

The Role of *Mycoplasma pneumoniae* Infection in Asthma

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Respiratory infections can cause wheezing episodes in children and can influence the onset and severity of asthma via complex and intersecting mechanisms. Infections can trigger atopic asthma, and atopy can cause wheezing during airway infections and modify the course of airway infections. *Mycoplasma pneumoniae* (*M. pneumoniae*), primarily recognized as a causative agent of community-acquired pneumonia, has recently been linked to asthma. Infections with *M. pneumoniae* can precede the onset of asthma, exacerbate asthmatic symptoms, and cause difficulties with asthma management.¹

The clinical association between *M. pneumoniae* infection and exacerbation of asthma symptoms has been suspected for longer than two decades; however, the nature of the correlation is still far from clear. In 1970, Berkovich et al.² provided the first prospective study showing serological evidence of infection with either *M. pneumoniae* or a respiratory virus in 27 of 84 (32%) asthma patients. Huhti et al.³ analyzed 63 patients after severe episodes of acute asthma and found that 19% had associated viral or mycoplasma infections. Biscardi et al.⁴ reported that 20% (24/119) of the patients with previously diagnosed asthma had simultaneous acute *M. pneumoniae* infection and asthma exacerbation; of 51 patients experiencing their first episode, acute infection with *M. pneumoniae* was identified in 26 (50%) of the patients. Therefore, based on the current literature, *M. pneumoniae* appears to be an important trigger for the acute exacerbation of asthma, accounting for 3.3%-50% of exacerbations.

Several recent studies have implicated *M. pneumoniae* infection in the pathophysiology of asthma in subsets of patients. In two of the most influential studies, Kraft et al.⁵ and Martin et al.⁶ used polymerase chain reactions (PCRs) to detect *M. pneumoniae* in the lower pulmonary airways in 25 of 55 (45%) adult patients with chronic stable asthma, compared with 1 of 11 (9%) controls. Using serology and PCR, Esposito et al.⁷ found *M. pneumoniae* significantly more often in children with acute episodes of wheezing than in controls, and infection was signifi-

cantly associated with a history of recurrent wheezing. Lieberman et al.⁸ showed in a prospective study using serological detection that *M. pneumoniae* infection was significantly associated with acute exacerbation of bronchial asthma. Furthermore, treatment with antibiotics against *M. pneumoniae* significantly improved pulmonary function in asthmatics with *M. pneumoniae* infection, suggesting a role for infection in chronic asthmatics.⁹

Although the evidence linking *M. pneumoniae* infection with exacerbation and chronic asthma is convincing, the role of *M. pneumoniae* as the cause of the initial onset of asthma remains unclear. In 1994, Yano et al.¹⁰ was first to describe a patient in whom a previous acute mycoplasmal respiratory infection led to an initial onset of bronchial asthma. In a follow-up study in 50 children, Mok et al.¹¹ reported that five children (10%) with *M. pneumoniae* respiratory illness developed clinical signs of asthma. All five children, however, had a family and personal history of atopy. It seems that acute infection with *M. pneumoniae* can initiate asthma in some previously asymptomatic patients and in some individuals with atopy. However, regarding a quantitative role of these bacteria or a direct cause-and-effect association as asthma initiators, additional large population-based prospective or cohort studies are necessary before definitive conclusions can be drawn.

The mechanisms of *M. pneumoniae* interactions with human airways are complex and multifactorial. Underlying mechanisms of *M. pneumoniae* infection-induced or exacerbated asthma may involve the stimulation of predisposing immune

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responses. Factors involved in these immune responses may include the induction of Th2 cytokines, immune cells, and IgE production; physiological changes such as bronchial obstruction, angiogenesis, edema, and cell wall thickening; and even neural mechanisms.^{5,6,10-12} Further elucidation of these mechanisms may enable the development of novel therapeutic strategies for the prevention and treatment of infection-induced asthma. The immune cells of bronchoalveolar lavage fluid in children with *M. pneumoniae* pneumonia were found to comprise high percentages of neutrophils and lymphocytes.¹² Thus, the exacerbation of asthma may be related to neutrophil cytokine signaling and degranulation, and cell lysis at the respiratory epithelial cell surface.^{13,14} In addition, asthmatics with infection had a significantly greater number of mast cells than asthma patients without infection.⁶ These observations suggest that *M. pneumoniae* infections, particularly in children, may result in a dominant Th2 response that induces increased IgE release, thereby predisposing patients to atopy.

Increased airway wall thickness has been observed in several different studies in asthma patients. Continued function requires extensive microvascular systems, and adding thickness to the airway wall further reduces airway conductance.¹⁵ Angiogenesis and edema have been associated with airway remodeling in asthma. These responses to *M. pneumoniae* infection of the airways may induce chronic asthma.¹⁶ However, studies about how this feature of asthma is affected during bacterial infection and the impact on treatment of the disease have only recently commenced.

Animal models of chronic airway infection with *M. pulmonis* (the murine equivalent of human *M. pneumoniae*) have been used to describe the mechanisms underlying angiogenesis, vascular remodeling, and airway wall thickening observed in asthma.¹⁵ Airway remodeling results from inflammatory responses that allow the movement of leukocytes and plasma proteins into the airway epithelium. This vascular leakage is promoted by vascular endothelial growth factor (VEGF).¹⁵

As presented in this issue of *Allergy, Asthma & Immunology Research*, Jeong et al.¹⁷ investigated the changes in VEGF and interleukin-5 (IL-5) serum levels in atopic children with *M. pneumoniae* pneumonia. The authors showed that the serum levels of VEGF and IL-5 were increased in atopic children with mycoplasma pneumonia compared with levels in other groups. Furthermore, the serum levels of VEGF and IL-5 were increased at the recovery phase compared with the admission phase. These results suggest an association between *M. pneumoniae* infection and VEGF or IL-5 in the pathogenesis of atopic asthma in children. A limitation to this study was the reliance on the past and family history of allergic diseases and IgE concentration to define atopy. Future studies will require a more definitive definition of atopy in study subjects. In addition, a long-term follow-up study examining the development of asthma in non-atopic individuals with mycoplasma infection would be

interesting. Further research will be required to demonstrate a link between the development of hypersensitivity and *M. pneumoniae* infection.

Despite recent advances in diagnostic technology and the development of animal models representative of human disease, well-designed and controlled human clinical studies and experimentation with animal models are needed to elucidate the role of *M. pneumoniae* infection in the predisposition for or protection from asthma. Future large, general population-based prospective studies will be necessary to investigate the development of asthma induced by *M. pneumoniae* infection in humans.

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