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Atopic Sensitization is Associated With Severe Lower Respiratory Illness in Children With Pandemic H1N1 Influenza Viral Infection

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Although most influenza A virus infections result in self-limited uncomplicated disease, it causes significant morbidity and mortality in children.[1] Influenza A accounts for the highest rates of influenza-related hospital admissions, especially in young children and elderly people, and pneumonia is one of the most common complications (10%-26%).[2,3] Furthermore, it was previously reported that 35% of influenza A (H1N1)-related deaths in children were due to pneumonia.[4] In addition to seasonal influenza A infection, there was an outbreak of pandemic H1N1 influenza A viral infection (pandemic H1N1 influenza) that was first reported in patients from Mexico and the United States in early April 2009. An outbreak of pandemic H1N1 influenza during 2009-2010 was responsible for severe respiratory disease and death, especially in children and elderly people with chronic respiratory diseases, even though its overall impact did not appear to cause more severe disease than seasonal influenza A.[5,6] A recently published case series of 122 children with pneumonia due to pandemic H1N1 influenza reported up to a 60% prevalence of underlying medical conditions, including asthma (29%), and described the need for intensive care in 20% of patients and mechanical ventilation in 10%.[7]

The relationship between viral infection and asthma has been investigated during the last few decades and evidence for such a link has been reported; however, the question of whether all respiratory viruses are equipotent remains unclear. As described in a recent review by Holt et al.[8], it was assumed that respiratory syncitial virus (RSV) was overwhelmingly the most important trigger of severe lower respiratory illness (LRI) in the first two years of life, and compelling data on the association between early RSV-induced LRI and subsequent development of persistent asthma have been published from independent prospective cohort studies. More recently, it was revealed that the contribution of human rhinovirus to LRI during infancy and the preschool years was considerably higher than previously believed, and that these infections are strongly linked to the risk of subsequent asthma.[8] Although the pathogenic nature of the relationship between asthma and H1N1 viral infection is unclear, several studies have reported that asthma is a risk factor for worsening respiratory conditions in pandemic H1N1 influenza patients.[6,7] However, there are several other reports that pandemic H1N1 influenza causes high rates of severe LRI (pneumonia, atelectasis), aggravation of asthma, and admission to intensive care units in patients with exisiting asthma or atopy.[6,9,10] In a recent animal study, high concentrations of virus-infected cells were found in the central and lower respiratory tracts of ferrets inoculated with H1N1 influenza virus compared to ferrets inoculated with seasonal influenza virus. This result suggests that pandemic H1N1 influenza replicated more extensively in the lower respiratory tract, causing more severe LRI than that caused by seasonal influenza virus.[11]

In this issue of *Allergy, Asthma & Immunology Research*, Kim et al.[12] report an increased prevalence of H1N1-induced severe lower respiratory tract disease in children with atopic sensitization. In aforementioned study, a high proportion of atopic children with pandemic H1N1 influenza had atelectasis and required ICU care and oxygen and steroid therapy. Based on these findings and the results of several animal studies, the authors suggest that atopic sensitization combined with pandemic H1N1 influenza infection can induce severe LRI. In addition, eosinophil recruitment into the lungs and enhancement of IL-10 production from CD4+ T cells may play a role in the development of severe LRI observed in pandemic H1N1 influenza patients.[13,14] Due to the small sample size, Kim et al.[12] could not confirm whether atopic sensitization itself, and not asthma, was

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associated with pandemic H1N1 influenza-induced severe LRI. Although the authors could not directly confirm that the atopic sensitization itself was the cause of severe LRI in pandemic H1N1 influenza, they demonstrated this relationship using proper statistical analyses. There was a recent study that also supports the notion that pandemic H1N1 influenza greatly increases the risk of severe LRI regardless of the severity of previous asthma or the presence of asthma in patients with atopic sensitization.[9] In addition, patients with atopy have been shown to exhibit low natural killer cell activity,[15] suggesting that both abnormal innate immune responses in atopic individuals and the affinity of the pandemic H1N1 virus for the respiratory tract may lead to increased susceptibility to severe LRI induced by pandemic H1N1 influenza.

Based on several recent studies, including the study by Kim et al.[12] reported in this issue, it is suggested that atopic sensitization itself can cause severe LRI. This has highlighted the importance of influenza prevention through vaccination, especially in children with atopic sensitization, even if the patients have no obvious history of clinical asthma or any other allergic disease.

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