

PEDIATRIC ASTHMA

Does a Parent-Reported History of Pneumonia Increase the Likelihood of Respiratory Symptoms Needing Therapy in Asthmatic Children and Adolescents?

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Background. Asthmatic children and adolescents attending outpatient clinics often have a history of pneumonia. Whether respiratory symptoms, lung function, and airway inflammation differ in asthmatic patients with and without a history of pneumonia remains controversial. **Aims.** To compare clinical, lung functional, and inflammatory variables in asthmatic outpatients with and without a history of pneumonia. **Methods.** In 190 asthmatic outpatients, aged 6–18 years, we assessed respiratory symptoms, lung function (flows, volumes, and pulmonary diffusion capacity, DLCO/VA), and atopic-airway inflammation as measured by the fractional concentration of exhaled nitric oxide (FE_{NO}). A previous medical and radiological diagnosis of pneumonia was defined as “recurrent pneumonia” if subjects had at least three pneumonia episodes or two episodes within a year. **Results.** Of the 190 outpatients studied, 38 (20%) had a history of pneumonia. These patients had more frequent upper-respiratory symptoms, nighttime awakenings in the past 4 weeks, daily use of inhaled corticosteroids, and lower FE_{NO} than the 152 asthmatic children without previous pneumonia (FE_{NO}: 20.6 ppb, 95% CI: 15.2–28.0 vs. 31.1 ppb, 95% CI: 27.0–35.8; $p < .05$). Of the 38 patients with previous pneumonia, 14 had recurrent pneumonia. Despite comparable lung volumes and flows, they also had lower DLCO/VA than asthmatic children with no recurrent pneumonia and asthmatic children without previous pneumonia (DLCO/VA%: 91.2 ± 11.3 vs. 108.5 ± 14.7 vs. 97.9 ± 18.6 , $p < .05$). **Conclusion.** Respiratory assessment in asthmatic children and adolescents with a history of pneumonia, especially recurrent pneumonia, often discloses symptoms needing corticosteroid therapy, and despite normal lung volumes and flows, mild reductions in the variables reflecting gas diffusion and atopic-airway inflammation (DLCO/VA and FE_{NO}). Whether these respiratory abnormalities persist in adulthood remains an open question.

Keywords exhaled nitric oxide, inflammation, inhaled corticosteroids, lung function, respiratory infection

INTRODUCTION

Studies in unselected populations show that infections of the lower respiratory tract can lead to asthma-like symptoms and long-term decreases in lung function (1–8). Pneumonia during the first 3 years of life is associated with an increased risk of subsequent persistent wheezing and diminished lung function at ages 6 and 11 years (6). Pneumonia in early childhood is also associated with impaired lung function in late adult life (4). Although ample evidence describes the long-term effects of pneumonia in unselected pediatric populations, whether a history of pneumonia influences lung function and pulmonary diffusion capacity in young asthmatic subjects remains unclear (9, 10). Nor do we know how a history of pneumonia in asthmatic children and adolescents influences atopic-airway inflammation as measured by the fractional concentration of exhaled nitric oxide (FE_{NO}). Some studies have reported contrasting results for FE_{NO} levels in an ongoing pneumonia

episode among non-asthmatic children and ventilated adult subjects (11, 12). Having this information could help estimate the late effects of respiratory infections in asthmatic patients and thus develop disease-modifying therapy.

We designed this cross-sectional study to find out whether a history of pneumonia influences clinical, functional, and inflammatory findings in young outpatients attending a pulmonary unit for asthma. To do so, we studied the frequency of respiratory symptoms needing corticosteroid therapy, tested lung function including lung volumes, flows and pulmonary diffusion capacity (DLCO/VA), and measured atopic-airway inflammation (FE_{NO}) in asthmatic outpatients with and without a clinical and radiological history of pneumonia.

METHODS

Subjects

We recruited 210 asthmatic patients, aged 6–18 years, attending our outpatient clinic for respiratory diseases. Asthma was classified in accordance with the Global Initiative for Asthma guidelines (13). Patients had previously documented bronchial hyperresponsiveness, as measured either by the bronchial response to salbutamol (forced

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expiratory volume in 1 second (FEV_1) increase, >12% of predicted) or a positive response to exercise testing (FEV_1 fall under 12% of baseline) (14). Subjects were included if they had fully controlled or partially controlled asthma according to Global Initiative for Asthma criteria (13). None of them had taken inhaled or oral corticosteroids in the previous 2 weeks, and needed only rescue medication with inhaled beta-agonists. No subject had experienced an acute respiratory illness during the 4 weeks before testing. Subjects with underlying illnesses such as aspiration syndrome, congenital pulmonary or cardiac defects, chronic pulmonary disease or immune disorders were not included. Written informed consent was obtained from parents; the study was approved by the Institutional Review Board.

Questionnaire

Parents were asked to complete a modified version of the American Society questionnaire on the child's present and past respiratory history (15). Detailed information was sought on children's respiratory symptoms, therapy, and their parents' cigarette smoking habits. No information was sought on asthma diagnosis preceding the first pneumonia episode. "Previous pneumonia" in a child was defined by a parent-reported history of pneumonia diagnosed by a physician according to clinical and radiological criteria. Subjects with previous pneumonia were further classified as having "recurrent pneumonia" if they had at least three pneumonia episodes or two episodes within a year (16).

Skin-Prick Tests

Atopy was assessed by means of skin-prick tests for common allergens (Soluprick, ALK-Abellø, Horsholm, Denmark), as described elsewhere (17). Atopy was defined as the presence of at least one positive skin reaction (wheal size ≥ 3 mm).

FE_{NO} Measurements

FE_{NO} was measured by chemiluminescence (Sievers NOATM 280, Sievers Instruments, Inc., Boulder, CO, USA), as previously reported (18) using the single-breath online technique with inhaled nitric oxide (NO)-free air (19). All participants were asked to avoid food intake and physical exercise for at least 2 hr before testing. Subjects did single-breath maneuvers in duplicate at a constant expiratory pressure (10 cm H_2O) and flow (50 ml/sec) (20, 21).

Lung Function

Spirometric variables were measured with a portable spirometer (heated Fleisch pneumotachograph ESS- γ , Biomedin s.r.l., Padova, Italy). Duplicate measurements from at least three acceptable maneuvers were obtained and recorded (22). Static volumes (wash-in helium dilution method) and diffusion capacity for carbon monoxide (single-breath method) were measured with a pulmonary function device (ESS- β Analyzer, Biomedin s.r.l.). Lung function measurements included FEV_1 ,

mid-maximal expiratory flow, functional residual capacity, residual volume, total lung capacity, and diffusion capacity corrected by alveolar volume (D_{LCO}/VA). All lung function values were expressed as percent of predicted (23).

Study Design

Parents completed a questionnaire on respiratory symptoms and medications, introduced as a general overview of their child's respiratory health. To reduce biased parental responses, questions on previous pneumonia episodes came after questions on respiratory symptoms. Patients underwent a clinical examination, followed by skin-prick testing, FE_{NO} measurement, and lung function testing. Subjects with a history of pneumonia were subgrouped as with or without recurrent pneumonia as previously defined.

STATISTICAL ANALYSIS

Non-normally distributed values were transformed to natural logarithms and expressed as geometric means and 95% confidence intervals (CIs). Normally distributed values were expressed as arithmetic means and their standard deviation. The Mann-Whitney test was used to compare two independent groups. The one-way analysis of variance (ANOVA) with post hoc Scheffe's test or the Kruskal-Wallis test was used to compare more than two independent groups, as needed. Contingency tables (the χ^2 test) with the Fisher's correction were used to compare the frequencies of categorical variables. A p -value < .05 was considered statistically significant. A statistical software program (SPSS, version 15; SPSS, Inc., Chicago, IL, USA) was used for the calculations.

RESULTS

Of the 210 subjects initially enrolled, 190 completed spirometry and 20 subjects were excluded: 12 refused to participate, 8 cooperated poorly or failed to complete the maneuvers. Of the 190 subjects included, 38 had a history referring to at least one pneumonia episode. Upper-respiratory symptoms and nighttime awakening in the past 4 weeks were more frequent, days/year of inhaled corticosteroids were longer, and FE_{NO} was lower in patients with a history of pneumonia than in those without (upper-respiratory symptoms and nighttime awakening: 63% vs. 42% and 13.2% vs. 3.9%, p < .05; days/year of inhaled corticosteroids: 59.8 (95% CI: 45.8–78.0) vs. 42.6 (95% CI: 37.1–48.9), p < .05; FE_{NO} : 20.6 (95% CI: 15.2–28.0) vs. 31.1 (95% CI: 27.0–35.8), p < .05). Clinical assessment showed a slightly higher frequency of wheeze in the past 12 months and history of bronchiolitis in children with a history of pneumonia than in those without, although both differences were statistically borderline (wheeze: 81.6% vs. 63.8%, p = .058; bronchiolitis: 18.4% vs. 7.2%, p = .072 by Fisher-corrected χ^2 test).

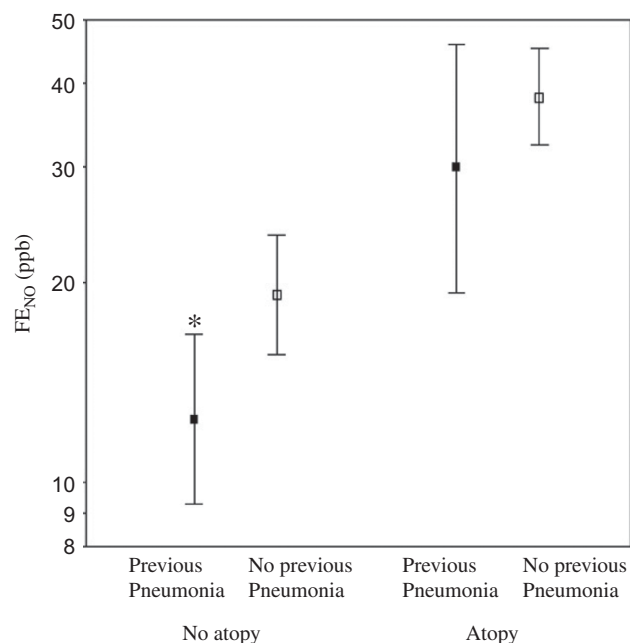


FIGURE 1.—Geometric mean FE_{NO} and 95% confidence intervals (CI) by a parent-reported history of pneumonia among non-atopic ($n = 62$) and atopic ($n = 128$) asthmatic children. Non-atopics (with vs. without previous pneumonia): 12.4 ppb, 95% CI: 9.3–16.7 vs. 19.2 ppb, 95% CI: 15.6–23.7, $*p = .020$; atopics (with vs. without previous pneumonia): 29.8 ppb, 95% CI: 19.3–46.0 vs. 38.2 ppb, 95% CI: 32.3–45.2, $p = .326$ by Mann–Whitney test.

Skin-prick test results identified 128 subjects as atopic (106 without and 22 with previous pneumonia) and 62 subjects as non-atopic (46 without and 16 with previous pneumonia). The frequency of pneumonia was similar in atopic and non-atopic asthmatic children (atopic: 17.2%, non-atopic: 25.8%; $p = .230$ by χ^2 test). No difference was found in geometric mean FE_{NO} and 95% CI among atopic subjects with or without a history of pneumonia, whereas among non-atopic subjects it differed significantly (Figure 1). No other variable differed significantly among atopic and non-atopic subjects subgrouped according to a history of pneumonia.

Among the 38 asthmatic patients with previous pneumonia, 14 fulfilled the criteria for recurrent pneumonia. All of these 14 children had their first pneumonia episode before age of 7 years and were younger than children without recurrent pneumonia (3.6 ± 1.5 vs. 5.9 ± 3.7 years, $p = .025$ by Mann–Whitney test) (Figure 2). A shorter time elapsed between the last pneumonia episode and our assessments in children with than in those without recurrent pneumonia (15.5 months, 95% CI: 8.1–29.5 vs. 24.5 months, 95% CI: 15.8–37.9, $p = .180$).

Nighttime symptoms in the past 4 weeks were more frequent, required more days/year of inhaled corticosteroids, and yielded a lower percent of predicted DLCO/VA in the 14 patients with recurrent pneumonia than in the 24 patients without previous recurrent pneumonia and the 152 patients without previous pneumonia (Table 1). Because the 14 subjects with recurrent pneumonia had their first pneumonia episode at a younger age than children without recurrent pneumonia, we

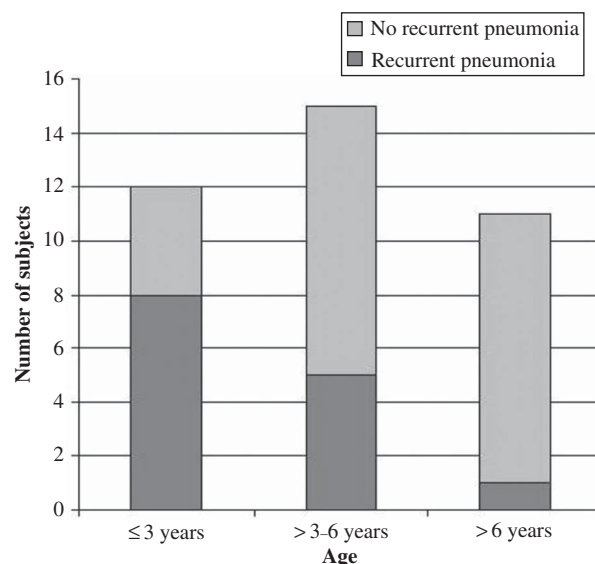


FIGURE 2.—Frequency of asthmatic children with recurrent pneumonia by age group at the first pneumonia episode.

analyzed the data again excluding the 8 subjects without recurrent pneumonia who had their first pneumonia episode after the age of 7 years. After excluding these 8 subjects, children with recurrent pneumonia still had a lower percent of predicted DLCO/VA than children without recurrent pneumonia ($91.2\% \pm 11.3$ vs. $106.0\% \pm 16.0$, $p = .005$ by Mann–Whitney test).

To exclude a history of bronchiolitis as a possible confounding factor influencing our results, we reevaluated the data including only those patients ($n = 172$) who did not have bronchiolitis (141 without pneumonia, 19 previous no recurrent pneumonia, and 12 previous recurrent pneumonia). Children with previous recurrent pneumonia still had the lowest FE_{NO} and DLCO values and needed inhaled corticosteroids for longer (Table 2).

DISCUSSION

As expected, in this cross-sectional study we found that several clinical, functional, and inflammatory variables differed markedly in children attending our outpatient clinic for asthma who had or did not have a parent-reported clinical and radiological diagnosis of pneumonia. For example, our asthmatic children with a history of pneumonia had more frequent respiratory symptoms (especially at nighttime), required more inhaled corticosteroids, and had lower FE_{NO} than asthmatic children without previous pneumonia. Despite comparable lung volumes and flows, children with a history of recurrent pneumonia also had lower diffusion capacity than asthmatic children with no recurrent pneumonia and asthmatic children without previous pneumonia. Our study therefore extends current knowledge on the clinical, functional, and inflammatory effects of recurrent pneumonia in asthmatic children suggesting that these children require more frequent corticosteroid therapy than

TABLE 1.—Characteristics of the 190 asthmatic subjects by a history of recurrent pneumonia.

Variables	No pneumonia (n = 152)	No recurrent pneumo- nia (n = 24)	Recurrent pneumonia (n = 14)
Anthropometric data			
M/F	102/50	16/8	9/5
Age (year)	10.2 ± 2.5	10.3 ± 2.4	9.7 ± 2.8
Weight (kg)	42.2 ± 16.6	40.4 ± 11.2	39.3 ± 13.5
Height (cm)	143.1 ± 17.9	144.4 ± 14.1	142.1 ± 17.3
Birthweight (g)	3375.1 ± 463.5	3287.9 ± 680.2	3307.8 ± 508.2
Gestational age (weeks)	39.2 ± 2.7	39.2 ± 2.5	38.9 ± 2.7
Atopy and respiratory health			
Positive skin-prick test	106 (69.7)	15 (62.5)	7 (50)
Wheeze in past 12 months	97 (63.8)	19 (79.2)	12 (85.7)
Age at the first pneumonia episode	—	5.9 ± 3.7	3.6 ± 1.5**
Lower respiratory symptoms in past 4 weeks	60 (39.5)	8 (33.3)	7 (50)
Upper-respiratory symptoms in past 4 weeks	64 (42)	15 (62.5)	9 (64.2)
Nighttime awakening with symptoms	6 (3.9)	2 (8.3)	3 (21.4)*
History of bronchiolitis	11 (7.2)	5 (20.8)	2 (14.3)
Passive smoke at home	53 (34.9)	11 (45.8)	7 (50)
Passive smoke during pregnancy	9 (5.9)	3 (17.6)	2 (18.2)
Days/year inhaled corticosteroid therapy	42.6 (37.1–48.9)	53.2 (37.5–75.4)	73.1 (47.2–113.4)*
Lung function			
FEV ₁ %	95.8 ± 13.6	98.97 ± 15.44	94.8 ± 14.6
FVC%	102.6 ± 12.6	102.6 ± 14.44	99.6 ± 12.5
FEV ₁ /FVC%	83.13 ± 7.57	86.0 ± 8.36	84.8 ± 6.19
FEF _{25–75} %	81.5 ± 25.5	89.8 ± 26.73	81.4 ± 20.8
FRC%	97.9 ± 16.7	104.2 ± 21.67	101.8 ± 24.4
TLC%	99.8 ± 15.0	101.6 ± 14.08	99.5 ± 16.8
RV/TLC%	20.9 ± 7.5	22.2 ± 8.4	21.8 ± 7.7
DLCO/VA%	97.9 ± 18.6	104.48 ± 14.7	91.18 ± 11.34 **
FE _{NO}	31.1 (27–35.8)	21.31 (14.2–31.9)	19.5 (11.5–32.8)*

Notes: Lung function variables are expressed as percent of predicted. Values are numbers with percentages, arithmetic means ± SD or geometric means (FE_{NO} and days/year of inhaled corticosteroids) and 95% confidence intervals. FEV₁, forced expiratory volume in 1 second; FEF_{25–75}, mid-maximal expiratory flow; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; DLCO/VA, diffusion capacity corrected by alveolar volume.

**p* < .05 recurrent pneumonia versus no previous pneumonia by χ^2 test (nighttime awakening) or by one-way ANOVA with post hoc Scheffe's test (FE_{NO} and days/year of inhaled corticosteroids).

***p* < .05 recurrent pneumonia versus no recurrent pneumonia by Mann–Whitney test (age at the first pneumonia episode) or by one-way ANOVA with post hoc Scheffe's test (DLCO/VA).

TABLE 2.—Main findings in the 172 asthmatic subjects without a history of bronchiolitis by a history of recurrent pneumonia.

Variables	No pneumonia (n = 141)	No recurrent pneumonia (n = 19)	Recurrent pneumonia (n = 12)
M/F	94/47	14/58	7/5
Age (years)	10.1 ± 2.6	10.1 ± 2.7	9.5 ± 3.3
Positive skin-prick test	100.0 (70.9)	12 (63.2)	6 (50)
Wheeze in past 12 months	89 (63.1)	14 (73.7)	10 (83.3)
Age at the first pneumonia episode	—	6.6 ± 3.8	3.6 ± 1.6**
Lower respiratory symptoms in past 4 weeks	54 (38.3)	8 (42.1)	6 (50)
Upper-respiratory symptoms in past 4 weeks	60 (42.6)	11 (57.9)	7 (58.3)
Nighttime awakening with symptoms	4 (2.8)	1 (5.3)	2 (16.7)
Days/year inhaled corticosteroid therapy	42.1 (36.6–48.5)	46.1 (32.8–64.8)	78.2 (47.0–129.9)*
DLCO/VA%	97.0 ± 18.5	102.8 ± 15.7	90.4 ± 11.9**
FE _{NO}	31.7 (27.5–36.6)	19.5 (12.5–30.4)	17.6 (9.7–31.8)*

Notes: Lung function variables are expressed as percent of predicted. Values are numbers with percentages, arithmetic means ± SD or geometric means (FE_{NO} and days/year of inhaled corticosteroids), and 95% confidence intervals.

**p* < .05 recurrent pneumonia versus no previous pneumonia by χ^2 test (nighttime awakening) or by one-way ANOVA with post hoc Scheffe's test (FE_{NO} and days/year of inhaled corticosteroids).

***p* < .05 recurrent pneumonia versus no recurrent pneumonia by Mann–Whitney test (age at the first pneumonia episode) or by one-way ANOVA with post hoc Scheffe's test (DLCO/VA).

those without previous pneumonia, regardless of a history of bronchiolitis.

The clinical findings in our asthmatic patients with previous pneumonia are in keeping with a recent study in 103 children followed for almost 6 years after hospital admission for community acquired pneumonia

(24). In this study, preexisting asthma coexisting with community acquired pneumonia conferred the greatest risk of persistent cough (24). Unfortunately, because we did not assess preexisting asthma we cannot fully compare findings in the two studies. The high frequency of respiratory symptoms and increased need for inhaled

corticosteroid therapy in our asthmatic children with recurrent pneumonia could depend on their repeated pulmonary infections and young age at the first pneumonia episode. Several studies suggest that pneumonia-induced damage and bronchial hyperreactivity can be more severe when they start at an early lung-developmental stage (25–29).

A possibly controversial finding is our patients' normal lung volumes and flows regardless of a history of pneumonia at any age. In contrast, studies in unselected populations report diminished lung function in childhood after pneumonia onset at an early age (6–8). We found that measurements of atopic-airway inflammation (FE_{NO}) and pulmonary gas diffusion (DLCO/VA) proved better than lung function tests in characterizing children with recurrent lung infections, in whom chronic respiratory disease is likely to develop in their adulthood (30–32). Even though recurrent respiratory symptoms suggest the need to use inhaled corticosteroids daily, because corticosteroid therapy decreases FE_{NO} levels (21) our patients were allowed to use rescue medication with inhaled beta-agonists only in the 2 weeks preceding the study.

Children whose parents reported previous pneumonia had similar gestational age and birth weight but suffered more frequently from bronchiolitis than patients without previous pneumonia, although the differences were not statistically significant. Our study was not designed to assess the impact of bronchiolitis on pneumonia. This aim could be reached with a larger sample because bronchiolitis is a known risk factor for long-term respiratory disease (2, 7, 33). Notwithstanding this limitation, analyzing the data only for those children who did not have bronchiolitis left our results almost unchanged, suggesting that a history of bronchiolitis had no influence on the effects of recurrent pneumonia in these asthmatic children.

In our small study sample of 128 atopic and 62 non-atopic outpatients, we found a similar frequency of pneumonia. Others have reported a comparable prevalence of positive skin-prick tests or mean IgE between subjects who had pneumonia, other lower respiratory tract illness without pneumonia, or no lower respiratory tract illness in a birth cohort of 888 children (6). Comparing atopic and non-atopic asthmatic Chilean children, the same investigators found that non-atopic asthmatic children more frequently had a history of pneumonia and tobacco consumption at home (34). None of these characteristics distinguished our atopic from our non-atopic asthmatic children. Our results presumably differed from those reported by others owing to geographical, environmental (particularly tobacco smoke exposure), and ethnic characteristics.

To make sure that we provided reliable data on how previous pneumonia influences atopic-airway inflammation as measured by FE_{NO} , we explicitly excluded confounding from atopy. Atopic asthmatic children tend to have elevated FE_{NO} levels, especially when they have increased numbers of airway or blood eosinophils (17,

35, 36). Conversely, non-atopic asthmatic children tend to have low FE_{NO} levels matching those measured in healthy children (17, 37). In these non-atopic patients, the predominant inflammatory cell pattern is neutrophilic (38–40). To avoid the influence of atopy, we separately compared FE_{NO} levels by a history of pneumonia among atopic and non-atopic patients. Non-atopic patients with a history of pneumonia had the lowest FE_{NO} levels. Although the underlying mechanisms remain unclear, these non-atopic children could have downregulated inducible NO synthase in their bronchial epithelium even before their first pneumonia episode. Support for this mechanism comes from recent evidence suggesting that pharmacological inhibition of inducible NO synthase can reduce FE_{NO} without inducing changes in airway hyperreactivity (41).

We found that children whose parent-reported pneumonia episodes could be classified as "recurrent" had lower, though only slightly lower pulmonary gas diffusion (DLCO/VA) than children with no recurrent pneumonia or those who never had pneumonia. In their study investigating the frequency of pulmonary involvement after pneumonia in non-asthmatic children, Marc et al. reported abnormally low pulmonary gas diffusion in some children 6 months after they recovered from *Mycoplasma pneumoniae* infections even if they remained free of respiratory symptoms and had normal lung volumes and spirometric tests. Their reduced pulmonary gas diffusion was related to delayed and short macrolide therapy (10). Collectively, current knowledge therefore suggests that the eventual link between mild pulmonary gas diffusion impairment (reduced DLCO/VA) after pneumonia and chronic respiratory disease in adulthood deserves further investigation.

Our results raise the question whether a preexisting condition could facilitate both recurrent pneumonia and asthma. Some evidence links early life viral respiratory infections with persistent wheeze and asthma. These infections elicit a predominant neutrophilic acute response, sometimes with a long-lasting airway inflammatory response (38). Recurrent pneumonia in asthmatic children could reflect a failure to overcome prolonged viral-induced inflammation.

Our study has several limitations. For example, compared with clinical and radiological assessment during the patient's disease, parent-reported pneumonia yields retrospective and relatively raw information. Neither did we assess respiratory symptoms and lung function longitudinally. Hence, we have no information on whether asthma in these children developed before or after their first pneumonia episode. Asthma-like symptoms can start either before or after hospitalization for pneumonia (1, 3). A follow-up study possibly describing the onset times for asthma and pneumonia could better distinguish our population from those previously studied. Nonetheless, parent reports on previous pneumonia, especially on recurrent disease, allowed us to identify a subset of asthmatic children with frequent symptoms and characteristic inflammatory and functional conditions.

CONCLUSION

A parent-reported history of pneumonia, especially recurrent pneumonia, increases the likelihood of respiratory symptoms needing therapy in asthmatic children and adolescents. How it does so remains unclear. Despite normal lung function (lung volumes and flows), these patients often have mild pulmonary gas diffusion impairment (DLCO/VA) and inflammatory changes unreflected by the commonly used atopic-airway inflammatory marker (FENO), suggesting neutrophilic inflammation. Whether these asthmatic children are a phenotype at high risk of chronic lung disease in adulthood awaits an answer from further longitudinal studies.

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DECLARATION OF INTEREST

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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