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Clinical features of *Chlamydia pneumoniae* acute respiratory infection

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*Chlamydia pneumoniae* is a worldwide respiratory pathogen involved in 6-20% of community-acquired pneumonias and in about 5% of acute exacerbations of chronic bronchitis. Preliminary data also indicate a possible association between *Chlamydia pneumoniae* infection and asthma. Further studies are needed to elucidate whether *Chlamydia pneumoniae* is merely a precipitant of asthma symptoms or is actually one of the causes of asthma.

**Key words**: *Chlamydia pneumoniae*, community-acquired pneumonia, asthma

*Chlamydia pneumoniae* has recently been recognized as a cause of respiratory tract infections [1,2]. It has been classified as a third species of the *Chlamydia* genus by means of ultrastructural and DNA homology analysis [3].

*C. pneumoniae* is an obligate intracellular, Gram-negative bacterium involved in a wide spectrum of respiratory tract infections of the upper respiratory tract (pharyngitis, sinusitis and otitis) and lower respiratory tract (acute bronchitis, exacerbation of chronic bronchitis and asthma, and community-acquired pneumonias) in both immunocompetent and immunocompromised subjects [4-21]. Several studies have recently stressed the importance of this agent in the development of respiratory diseases, showing a high incidence and prevalence of infections worldwide. Specific antibody prevalence in Western countries is low in pre-school children and climbs to over 50% in adults, remaining high in old age due to *C. pneumoniae* reinfection among adults [7].

In this paper the clinical characteristics of *C. pneumoniae* acute infection will be discussed, focusing on the possible pathogenetic role of this agent in asthma.

**DISEASES ASSOCIATED WITH ACUTE C. PNEUMONIAE INFECTION**

*C. pneumoniae* seems to be an important cause of human respiratory tract disease. Several reports show a high incidence of infection in community-acquired pneumonia, ranging from 6% to 25%, and a remarkable role in pneumonia outbreaks in closed communities like military garrisons, schools and families [8,12-16]. Further, *C. pneumoniae* is involved in upper respiratory tract infections (pharyngitis, sinusitis, otitis), acute bronchitis and exacerbations of chronic bronchitis [5,6]. Recently, Hahn et al [10] reported a possible etiopathogenetic role of this pathogen in adult onset of asthma and in asthma exacerbation.

Several other diseases associated with *C. pneumoniae* infection, such as erythema nodosum, Guillain-Barré syndrome, culture-negative endocarditis, thyroiditis, arthritis and encephalitis, have been sporadically reported [22,24]. Seroepidemiologic evidence of a possible association between *C. pneumoniae* infection and sarcoidosis has also been suggested [25]. Saikku et al [26,27] and other authors [28-32] also found an association between *C. pneumoniae* and coronary artery disease. Table 1 summarizes published data on the incidence of *C. pneumoniae* infections.

| Disease                              | Range of incidence |
|--------------------------------------|--------------------|
| Asymptomatic infection               | Common             |
| Flu-like syndrome                    | Common             |
| Community-acquired pneumonia         | 6-25%              |
| Outbreaks in closed communities      |                    |
| Family outbreaks                     |                    |
| Upper respiratory tract infections   | 5-10%              |
| COPD exacerbations                   | 4-5%               |
| Asthma attacks                       | 1-18%              |
UPPER RESPIRATORY TRACT INFECTION

*Chlamydia pneumoniae* is involved in the etiology of acute pharyngitis, otitis and sinusitis with an incidence ranging from 5% to 10% [32,33]. In these diseases, no specific clinical manifestations have been shown. However, acute pharyngitis could be relatively severe with hoarseness, and one-third of patients present exudates without fever. Upper respiratory tract infections often herald or are associated with infections of the lower respiratory tract.

LOWER RESPIRATORY TRACT INFECTION (LRTI)

*Chlamydia pneumoniae* is increasingly reported as an important etiologic agent of LRTI. About 5% of COPD exacerbations are sustained by *C. pneumoniae*. Possible chronic *C. pneumoniae* infection in chronic bronchitis was suggested by Blasi et al [6], who found a significantly higher frequency of IgG anti-*Chlamydia pneumoniae* antibody, exceeding 63%, in patients with exacerbations of COPD compared to controls. This markedly higher prevalence could be due to either chronic infection by *C. pneumoniae*, as suggested by the increase of specific IgG prevalence and geometric mean titer with age, or a higher rate of acute infection in such patients. Von Hertzen et al [34] found no differences in serum IgG antibodies between patients and controls, but the difference in serum IgA prevalence was significant. Moreover, local sputum IgA antibodies against *C. pneumoniae*, absent in the majority of pneumonia patients, were a common finding in the sputa of chronic bronchitis patients, along with local antibodies against *Haemophilus influenzae* and *Branhamella catarrhalis*. *C. pneumoniae* might therefore be added to these bacteria, which have invariably been associated with the pathogenesis of chronic bronchitis.

Most reports rank this agent as being among the three most common etiologic agents of community-acquired pneumonia, generally presenting a mild, and in some cases self-limiting, clinical course [35,36], although sporadic cases of severe pneumonia have been reported [36,37]. The radiographic pattern of pneumonia is extremely variable, with a reported high incidence of sub-segmental consolidation [38,39].

Kleemola et al reported a seroepidemiologic study showing pneumonia epidemics in military garrisons sustained by *C. pneumoniae*, each epidemic lasting more than 6 months with an infective rate of about 80 per 1000 [8].

Family transmission, child to child, was described in Japan in 1990 [13]. Mordhorst et al [14] described an outbreak of *C. pneumoniae* infections in four farm families living close together in Denmark, with an unusually high incidence of symptomatic infections, particularly lower respiratory tract infections, among family members. These data support the human-to-human contact spread of *C. pneumoniae* infection, and point to the role of this agent in family cluster respiratory infections, although Aldous et al [15], in a serologic study of family serum samples conducted in 1966–1969, reported that acute infections more often affected a single family member than multiple members.

Blasi et al recorded a high rate (75%) of infection in two family outbreaks [16]. These data are in contrast to the low incidence of infection recorded during epidemics in military trainees in Finland [8] and in the serologic study of Aldous et al [15], while they are consistent with those reported by Mordhorst et al [14], who observed a family cluster with relatively high rate of infection.

In contrast to the numerous epidemiologic studies carried out in the general population, only limited data on *C. pneumoniae* infection in immunocompromised subjects are present in the literature [17–21]. Blasi et al have recently published preliminary results on *C. pneumoniae* seroprevalence in HIV-1-infected intravenous drug users and HIV-1 vertically infected children [17]. The seroprevalence of *C. pneumoniae* in the HIV-1-infected intravenous drug users (IDUs) was significantly higher than in both HIV-1-negative IDUs and immunocompetent subjects matched for age and sex. Recent reports suggest a possible role of *C. pneumoniae* as an etiologic agent of pneumonia in HIV-1-positive subjects [18–21]. A retrospective serologic study, Blasi et al [21] observed an outbreak of *C. pneumoniae* infection in an ex-injection drug user community, where almost 25% of the residents were HIV-1 positive. The epidemic occurred in a small group of 26 subjects living and working in the same place. Their rate of HIV-1 positivity was remarkably high (50%). A higher *C. pneumoniae* infection rate in HIV-1-positive subjects was observed, with more than 76% of HIV-1-positive patients compared to only 38% of HIV-negative subjects suffering from acute *C. pneumoniae* infections. Moreover, most pneumonias occurred in HIV-1-positive patients. All lung infections were mild to moderate in severity, with a spontaneous recovery in one HIV-1-negative subject.

ASTHMA

Hyperresponsiveness is a key factor in the pathogenesis of asthma that might be determined by genetic factors and/or environmental exposures. Atopy, air pollution and smoke seem to be strongly associated with bronchial hyperresponsiveness. Moreover, familial
predisposition and/or genetic transmission of bronchial hyperresponsiveness have recently been observed [40,41]. In children, the role of viral infection in acute exacerbations of asthma has long been recognized, although its role in the pathogenesis of asthma is still controversial [42]. Less is known about the association between infections and asthma in adults. Commonly, infection and acute exacerbation. This has been inferred from several epidemiologic studies, mainly conducted in the pediatric population [43,44].

The role of viruses as precipitants of asthma symptoms in adults seems to be less relevant than in children, but epidemiologic data are conflicting. Beasley et al [45] reported an etiologic role of viruses in 10% of acute exacerbations of asthma, with a higher incidence (36%) in severe attacks. However, Sokhandan et al [46] did not find any evidence of viral infection in a small group of patients with acute asthma exacerbations. More recently, Nicholson et al [47] reported that 89% of patients with a cold had asthma symptoms. Moreover, the authors found that 44% of episodes with reductions in mean peak expiratory flow rate ≥50 l/min were associated with laboratory-confirmed infections, rhinoviruses and coronaviruses being predominant.

Bacterial infection seems to play a minor role in asthma attacks [48], although some evidence has drawn attention to *Mycoplasma pneumoniae* and recently to *C. pneumoniae* [10,49]. The latter plays an important aetiopathogenetic role in the development of acute respiratory tract infections [2,6] and Hahn et al [10] 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 titer level and prevalence of wheeze. Moreover, four out of 19 patients with acute *C. pneumoniae* infection subsequently developed asthma, and four others had exacerbation of previously diagnosed asthma.

Allegra et al [11] showed that acute exacerbation of asthma was associated with infection in 20% of their patients. Interestingly, viruses were involved in about 9% of asthma attacks, while acute infection with intracellular bacteria was detected in 11% of cases. Most of the latter (7/8 cases) were due to *C. pneumoniae* infection. Emre et al [50] reported the association of *C. pneumoniae* infection and reactive airway disease in children. The authors indicated that *C. pneumoniae* was a trigger of wheezing in asthmatic children and that treatment with macrolides, which are active against this agent, may improve the course of reactive airway disease in these patients.

Other findings also seem to indicate *C. pneumoniae* infection as a possible explanation for an increase of asthma in recent years [51]. For instance, cross-sectional data indicate an age-specific seroprevalence pattern [52] similar to the prevalence pattern of adult asthma [53]. *C. pneumoniae* infection preceding symptomatic adult asthma by about 10 years. Seroepidemiologic data from Finland [54] also show an increasing seroprevalence rate associated with increased asthma prevalence. Hahn and Golubjatnikov [55] reported a study on patients with adult-onset asthma in which 100% of patients were *C. pneumoniae* seroreactive.

*C. pneumoniae* has also been cultured from adult patients with acute exacerbation of asthma [56,57]. Moreover, Emre et al [50] identified the agent by culture in children with symptomatic asthma. In another study, Cunningham et al [58] showed that *C. pneumoniae* could be detected by polymerase chain reaction in a large proportion (47%) of children with asthma, both during exacerbations (24%) and when asymptomatic (27.7%). The latter study seems to support the hypothesis of a possible *C. pneumoniae* chronic infection in subjects with asthma.

Hahn has recently defined a 'Chlamydia-asthma' hypothesis [59]. The hypothesis is based on the following evidence.

1. Production of *C. pneumoniae*-specific IgE and cytokines, along with a direct lesion of epithelial cells by the agent, leading to inhibition of ciliary motion [60] and a possible shedding of cells with an enhanced penetration of aeroallergens.
2. The capacity of *Chlamydia*, during reinfection or chronic infection, to produce T-cell-mediated immunopathologic diseases, with the possibility that *C. pneumoniae* could act as a long-term asthma promoter.
3. *C. pneumoniae* could infect vascular smooth muscle [61] and promote bronchial hyperreactivity via bronchial muscle infection.

Hence, the data available to date seem to support an etiologic link between *C. pneumoniae* infection and asthma, in both adults and children.

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