Can acute *Chlamydia pneumoniae* respiratory tract infection initiate chronic asthma?

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Background: *Chlamydia pneumoniae* infection can cause acute respiratory illnesses (including sinusitis, bronchitis, and pneumonia) that are sometimes associated with wheezing. Little is known about whether acute infection in a previously unexposed, nonasthmatic individual can produce persistent wheezing leading to a diagnosis of chronic asthma.

Objective: We sought to determine whether patients with acute *C. pneumoniae* respiratory tract infections would develop chronic asthma.

Methods: A consecutive series of 163 primary care outpatient adolescents and adults (average age 43, 45% male) who had acute wheezing illnesses or chronic asthma were evaluated for *C. pneumoniae* infection by serologic testing. A subgroup of these patients also had nasopharyngeal cultures for *C. pneumoniae*.

Results: Twenty patients (12%) were diagnosed with *C. pneumoniae* infection defined by serology (15), culture isolation (3), or both (2). Of these 20, 10 patients wheezed for the first time and 6 of them subsequently developed chronic asthma (5) or chronic bronchitis (1) along with a serologic profile suggesting chronic infection. The other 10 patients diagnosed with *C. pneumoniae* infection already had a diagnosis of chronic asthma. In these patients initial serologic findings suggested chronic rather than acute infection.

Conclusions: Acute *C. pneumoniae* respiratory tract infections in previously unexposed, nonasthmatic individuals can result in chronic asthma. Patients previously diagnosed with chronic asthma should be evaluated for possible chronic *C. pneumoniae* infection.

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INTRODUCTION

Asthma is recognized as a chronic inflammatory bronchial condition of uncertain etiology. Unexplained worldwide increases in asthma morbidity and mortality support the need to consider novel potential underlying causes for asthma. An atopic disposition has long been recognized as an important predisposing factor associated with some forms of asthma. For example, most children with asthma have positive skin tests with one or more common aeroallergens. In adults with asthma, skin test positivity is not present as often, and the onset of asthma frequently is associated with antecedent upper and lower respiratory illnesses.[1–4]

Acute respiratory infections can trigger asthma exacerbations in all age groups.[5–7] Many studies[1–4,8–10] have demonstrated an association of previous acute respiratory illnesses and asthma. It has even been suggested that acute respiratory tract infections can induce or cause the onset of asthma and other obstructive lung disorders.[8]

Chlamydia pneumoniae is an established cause for acute respiratory illnesses including sinusitis, bronchitis, and pneumonia.[11,12] Infection by chlamydia species can persist in target organs, and seroepidemiologic studies suggest that chronic *C. pneumoniae* respiratory infection may contribute to symptoms of chronic obstructive pulmonary disease[13,14] and asthma.[15,16] A few case reports of acute *C. pneumoniae* infection preceding a diagnosis of chronic asthmatic bronchitis[17,18] have suggested that such infection can initiate asthma, but the clinical evidence supporting this possibility is sparse. In this study, our primary goal was to determine whether previously asymptomatic patients would develop chronic asthma after an initial wheezing illness caused by acute *C. pneumoniae* infection. A second goal was to determine whether patients with chronic asthma would have diagnostic findings compatible with chronic *C. pneumoniae* infection.

MATERIALS AND METHODS

The study population was drawn from a community-based family practice office located in a midsized midwestern city with a population which is mostly white and middle class. The study population consisted of a consecutive series of 163 adolescent and adult primary care outpatients with reactive airways disease syndromes (defined below) first encountered between 1988 and 1994. Data obtained from these patients by the principal investigator (D.L.H., a clinician in fulltime private practice) were prospectively entered into a computerized database. The data included standard demographic, clinical and spirometric measures, as well as results of *C. pneumoniae* testing. Age of onset of first symptoms attributable to reactive airways (irrespective of date of diagnosis of asthma which may have been later) was also recorded. Ten patients, each of whom denied previous wheezing and was evaluated during the initial wheezing episode, were classified as having de novo wheezing. One hundred fifty-three patients who reported previous wheezing episodes were classified as having chronic asthma (see below).

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The medical records of all patients meeting criteria for *C. pneumoniae* infection were completely reviewed to document sequelae.

Reactive Airways Syndromes

Patients with a first-ever wheezing episode were classified as having de novo wheezing. Patients with chronic asthma were classified either as acute asthmatic bronchitis (AAB), chronic asthma (CA) or asthma with chronic airways obstruction (AS-CAO). AAB was defined as symptomatic wheezing during episodes of acute infectious bronchitis.[19] Chronic asthma (CA) was diagnosed according to American Thoracic Society (ATS) guidelines.[20] Asthma with chronic airways obstruction was defined as a subgroup of patients with chronic asthma that had evidence for co-existing irreversible airways obstruction.[21] Clinical diagnoses that may be synonymous with AS-CAO include "chronic obstructive pulmonary disease with asthma" or "chronic asthmatic bronchitis" if sputum production is a prominent feature.

Spirometric Testing

Spirometric testing was performed using a Gould spirometer (System 21, Gould Medical Products Inc., Dayton, Ohio). Diagnoses of CA and AS-CAO were supported by ATS spirometric criteria, namely a 12% or greater increase in FEV_1 ($\geq$200 mL) after treatment.[22] Acute asthmatic bronchitis was diagnosed in patients with reactive airways symptoms (nocturnal chest tightness, wheeze and shortness of breath) who may have had lesser degrees of reversibility.[19]

Microbiologic and Serologic Methods

Chlamydia pneumoniae-specific IgM and total Ig (combined IgM, IgA, and IgG) antibodies were measured in all patients using a microimmunofluorescence (MIF) test.[23] IgG and IgA antibodies were measured individually in a subgroup of patients for whom sera were available. Presence of IgA was determined after absorption of IgG from serum.[24] Culture isolation in selected patients was attempted from nasopharyngeal swabs using Hep-2 cells.[25] All microbiologic and serologic testing was performed by laboratory personnel who were unaware of the clinical features of the patients being studied.

Criteria for Diagnosing C. pneumoniae *Infection*

Chlamydia pneumoniae infection was diagnosed if the organism was detected one or more times by culture, or if a patient met accepted serologic criteria for acute infection: an IgM antibody titer of 1:16 or greater, a fourfold or greater rise in IgM, IgG or total Ig titer between acute and convalescent sera, or a single IgG or total Ig titer of 1:512 or greater.[11] Criteria for an acute primary (first exposure) *C. pneumoniae* infection include the presence of IgM antibody in a titer of 1:16 or greater whereas IgM is absent in acute secondary infection (re-exposure).[26] In the setting of acute bronchitis or pneumonia, a single IgG titer of 1:512 or greater correlates with organism identification and is also indicative of acute infection.[27]

RESULTS

Data were recorded on 163 patients, aged 15 years and older, with reactive airways disease syndromes encountered over a 9-year (1988–1996) observation period (Tables 1 and 2). Study subjects were mainly adults averaging 43 years of age; 45% were male and 34% were current smokers. Ten patients were first evaluated during an initial wheezing episode (Table 1). The remaining 153 patients (Table 2) had recurrent acute wheezing or chronic wheezing. Of these 153, AAB was diagnosed in 21%, CA was present in 64%, and AS-CAO in the remaining 15%.

Chlamydia pneumoniae *Infection*

Chlamydia pneumoniae infection was diagnosed in 20 (12%) of 163 study subjects on the basis of the antibody serologic profile (15 patients), a positive culture (3 patients) or both (2 patients). Ten of these patients (50%) had de novo wheezing (Table 3) and 10 (50%) had chronic asthma (Table 4).

Chlamydia pneumoniae *Infection and de novo Wheezing (Table 3)*

All 10 patients with de novo wheezing met criteria for an acute primary infection (IgM antibody, 8 patients) or an acute reinfection (4-fold or greater IgG titer rise without IgM antibody, 2 patients). Four of these ten patients (Table 3, patients 1–4) had a single episode of wheezing associated with a respiratory illness (bronchitis or pneumonia) and did not develop chronic asthma during the 9-year observation period (1988–1996). Sera were unavailable for measurement of IgA antibodies in these four patients.

Of the remaining 6 patients, 5 developed chronic asthma and 1 developed chronic bronchitis during long-term followup after the initial wheezing episode. The only patient (case 8) evaluated within 1 week of onset of de novo wheezing lacked detectable serum IgA initially but had detectable IgA antibody later when asthma was diagnosed. The other 5 patients with chronic sequelae (asthma or chronic bronchitis) had IgA antibodies detected persistently.

Case 9 developed community-acquired pneumonia with wheezing and

Table 1. Characteristics of 10 Patients with a First Ever (de novo) Wheezing Episode

No. patients	10
Age: mean (range)	46 (35–49)
Sex: % male	50
Current smokers: % (no with data recorded)	56 (9)
Spirometry*	
Prebronchodilator FEV_1: mean (median) %predicted	62 (63)
Post-bronchodilator FEV_1: mean (median) %predicted	79 (81)

* For six patients who developed chronic asthma or chronic bronchitis. Pulmonary function results were not obtained for four patients who did not develop chronic wheezing.

Table 2. Characteristics of 153 Patients with Recurrent Acute Wheezing or Chronic Wheezing

	Clinical Syndrome*		
	AAB	CA	AS-CAO
No patients (%)	32 (21)	98 (64)	23 (15)
Age: Mean (range)†	37 (15–66)	38 (7–78)	66 (46–80)
Sex: % Male	41	46	43
Current smokers: % (No with data recorded)¶	40 (30)	24 (86)	55 (22)
Spirometry:			
Prebronchodilator FEV_1: mean (median) %predicted†	82 (84)	73 (73)	43 (42)
Post-bronchodilator FEV_1: mean (median) %predicted†	91 (92)	89 (88)	55 (50)
Post-bronchodilator FEV_1/FVC: mean (median)†	80 (81)	78 (78)	54 (55)

* AAB: acute asthmatic bronchitis; CA: chronic asthma; AS-CAO: asthma with chronic airways obstruction. See "Methods" for definitions.
† Groups differ by $P \leq .0001$.
¶ Groups differ by $P < .02$.

received a 2-week treatment course with a macrolide antibiotic for serologically diagnosed acute *C. pneumoniae* infection. He subsequently developed a chronic productive cough diagnosed as chronic bronchitis. He also had persistent detection of IgA antibody, and *C. pneumoniae* was isolated during the chronic phase of his illness.

Chlamydia pneumoniae *Infection and Chronic Asthma (Table 4)*

Of the 153 patients with chronic asthma, 10 (7%) had strong evidence for *C. pneumoniae* infection (Table 4). Seven of these 10 patients had high serum IgG antibody titers that met or exceeded the 1:512 threshold which has been considered evidence of current or recent infection.[11] IgG titers in the remaining 3 chronic asthma patients (cases 5–7) did not achieve the diagnostic threshold of 1:512 but these patients were culture positive on one or more occasions. *Chlamydia pneumoniae*-specific serum IgA antibody titers were measured in 9 of these 10 patients. High titer IgA antibody was detected in all sera (21 sera in 9 patients) tested.

DISCUSSION

One major finding of this study is that half (5 of 10) of the patients with first ever wheezing and acute *C. pneumoniae* infection diagnosed by standard serologic criteria subsequently developed chronic asthma (Table 3). This finding supports and extends previous observations that acute *C. pneumoniae* infection can lead to the development of chronic asthma. In 1989 Frydén et al[17] first reported a case of serologically diagnosed acute *C. pneumoniae* infection (then called TWAR) that progressed to chronic asthmatic bronchitis. Hammerschlag et al[18] reported a similar culture-confirmed case in 1992. Thom et al[27] also have reported an adult with persistent new reactive airway disease following acute *C. pneumoniae* infection.

A variety of respiratory pathogens including respiratory viruses, *Mycoplasma pneumoniae* and *C. pneumoniae* can trigger acute wheezing illnesses.[27] Results of the current study provide evidence that acute wheezing illnesses due to *C. pneumoniae* infection can develop into chronic asthma in previously asymptomatic individuals. In a preliminary report from another study, *C. pneumoniae* was isolated in 9 of 16 patients after clinical resolution of acute bronchitis and pneumonia following standard antimicrobial therapy,[28] suggesting that persistent infection may be common after conventional courses of antibiotics. In our series, post-treatment cultures of the nasopharynx were positive for *C. pneumoniae* in 3 study subjects during the development of chronic asthma or chronic bronchitis symptoms (Tables 3 and 4). These culture isolations support the hypothesis that acute chlamydial infections can persist and may be associated with the development of chronic respiratory sequelae including asthma and chronic bronchitis. The known propensity for chlamydial infection to become chronic and to produce immunopathologic damage in target organs lends plausibility to this hypothesis.

Because the patients were not composed of a random sample of the general population, the rate of development of chronic sequelae after acute *C. pneumoniae* infection cannot be determined from the results of this study. The incidence of adult-onset asthma is 1 per 1,000 adults per year.[1] Even assuming that patients will seek medical care for de novo asthma symptoms, this condition will be encountered infrequently in medical care settings.

A secondary goal of this study was to determine whether patients with established chronic asthma would have a serologic profile compatible with chronic *C. pneumoniae* infection. Indeed, ten patients with chronic asthma met accepted serologic criteria for a current or recent infection on the basis of an Ig or IgG antibody titer of 1:512 or greater or because they were culture positive (Table 4). Notably, none of these patients had a 4-fold or greater rise in titer compatible with an acute primary or secondary infection.

Serologic criteria for chronic infection are not well established but have been suggested to include the presence of IgG (or total Ig) accompanied by an IgA titer of 1:16 or greater in the context of chronic respiratory illnesses such as chronic bronchitis[13] and asthma.[29] Overall, 63 of 125 patients (50%) with a diagnosis of chronic asthma in this study population had an IgA antibody titer of ≥1:16, including 44% of 110 chronic asthma patients without additional strong evidence for infection. IgA antibodies against *C. pneumoniae* have been associated with adult-onset asthma in a case-control study,[30] but further investigation is re-

Table 3. Clinical Data in 10 Patients with *Chlamydia pneumoniae* Infection and de novo Wheezing*

Age, Sex	Date	Total Ig	IgM	IgG	IgA	Clinical Description
1) 37 M	10/13/88 (4d)†	128	16			Bronchitis with wheezing
	11/14/88	128	0			
	9/13/89	128	0			No asthma
2) 39 M	11/21/88 (5d)	0	16			Laryngitis, bronchitis with wheezing
	12/23/88	256	128			
	4/17/89	64	16			
	6/29/89	32	0			No asthma
3) 59 F	3/9/89 (7d)	16	32			Pneumonia with wheezing
	4/3/89	256	512			
	7/28/89	64	64			
	11/27/89	32	0			No asthma
4) 35 F	8/22/89 (24d)	512	0			Bronchitis with wheezing¶
	10/16/89	4096	0			
	9/18/91	256	0			No asthma
5) 55 M	1/26/89 (4d)	64	16			COPD, pneumonia with wheezing
	1/10/92	512	0	256	256	Asthma diagnosed
	2/6/92	256	0	256	256	
6) 47 F	3/21/89 (48d)	256	16			Bronchitis with wheezing
	4/21/89	256	0			Persistent wheezing
	9/16/89	256	0			Asthma diagnosed
	2/3/92	256	0	256	16	
	3/5/92	512	0	256	16	
	2/18/93	256	0	512	16	
	5/26/93	256	0	256	16	
	1/17/96	256	0		32	
7) 51 M	4/24/90 (35d)	256	64			COPD, bronchitis with wheezing
	5/21/90	128	128			Persistent wheezing
	11/11/91	256	0	128	16	Asthma diagnosed
	12/11/91	256	0	128	16	
	3/6/92	256	0	128	16	
	2/19/93	256	0	128	16	
8) 39 F	10/29/93 (3d)	32	0		<8	Bronchitis with wheezing
	3/24/94	128	0		16	Asthma diagnosed
9) 56 M	4/11/94 (70d)	512	256		≥64	Community-acquired pneumonia with wheezing
	6/17/94	1024	32		≥64	Chronic bronchitis diagnosed¶
	3/31/95	512	8		64	
10) 35 F	7/7/94 (66d)	1024	128		≥64	Bronchitis with wheezing
	8/5/94	1024	64		≥64	Persistent wheezing
	10/17/94	1024	16		≥64	
	12/19/94	1024	8		≥64	Asthma diagnosed

* Defined as the first ever wheezing episode experienced by the patient. Missing IgG and IgA results were due to unavailability of sera.
† Days post-illness onset.
¶ Culture positive.

quired before IgA can be recommended as a diagnostic test for chronic infection.

Since *C. pneumoniae* seropositive patients with recent-onset asthma may benefit from antimicrobial treatment,[31] we suggest that patients with newly diagnosed asthma should be evaluated for *C. pneumoniae* infection. Antimicrobial treatment is also beneficial in some cases of severe asthma associated with serologic titers suggesting chlamydial infection.[32] Patients previously diagnosed with chronic asthma and not well controlled on conventional antiasthma medications should also be evaluated for *C. pneumoniae* infection.

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Table 4. Clinical Data in 10 Patients with *Chlamydia pneumoniae* Infection and Chronic Asthma*

Age, Sex	Date	Total Ig	IgM	IgG	IgA	Clinical Description**
1) 64 M	11/21/89 (?y)†	512	0			AS-CAO
	12/21/89	512	0			
	1/9/90	512	0			
	6/7/90	512	0			
2) 72 F	10/25/91 (7y)	512	0	512	128	AS-CAO
	10/17/92	256	0	256	128	
	12/17/92	256	0	256	128	
	6/10/93	256	0	256	128	
3) 77 M	2/13/92 (2y)	512	0	512	128	AS-CAO
4) 43 M	11/6/92 (5y)	512	0	256	32	CA
	1/15/93	512	0	512	32	
5) 44 F	5/28/93 (4y)	256	0	128	256	CA¶¶
	10/27/93	256	0	128	256	
	9/27/95				≥64	
	3/14/96				≥64	
6) 46 M	4/22/93 (14y)	16	0		16	CA¶
7) 40 M	7/15/93 (6y)	128	0	64	64	CA¶¶¶
	10/4/93	128	0	64	64	
	3/11/94	64	0		≥64	
	6/3/94	64	0		64	
	11/18/94				64	
	10/17/95				32	
8) 48 M	2/11/94 (40+y)	1024	0		64	CA
	11/18/94	1024	0			
	10/17/95	1024	0			
9) 66 M	2/16/94 (1y)	512	0		64	CA
	12/18/94	512	0			
10) 48 F	11/2/94 (2y)	512	0			CA
	2/18/95				16	

* Asthma of ≥1 year duration when serologic evaluation undertaken. Missing IgG and IgA results were due to unavailability of sera.
† Years post-asthma diagnosis.
** AS-CAO: asthma with chronic airways obstruction, CA: chronic asthma (see "Methods" for definitions).
¶ Culture positive (multiple symbols = number of positive cultures over time).

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