CHEST

Protracted Bacterial Bronchitis in Children

Natural History and Risk Factors for Bronchiectasis

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BACKGROUND: Protracted bacterial bronchitis (PBB) and bronchiectasis are distinct diagnostic entities that share common clinical and laboratory features. It is postulated, but remains unproved, that PBB precedes a diagnosis of bronchiectasis in a subgroup of children. In a cohort of children with PBB, our objectives were to (1) determine the medium-term risk of bronchiectasis and (2) identify risk factors for bronchiectasis and recurrent episodes of PBB.

METHODS: One hundred sixty-one children with PBB and 25 control subjects were prospectively recruited to this cohort study. A subset of 106 children was followed for 2 years. Flexible bronchoscopy, BAL, and basic immune function tests were performed. Chest CT was undertaken if clinical features were suggestive of bronchiectasis.

RESULTS: Of 161 children with PBB (66% boys), 13 were diagnosed with bronchiectasis over the study period (8.1%). Almost one-half with PBB (43.5%) had recurrent episodes (> 3/y). Major risk factors for bronchiectasis included lower airway infection with *Haemophilus influenzae* (recovered in BAL fluid) ($P = .013$) and recurrent episodes of PBB ($P = .003$). *H influenzae* infection conferred a more than seven times higher risk of bronchiectasis (hazard ratio, 7.55; 95% CI, 1.66-34.28; $P = .009$) compared with no *H influenzae* infection. The majority of isolates (82%) were nontypeable *H influenzae*. No risk factors for recurrent PBB were identified.

CONCLUSIONS: PBB is associated with a future diagnosis of bronchiectasis in a subgroup of children. Lower airway infection with *H influenzae* and recurrent PBB are significant predictors. Clinicians should be cognizant of the relationship between PBB and bronchiectasis, and appropriate follow-up measures should be taken in those with risk factors.

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ABBREVIATIONS: CFU = colony-forming units; IQR = interquartile range; PBB = protracted bacterial bronchitis

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Protracted bacterial bronchitis (PBB), first described in 2006, is a major cause of chronic cough in children.[1,2] PBB has been studied by research groups in Australia,[1-3] Europe,[4] and the United States, with similar findings.[5,6] PBB is characterized by persistent wet cough, response to 2 weeks of appropriate antibiotic therapy, and absence of indicators to suggest an alternative cause for cough.[1,7] PBB is more common in young boys and children who have attended child care.[8] When compared with control subjects, children with PBB are more likely to have lower airway infection with common respiratory bacteria and viruses.[8]

Currently, there are limited published data[9] and no prospective follow-up studies evaluating the outcomes of children with PBB. This research gap limits the clinician's ability to prognosticate on the likely natural history of PBB in any given child. Anecdotally, many otherwise healthy children experience recurrent episodes of PBB without appreciable longer-term consequences. However, in a subgroup of children, recurrent PBB appears to be associated with a future diagnosis of bronchiectasis.

PBB and bronchiectasis share many common features, spanning from respiratory symptoms (ie, chronic wet cough) to intense neutrophilic lower airway inflammation and innate immune system activation.[10-12] Lower airway microbiota,[13] including the presence of adenovirus type C[14] and a predominance of non-typeable *Haemophilus influenzae*[1,8] are also alike. These similarities underpin the notion that PBB and bronchiectasis represent a clinical continuum.[15,16] To date, the accuracy of this proposed continuum is uncertain and warrants evaluation in a prospective cohort study.

Hence, in 161 children with PBB and 25 control subjects, we aimed to determine (1) the 2-year outcomes of children with PBB with respect to a diagnosis of bronchiectasis and (2) risk factors for bronchiectasis and recurrent episodes of PBB.

Methods

Study Participants

Participants were enrolled as part of a larger prospective cohort study aimed at evaluating the long-term outcomes of children with chronic cough. Written informed consent was obtained from all parents/guardians, and ethics approval was granted by The Queensland Children's Health Services Human Research Ethics Committee (HREC/03/QRCH/17).

Between March 2008 and October 2012, 343 children were enrolled. Of them, 161 fulfilled criteria for PBB; 25 were recruited as control participants (15 undergoing evaluation for respiratory symptoms other than chronic cough plus 10 healthy control subjects). Data from the 15 children undergoing respiratory evaluation have been previously described[8] (e-Appendix 1). The 10 healthy control subjects were recruited from colleagues and friends.

All children (excluding the 10 healthy control subjects) underwent flexible bronchoscopy and BAL per clinical indication and were recruited prior to the bronchoscopy procedure. BAL was processed for cellularity and microbiological features. Bacterial infection was defined as a bacterial load of $\geq 10^4$ colony-forming units (CFU)/mL BAL fluid.[8,11] Laboratory tests for suppurative lung diseases were performed, as described previously.[14] *H influenzae* characterization was undertaken at a research laboratory (Menzies School of Child Health Research, Darwin, Australia) when BAL fluid was available (e-Appendix 2).

Follow-up

Follow-up included monthly contact (phone calls or e-mails by research nurses) to capture respiratory exacerbations. Parents completed cough diaries during periods of illness. Antibiotic therapy was usually prescribed by a family doctor when appropriate according to usual clinical management. The majority of children were seen by their pediatric pulmonologist three to four times per year as part of routine clinical follow-up. At 2 years, a subset (n = 106) also underwent clinical assessment for bronchiectasis (D. F. W. or A. B. C., or both).

Given the ethical considerations pertaining to research-related chest CT in children,[17,18] CT imaging was performed only when clinical features of bronchiectasis were present.[19] Clinicians had similar practices, whereby chest CT imaging was undertaken for (1) chronic wet cough that was nonresponsive to 4 weeks of antibiotic therapy,[20] (2) persistent chest radiographic changes despite appropriate antibiotic therapy, or (3) recurrent hospitalizations for acute respiratory events.

Definitions

PBB was defined as (1) a history of chronic ($\geq$ 4 weeks) wet cough, (2) prospective evidence (supported by cough diaries) of response to 2 weeks of treatment with amoxicillin clavulanate, and (3) an absence of clinical pointers suggesting an alternative cause for cough.[1] Diagnosis of bronchiectasis was based on pediatric

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