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Acute exacerbations of asthma in adults: role of *Chlamydia Pneumoniae* infection

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Acute exacerbations of asthma in adults: role of Chlamydia Pneumoniae *infection. L. Allegra, F. Blasi, S. Centanni, R. Cosentini, F. Denti, R. Raccanelli, P. Tarsia, V. Valenti. ©ERS Journals Ltd 1994.*

ABSTRACT: Respiratory infections precipitate wheezing in many asthmatic patients and may be involved in the aetiopathogenesis of asthma. Several studies have demonstrated that viral infections may provoke asthma. Bacterial infections seem to play a minor role. However, *Chlamydia pneumoniae* has been recently reported as a possible cause of asthma. The aim of the present study was to evaluate the role of *C. pneumoniae* infection in acute exacerbations of asthma in adults.

Seventy four adult out-patients with a diagnosis of acute exacerbation of asthma were studied. Acute and convalescent (≥3 weeks) serological determination of antibodies to cytomegalovirus, respiratory syncytial virus, adenovirus, influenza A and B, parainfluenza 1 and 3, *Mycoplasma pneumoniae* and *Legionella pneumophila* were performed by means of immunofluorescence tests. *C. pneumoniae* specific antibodies were detected by two microimmunofluorescence tests using a specific antigen (TW-183) and a kit with three chlamydial antigens. Pharyngeal swab specimens were also obtained for *C. pneumoniae* identification. Samples for bacterial culture were obtained in patients with productive cough (15 out of 74 patients).

Fifteen patients (20%) presented seroconversion to at least one of the studied pathogens. Seven were found to be infected by virus, six by *C. pneumoniae* alone, and one by *M. pneumoniae*. One more patient showed seroconversion to *C. pneumoniae* and cytomegalovirus. In one out of 15 patients with productive cough, sputum culture yielded *H. influenzae* 10^5 colony forming units (cfu)·ml^{-1}.

In conclusion, viruses were involved in about 9% of asthma attacks, while acute infection with intracellular bacteria was detected in 11% of cases. Notably, most of the latter (7 out of 8 cases) were due to *C. pneumoniae* infection. Further studies are needed in order to elucidate whether *C. pneumoniae* plays a role only as precipitant of asthma symptoms or is actually one of the causes of asthma.

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The association between respiratory tract infections and acute exacerbation of asthma has long been recognized [1]. Influenza and common cold frequently precede asthma attacks, suggesting an aetiopathogenetic link between viral infection and acute exacerbation. This observation has been inferred from several epidemiological studies mainly conducted in the paediatric population [2, 3]. The role of viruses as precipitants of asthma symptoms in adults seems to be less relevant than in children but epidemiological data are conflicting. BEASLEY *et al.* [4] reported an aetiological role for viruses in 10% of acute exacerbations of asthma, with a higher incidence (36%) in severe attacks. However, SOKHANDAN *et al.* [5] found no evidence of viral infection in a small group of patients with acute asthma exacerbations. More recently, NICHOLSON *et al.* [6] reported that 89% of patients with cold had asthma symptoms. Moreover, the authors found that 44% of episodes with reductions in mean peak expiratory flow rate ≥50 *l*·min^{-1} were associated with laboratory confirmed infections, rhinoviruses and coronaviruses being predominant.

Bacterial infection seems to play a minor role in asthma attacks [7], although some evidence has drawn attention to *Mycoplasma pneumoniae* and, recently, to *Chlamydia pneumoniae* [8, 9]. *C. pneumoniae* plays an important aetiopathogenetic role in the development of acute respiratory tract infections [10, 11], and HAHN *et al.* [9] reported a possible association of *C. pneumoniae* infection with wheezing and adult-onset asthma. The results of this study showed a dose-response relationship between specific antibody titre level and prevalence of wheeze; moreover, 4 out of 19 patients with acute *C. pneumoniae* infection subsequently developed asthma, and four others had exacerbation of previously diagnosed asthma.

The aim of the present study was to evaluate the role of respiratory tract infections, and particularly *C. pneumoniae,* in acute exacerbations of asthma in adults.

Methods

Between January 1992 and June 1993, 74 consecutive adult out-patients (23 males and 51 females; mean age 42 yrs, range 17–54 yrs) with a diagnosis of acute exacerbation of asthma were enrolled in the study. All patients were recruited through an allergy clinic. Fifty seven subjects had skin prick test positive for at least one common antigen, whilst 17 were suffering from intrinsic asthma.

All patients had mild to moderate asthma with sporadic use of $beta_2$-agonists and hyperreactivity to aspecific stimuli. Table 1 shows mean basal pulmonary function data of the enrolled patients.

Acute exacerbation was defined as: reported increase in asthma symptoms and/or increase in use of $beta_2$-agonists, and objective evidence of wheezing, with fall of forced expiratory volume in one second FEV_1 value (>20%), with or without increase in dyspnoea and presence of sputum.

At enrolment, a serological determination of specific antibodies (immunoglobulin G (IgG)) to cytomegalovirus, respiratory syncytial virus, adenovirus, influenza A and B, and parainfluenza 1 and 3, by means of a immunofluorescence test (BIOS, GmbH, Labordiagnostik, Munchen, Germany) was performed for each patient. At least three weeks after enrolment, serological determinations were repeated. A fourfold rise in antibody titre was required as evidence of infection for the above tests.

Mycoplasma pneumoniae and *Legionella pneumophila* antibody titre (immunoglobulin M (IgM) and IgG) was determined by an immunofluorescence test. *C. pneumoniae* specific antibodies (IgG and IgM) were detected by a microimmunofluorescence assay using two tests: one with a specific antigen (TW-183) prepared by the Washington Research Foundation, Seattle, USA; and the second using a Labsystems kit (Helsinki, Finland) composed of slides with 21 "wells" dotted with three chlamydial antigens *(Chlamydia pneumoniae, Chlamydia trachomatis* and *Chlamydia psittaci).*

Table 1. – Mean basal pulmonary function data of asthmatic patients enrolled in the study

FEV_1 *l*	3.01±0.78
FEV_1 % pred	91±11
FVC *l*	3.8±1.04
FVC % pred	98±14
FEV_1/FVC % pred	95±12

Data are presented as mean±SD. FEV_1: forced expiratory volume in one second; % pred: percentage of predicted; FVC: forced vital capacity.

Microimmunofluorescence results were classified as reported previously [12]. For each patient all the above-mentioned serological tests were performed in parallel on the same sample.

In all patients, an indirect immunofluorescence test (Cellabs, Brookvale, Australia) on pharyngeal swab specimens for *C. pneumoniae* identification was also performed; all tests were run in duplicate.

In patients with productive cough (15 out of 74 patients) samples for bacterial culture were obtained. Informed consent to participate to the study was obtained from all subjects. The study was approved by the Ethics Committee of the University of Milan.

Results

Fifteen patients (20%) presented seroconversion to at least one of the studied pathogens. Seven (9%) were found to be infected by virus (4 influenza, 2 parainfluenza, 1 adenovirus) (table 2), 6 (8%) by *C. pneumoniae* alone, and 1 (2%) by *M. pneumoniae*. One more patient showed seroconversion to *C. pneumoniae* and high IgG titre (1:80) to cytomegalovirus. In 2 out of 7 patients with *C. pneumoniae* seroconversion, the pathogen was also identified in pharyngeal swab specimens (table 3).

No cases of *C. trachomatis* or *C. psittaci* were found, and no significant differences in the serological results for *C. pneumoniae* were observed between the two methods employed for the identification of this agent.

In one out of 15 patients with productive cough, sputum culture yielded *Haemophilus influenzae* 10^5 colony forming units (cfu)·ml^{-1}.

Table 2. – Demographic characteristics and serological data in patients with acute exacerbation of asthma due to viral infection

Patient No./Sex	Age yrs	Pathogen	Serum samples Days after onset	IgG titre
1/M	35	Adenovirus	2	<1:10
			17	1:20
			26	1:40
2/F	38	Influenza	1	1:10
			29	1:160
3/F	25	Influenza	3	1:10
			15	1:40
			20	1:40
4/F	41	Influenza	3	<1:10
			19	1:80
5/F	36	Influenza	7	1:20
			16	1:80
6/M	28	Parainfluenza	3	<1:10
			21	1:80
7/F	47	Parainfluenza	8	1:20
			25	1:80

M: male; F: female; IgG: immunoglobin G.

Table 3. – Demographic characteristics and serological data in patients with acute exacerbation of asthma due to intracellular bacteria infection

Patient No.	Sex	Age yrs	Pathogen	Serum samples Days after onset	IgM/IgG titre	Pharyngeal swab †	Therapy§	Outcome
1	M	20	*Chlamydia pneumoniae*	1 45	neg/64 neg/1024	Negative	A⇒Cl	Failed⇒ Cured
2	F	19	*Chlamydia pneumoniae*	16 97	16/128 neg/256	Positive	E	Cured
3	F	54	*Chlamydia pneumoniae*	2 27	neg/128 neg/1024	Negative	C	Improved
4	F	25	*Chlamydia pneumoniae*	8 63	neg/neg 16/64	Negative	Az⇒D	Failed⇒ Cured
5	M	38	*Chlamydia pneumoniae*	10 24	neg/128 neg/512	Negative	Cl	Improved
6	F	20	*Chlamydia pneumoniae*	3 41	neg/neg neg/256	Negative	E⇒D	Relapsed ⇒Cured
7	M	31	*Chlamydia pneumoniae**	7 36	neg/neg neg/256	Positive	Cl	Cured
8	F	28	*Mycoplasma pneumoniae*	4 30	neg/neg 16/128	Negative for *Chlamydia pneumoniae*	C	Improved

†: for *Chlamydia pneumoniae* *: serology (day 7 and day 36) positive for cytomegalovirus (IgG titre 1:80); §: A=amoxycillin/clavulanate 3 g·day^{-1} (5 days); E=erythromycin 3 g·day^{-1} (2–3 weeks); C=ciprofloxacin 1 g·day^{-1} (10–12 days); Cl=Clarithromycin 750 mg·day^{-1} (2–3 weeks); Az=azithromycin 500 mg·day^{-1}; D=doxycycline 200 mg·day^{-1} (2 weeks). ⇒: followed by; F: female; M: male; neg: negative.

Discussion

Our data show that acute exacerbation of asthma was associated with infection in 20% of our patients. Interestingly, viruses were involved in about 9% of asthma attacks, whilst acute infection with intracellular bacteria was detected in 11% of cases. Notably, most of the latter (7 out of 8 cases) were due to *Chlamydia pneumoniae* infection.

The rate of identification of pathogens in our study (20%) is similar to that reported in the past [4, 8], but is remarkably lower in comparison to that found by NICHOLSON *et al*. [6] (over 40%). These authors, in fact, used new methods to identify rhinoviruses and coronaviruses. These two pathogens alone accounted for the majority of infections associated with asthma exacerbations. The low incidence of viral infection found in our study is probably due to the lack of sophisticated methods for identification of rhinoviruses and coronaviruses. On the other hand, the relatively high incidence of *Chlamydia pneumoniae* can probably be explained by the use of highly sensitive and specific techniques for the identification of this agent. The negligible incidence of Chlamydial infection in the study by NICHOLSON *et al*. [6] is probably due to the use of low sensitivity and specificity techniques (complement fixation (CF)). Furthermore, no cases of *Chlamydia psittaci* or *C. trachomatis* were identified in our study, whereas NICHOLSON *et al*. [6] reported three cases of *Chlamydia psittaci* infection. Given the low specificity of CF in discriminating between Chlamydial species, the three cases of *C. psittaci* reported could in fact be due to *C. pneumoniae*. Our results are consistent with those reported by HAHN *et al*. [9], where *C. pneumoniae* acute respiratory infection was associated with acute exacerbation of asthma, and a dose-response relationship was found between specific antibody titre and wheeze.

C. pneumoniae is a worldwide respiratory pathogen involved in about 13% of community-acquired pneumonias and 5% of acute exacerbations of chronic bronchitis in our area [10, 13]. Our preliminary data represent the first evidence of association between *C. pneumoniae* infection and asthma attacks in our country.

Atopy, air pollution and smoke appear to be strongly associated with bronchial hyperresponsiveness [14, 15]. A role for virus infection has also been suggested [1, 4, 6]. Our results add *Chlamydia pneumonia*e infection to this list. Further studies are needed in order to elucidate whether *Chlamydia pneumoniae* plays a role only as a precipitant of asthma symptoms or is actually one of the causes of asthma.

References

1. Sterk PJ. Virus-induced airway hyperresponsiveness in man. *Eur Respir J* 1993; 6: 894–902.
2. Johnston SL, Pattemore PK, Smith S, *et al*. Viral infections in exacerbations in school children with cough and wheeze: a longitudinal study. *Am Rev Respir Dis* 1992; 145: A546.
3. Pattemore PK, Johnston SL, Bardin PG. Viruses as precipitants of asthma symptoms. I. Epidemiology. *Clin Exp Allergy* 1992; 22: 325–336.
4. Beasley R, Coleman ED, Hermon Y, Holst PE, O'Donnell TV, Tobias M. Viral respiratory tract infection and exacerbations of asthma in adult patients. *Thorax* 1988; 43: 679–683.

5. Sokhandan M, McFadden ER, Huang YT, *et al*. The contribution of respiratory viruses to exacerbations of asthma in adults. *Am Rev Respir Dis* 1992; 145: A691.
6. Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. *Br Med J* 1993; 307: 982–986.
7. Frick WE, Busse WW. Respiratory infections: their role in airway responsiveness and pathogenesis of asthma. *Clin Chest Med* 1988; 9: 539–549.
8. Huhti E, Mokka T, Nikoskelainen J, Halonen P. Association of viral and mycoplasma infections with exacerbations of asthma. *Ann Allergy* 1974; 33: 145–149.
9. Hahn DL, Dodge RW, Golubjatnikov R. Association of *Chlamydia pneumoniae* (strain TWAR) infection with wheezing, asthmatic bronchitis, and adult-onset asthma. *J Am Med Assoc* 1991; 266: 225–230.
10. Blasi F, Legnani D, Lombardo VM, *et al*. *Chlamydia pneumoniae* infection in acute exacerbations of COPD. *Eur Resp J* 1993; 6: 19–22.
11. Marrie TJ. *Chlamydia pneumoniae*. *Thorax* 1993; 48: 1–4.
12. Thom DH, Grayston JT. Infections with *Chlamydia pneumoniae* strain TWAR. *Clin Chest Med* 1991; 12: 245–256.
13. Blasi F, Cosentini R, Legnani D, Denti F, Allegra L. Incidence of community-acquired pneumonia caused by *Chlamydia pneumoniae* in Italian patients. *Eur J Clin Microbiol Infect Dis* 1993; 12: 696–699.
14. Paoletti P, Viegi G, Carrozzi L. Bronchial hyperresponsiveness, genetic predisposition and environmental factors: the importance of epidemiological research. *Eur Respir J* 1992; 5: 910–912.
15. Peat JK, Salome CM, Woolcock AJ. Factors associated with bronchial hyperresponsiveness in Australian adults and children. *Eur Respir J* 1992; 5: 921–929.