Hartmann IJC, Gerbrands K, van Straten M, Hop WCJ, Tiddens HAWM. Cystic fibrosis: are volumetric ultra-low-dose expiratory CT scans sufficient for monitoring related lung disease? Radiology 2009;253:223–229.
7. Boren EJ, Teuber SS, Gershwin ME. A review of non-cystic fibrosis pediatric bronchiectasis. Clin Rev Allergy Immunol 2008;34:260–273.
8. Eastham KM, Fall AJ, Mitchell L, Spencer DA. The need to redefine non-cystic fibrosis bronchiectasis in childhood. Thorax 2004;59:324–327.
9. Karadag B, Karakoc F, Ersu R, Kut A, Bakac S, Dagli E. Non-cystic-fibrosis bronchiectasis in children: a persisting problem in developing countries. Respir Int Rev Thorac Dis 2005;72:233–238.
10. Li AM, Sonnappa S, Lex C, Wong E, Zacharasiewicz A, Bush A, Jaffe A. Non-CF bronchiectasis: does knowing the aetiology lead to changes in management? Eur Respir J 2005;26:8–14.
11. Santamaria F, Montella S, Pifferi M, Ragazzo V, De Stefano S, De Paulis N, Maglione M, Boner AL. A descriptive study of non-cystic fibrosis bronchiectasis in a pediatric population from Central and Southern Italy. Respir Int Rev Thorac Dis 2009;77:160–165.
12. Boesch RP, Daines C, Willging JP, Kaul A, Cohen AP, Wood RE, Amin RS. Advances in the diagnosis and management of

chronic pulmonary aspiration in children. Eur Respir J 2006; 28:847–861.
13. Hutton JL. Cerebral palsy life expectancy. Clin Perinatol 2006;33:545–555.
14. Morton RE, Wheatley R, Minford J. Respiratory tract infections due to direct and reflux aspiration in children with severe neurodisability. Dev Med Child Neurol 1999;41:329–334.
15. Reddihough DS, Baikie G, Walstab JE. Cerebral palsy in Victoria, Australia: mortality and causes of death. J Paediatr Child Health 2001;37:183–186.
16. Colombo JLSP. Aspiration Syndromes. In: Taussig LMLL, editor. Pediatric Respiratory Medicine. St. Louis: Mosby; 1999. p 435–443.
17. Mahut B, De Blic J, Emond S, Benoist MR, Jarreau PH, Lacaze-Masmonteil T, Magny JF, Delacourt C. Chest computed tomography findings in bronchopulmonary dysplasia and correlation with lung function. Arch Dis Child Fetal Neonatal Ed 2007;92:F459–F464.
18. Leder SB, Karas DE. Fiberoptic endoscopic evaluation of swallowing in the pediatric population. Laryngoscope 2000;110: 1132–1136.
19. Martin-Harris B, Logemann JA, McMahon S, Schleicher M, Sandidge J. Clinical utility of the modified barium swallow. Dysphagia 2000;15:136–141.
20. Chien W, Ashland J, Haver K, Hardy SC, Curren P, Hartnick CJ. Type 1 laryngeal cleft: establishing a functional diagnostic and management algorithm. Int J Pediatr Otorhinolaryngol 2006;70:2073–2079.
21. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology 2008;246:697–722.
22. Ilowite J, Spiegler P, Kessler H. Pharmacological treatment options for bronchiectasis: focus on antimicrobial and anti-inflammatory agents. Drugs 2009;69:407–419.
23. Murray MP, Pentland JL, Hill AT. A randomised crossover trial of chest physiotherapy in non-cystic fibrosis bronchiectasis. Eur Respir J 2009;34:1086–1092.
24. Fitzgerald DA, Follett J, Van Asperen PP. Assessing and managing lung disease and sleep disordered breathing in children with cerebral palsy. Paediatr Respir Rev 2009;10:18–24.
25. Rosen R, Nurko S. The importance of multichannel intraluminal impedance in the evaluation of children with persistent respiratory symptoms. Am J Gastroenterol 2004;99:2452–2458.
26. Colombo JL, Hallberg TK. Recurrent aspiration in children: lipid-laden alveolar macrophage quantitation. Pediatric Pulmonol 1987;3:86–89.
27. Colombo JL, Hallberg TK, Sammut PH. Time course of lipid-laden pulmonary macrophages with acute and recurrent milk aspiration in rabbits. Pediatric Pulmonol 1992;12: 95–98.
28. Ding Y, Simpson PM, Schellhase DE, Tryka AF, Ding L, Parham DM. Limited reliability of lipid-laden macrophage index restricts its use as a test for pulmonary aspiration: comparison with a simple semiquantitative assay. Pediatr Dev Pathol 2002; 5:551–558.
29. Kazachkov MY, Muhlebach MS, Livasy CA, Noah TL. Lipid-laden macrophage index and inflammation in bronchoalveolar lavage fluids in children. Eur Respir J 2001;18:790–795.
30. Knauer-Fischer S, Ratjen F. Lipid-laden macrophages in bronchoalveolar lavage fluid as a marker for pulmonary aspiration. Pediatric Pulmonol 1999;27:419–422.