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Streptococcus pyogenes upper respiratory infections and their effect on atopic conditions

See linked article by Juhn *et al.* on pg 153

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The effect of the upper airway on the lower airway was recognised as early as the second century by Claudius Galenus, who defined the nose as a 'respiratory instrument' in his work *De usu partium (On the usefulness of the [body] parts)*.¹ However, the modern concept of the upper and lower respiratory passages being a continuum and forming a single unified airway has been highlighted only over the last 10-15 years.²

The Allergic Rhinitis and its Impact on Asthma (ARIA) initiative focused on the co-morbidities of allergic rhinitis and included

involvement of the eyes, the paranasal sinuses and the lower airways.³ The nasal and bronchial mucosa present a number of similarities, and one of the most important concepts regarding nose/lung interactions is their functional complementarity.⁴ Interactions between the upper and lower airways are well known; it has been observed that over 80% of asthma patients have rhinitis and 10-40% of patients with rhinitis have asthma.³

The role of upper respiratory tract infections (URTIs) and how they affect the lower respiratory tract have been less well studied compared to the role of allergic diseases. Similarly, the effects of URTIs on atopic conditions (other than asthma) have also not been documented to any appreciable extent. Asthma in children is associated with an increased risk of *Streptococcus pyogenes* upper respiratory infections,⁵ even though *Strep. pyogenes* is not known to be a cause of asthma exacerbations.⁶

Strep. pyogenes is a well-known causative agent of a number of autoimmune conditions. The relatively new disease PANDAS,⁷ supposedly of post-streptococcal etiology, is the acronym for Paediatric Autoimmune Neuropsychiatric Disease Associated with Streptococcal

infection. Tics and obsessive-compulsive symptoms are the major clinical signs of the disease, which develops after *Streptococcus* infection and which is almost certainly caused by autoimmune mechanisms (though the exact nature of the autoimmune mechanism remains unclear). Some cases of chronic urticaria are also reported to be associated with chronic tonsillitis,⁸ although the primary role of infection in chronic urticaria is controversial.

Mast cells play a key role in the pathogenesis of atopic diseases as well as in asthma. They are important effector cells in innate immune responses to bacterial infections, and are critically involved in initiating and modulating optimal host responses to bacteria by either inflammatory or anti-inflammatory effects depending on the course of the host reaction induced by the pathogen. The exact mechanism for this is not known.⁹ However, one possible mechanism is via the Th-1 pathway through the induction of interleukin-12 (IL-12); a topical preparation OK-432, prepared from the penicillin-treated Su strain of type III Group A *Strep. pyogenes*, has been shown to be effective for treating atopic dermatitis.¹⁰

Children sensitised to house dust mite (HDM) have early defective antibody responses to bacteria that are associated with asthma, and the presence of antibacterial IgE has been associated with a reduced risk for asthma.¹¹ This suggests that a functioning humoral immune system prevents the development of asthma, and possibly the development of other atopic diseases as well. The immune system's response to infections and its effects on allergy have been studied by Essliffe and co-workers in BALB/c mice.¹² These workers found that the combination of infection and allergic airways disease promotes bacterial persistence, leading to the development of a phenotype similar to steroid-resistant neutrophilic asthma – and hence the suggestion that steroid-resistant asthma may result from dysfunction in innate immune cells. Targeting bacterial infection in steroid-resistant asthma may therefore have therapeutic benefit.

In this issue of the *PCRJ*, Juhn and colleagues have retrospectively studied the association of *Strep. pyogenes* and atopic conditions other than asthma in children under the age of 18 years¹² – an area of research which has been poorly studied in the past. They selected 143 (44%) of their total sample size who met the criteria of having atopic conditions other than asthma. They collected the laboratory test results of cultures, rapid antigen detection, and polymerase chain reaction tests for *Strep. pyogenes* infections during the first 18 years of life, and compared the incidence of *Strep. pyogenes* infections between children with and without a physician diagnosis of an atopic condition. They used a Poisson regression to determine the association between asthma and *Strep. pyogenes* infections, controlling for other covariates including asthma. They found that the incidence of *Strep. pyogenes* infections in children with atopic conditions other than asthma, and those without atopic conditions, was 0.24 per person-year and 0.18 per person-year, respectively. They conclude that, in addition to asthma, allergic rhinitis but not atopic dermatitis is associated with an increased risk of *Strep. pyogenes* URTIs.

The authors have looked at many potential hypotheses to explain this linkage, but none with any amount of convincing evidence.¹² In addition, and as stated by the authors themselves, there are several limitations to this study, not least the fact that it is retrospective and

observational, so only an associational relationship could be documented. Furthermore, relevant risk factors like exposure to indoor cigarette smoking or allergic sensitisation status data were not available, and the study population was predominantly Caucasian.

Nevertheless, the overall results of this study suggest that there may be a link between the immunogenetic predisposition to atopy and susceptibility to *Strep. pyogenes* infection, thus opening up a new area for research. Primary care practitioners are advised to keep this in mind when they see patients with repeated URTIs. In addition, repeated URTIs in children with symptoms of tics – such as repeated eye blinking or clearing of the throat – may be an early sign of chronic *Strep. pyogenes* infection and PANDAS. One must also not forget to examine for additional allergy-associated conditions including (but not limited to) asthma.

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