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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 significantly 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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REFERENCES

1. MacDowell AL, Bacharier LB. Infectious triggers of asthma. Immunol Allergy Clin North Am 2005;25:45-66.
2. Berkovich S, Millian SJ, Snyder RD. The association of viral and mycoplasma infections with recurrence of wheezing in the asthmatic child. Ann Allergy 1970;28:43-9.
3. Huhti E, Mokka T, Nikoskelainen J, Halonen P. Association of viral and mycoplasma infections with exacerbations of asthma. Ann Allergy 1974;33:145-9.
4. Biscardi S, Lorrot M, Marc E, Moulin F, Boutonnat-Faucher B, Heilbronner C, Iniguez JL, Chaussain M, Nicand E, Raymond J, Gendrel D. Mycoplasma pneumoniae and asthma in children. Clin Infect Dis 2004;38:1341-6.
5. Kraft M, Cassell GH, Henson JE, Watson H, Williamson J, Marmion BP, Gaydos CA, Martin RJ. Detection of Mycoplasma pneumoniae in the airways of adults with chronic asthma. Am J Respir Crit Care Med 1998;158:998-1001.
6. Martin RJ, Kraft M, Chu HW, Berns EA, Cassell GH. A link between chronic asthma and chronic infection. J Allergy Clin Immunol 2001;107:595-601.
7. Esposito S, Blasi F, Arosio C, Fioravanti L, Fagetti L, Droghetti R, Tarsia P, Allegra L, Principi N. Importance of acute Mycoplasma pneumoniae and Chlamydia pneumoniae infections in children with wheezing. Eur Respir J 2000;16:1142-6.
8. Lieberman D, Lieberman D, Printz S, Ben-Yaakov M, Lazarovich Z, Ohana B, Friedman MG, Dvoskin B, Leinonen M, Boldur I. Atypical pathogen infection in adults with acute exacerbation of bronchial asthma. Am J Respir Crit Care Med 2003;167:406-10.
9. Kraft M, Cassell GH, Pak J, Martin RJ. Mycoplasma pneumoniae and Chlamydia pneumoniae in asthma: effect of clarithromycin. Chest 2002;121:1782-8.
10. Yano T, Ichikawa Y, Komatu S, Arai S, Oizumi K. Association of Mycoplasma pneumoniae antigen with initial onset of bronchial asthma. Am J Respir Crit Care Med 1994;149:1348-53.
11. Mok JY, Waugh PR, Simpson H. Mycoplasma pneuminia infection. A follow-up study of 50 children with respiratory illness. Arch Dis

Child 1979;54:506-11.
12. Koh YY, Park Y, Lee HJ, Kim CK. Levels of interleukin-2, interferon-gamma, and interleukin-4 in bronchoalveolar lavage fluid from patients with Mycoplasma pneumonia: implication of tendency toward increased immunoglobulin E production. Pediatrics 2001;107:E39.
13. Kazachkov MY, Hu PC, Carson JL, Murphy PC, Henderson FW, Noah TL. Release of cytokines by human nasal epithelial cells and peripheral blood mononuclear cells infected with Mycoplasma pneumoniae. Exp Biol Med (Maywood) 2002;227:330-5.
14. Wark PA, Johnston SL, Moric I, Simpson JL, Hensley MJ, Gibson PG. Neutrophil degranulation and cell lysis is associated with clinical severity in virus-induced asthma. Eur Respir J 2002;19:68-75.
15. McDonald DM. Angiogenesis and remodeling of airway vasculature in chronic inflammation. Am J Respir Crit Care Med 2001;164:S39-45.
16. Chu HW, Kraft M, Rex MD, Martin RJ. Evaluation of blood vessels and edema in the airways of asthma patients: regulation with clarithromycin treatment. Chest 2001;120:416-22.
17. Jeong YC, Yeo MS, Kim JH, Lee HB, Oh JW. Mycoplasma pneumoniae infection affects the serum levels of vascular endothelial growth factor and interleukin-5 in atopic children. Allergy Asthma Immunol Res 2012;4:92-7.