Editorial

New Developments in Comorbidities of Atopic Dermatitis

Jonathan Silverberg, MD, PhD, MPH; Nitin Garg, MD; Nanette B. Silverberg, MD

Atopic dermatitis (AD) is a systemic illness and not just a cutaneous disease. Children with AD experience a high prevalence of comorbid allergic disorders compared with their peers.[1] Silverberg and Simpson[2] used the 2007 National Survey of Children's Health (NSCH), a population-based study of 91,642 children aged 0 to 17 years, to determine the burden of allergic comorbidity in childhood AD. Children with AD had a higher prevalence of comorbid asthma (25.1% vs 12.3%), hay fever (34.4% vs 14.3%), and food allergies (15.1% vs 3.6%) compared to children without AD. Furthermore, AD severity was associated with a higher prevalence of comorbid allergic disorders as well as increased severity of the comorbidities.[2] Similarly, another study of 27,157 adults demonstrated the US prevalence of eczema to be 10.2%; those with eczema have a higher prevalence of comorbid asthma (14.8% vs 7.5%) and hay fever (15.7% vs 6.9%) compared to adults without AD, suggesting that AD plays an ongoing role in systemic allergic disease into adulthood.[3]

It is well established that children with AD are at a higher risk for cutaneous infections and generalization of these infections, including *Staphylococcus aureus*, group A streptococci, herpes simplex virus, vaccinia virus or Kaposi varicelliform eruption, Coxsackievirus or eczema coxsackium, molluscum, and fungal infections, among many others,[4,5] likely in part due to impaired epidermal barrier function. Using data from the 2007 National Health Interview Survey, Silverberg and Silverberg[6] showed that AD in children was associated with a higher prevalence of extracutaneous infections such as influenza and pneumonia, urinary tract infections, chickenpox, recurrent ear infections, sinus infections, sore throat, and head or chest colds. Interestingly, children with AD and warts from cutaneous human papillomavirus infections were at an even higher risk for developing infections and other allergic diseases, a finding that suggests children expressing a cophenotype of AD and warts exhibit greater impairment of the skin barrier than those with AD but no warts. Atopic dermatitis also was associated with slightly lower prevalence of warts, but children with AD in addition to other atopic diseases had higher odds of warts.[6] Another study showed that AD was associated with other complications that may or may not be attributed to infectious processes, such as impaired dental hygiene (eg, bleeding gums, toothache) and increased visual problems.[2]

Findings of cutaneous and extracutaneous infections in patients with AD may be a reflection of deficiencies in innate and/or adaptive immune responses. For example, AD expression and severity is associated with epidermal barrier defects and defects in pattern recognition receptors (eg, toll-like receptors) that normally allow keratinocytes to respond to microbial invasion and release cytokines.[7] Diminished recruitment of neutrophils to the skin may occur in patients with AD, and upregulation of T helper 2 cell (T_H2) cytokines may inhibit the expression of certain antimicrobial peptides.[8] The role of such aberrations in the innate and/or adaptive immune systems with regard to increased risk for infection has not been fully elucidated. Future studies may stimulate the development of therapeutic and/or preventative approaches against secondary infections.

There is an increasingly recognized association between AD and psychological and behavioral comorbidities. A systematic review concluded that AD is independently associated with attention deficit hyperactivity disorder (ADHD).[9] A study of the 2007 NSCH data demonstrated an increased prevalence of comorbid ADHD, depression, anxiety, conduct disorder, and autism in children with AD compared to children without AD.[10] This association remained significant ($P<.03$) after controlling for multiple confounders and disease severity. Although the mechanisms underlying this association are unknown, we speculate that sleep

Drs. J. Silverberg and Garg are from the Department of Dermatology, Northwestern University, Chicago, Illinois; Dr. Silverberg also is from the Departments of Preventative Medicine and Medical Social Sciences. Dr. N.B. Silverberg is from the Department of Dermatology, Mt. Sinai St. Luke's of the Icahn School of Medicine at Mount Sinai, New York, New York.
The authors report no conflict of interest.
Correspondence: Nanette B. Silverberg, MD, Department of Dermatology, 1090 Amsterdam Ave, Ste 11D, New York, NY 10025 (nsilverb@chpnet.org).

disturbances accompanying allergic disorders may play an important role. Furthermore, AD, depression, and anxiety are all characterized by an increase in proinflammatory cytokines. The shared presence of inflammation may have wide-ranging effects, leading to the coexpression of allergic and psychiatric disorders. Given the cross-sectional nature of this study, it is difficult to ascertain if the psychological disorders or AD appeared first.[10]

In their analysis of NSCH data from 27,556 children aged 0 to 5 years, Garg and Silverberg[11] revealed that young children with AD carry an increased risk for injuries requiring medical attention. The authors found that this association was due in part to psychological comorbidities, including attention deficit disorder (with or without hyperactivity), depression, anxiety, conduct disorder, and learning delays.[11] This research is of particular importance given that unintentional injury is the leading cause of mortality in children and young adults.[12] Identifying risk factors for these injuries could lead to tailored interventions for injury prevention. It is likely that the characteristic inattentiveness of children with ADHD predisposes them to injury. Additionally, depression and anxiety are known to impair concentration, attention, memory, decision-making abilities, visuospatial functioning, and reaction time,[13-20] which are all plausible risk factors that may predispose a child to injury. Further, sleep loss and the use of sedating antihistamines often associated with allergic disorders may contribute to injury risk, but the authors were unable to assess the influence of these factors.[11] Further exploration of these factors is warranted.

In addition to neuropsychiatric disorders, AD also appears to be associated with epilepsy in children aged 0 to 17 years. In a recent population-based study, the authors demonstrated an odds ratio of 1.73 (95% confidence interval, 1.17-2.56) between the prevalence of AD in childhood and ever being diagnosed with epilepsy.[20] Similar associations between asthma and epilepsy have been described in adults.[21,22] The mechanism underlying this association currently is unknown. B cells and T cells have been shown to infiltrate the brain after a seizure and convert into IL-4+ cells and IgE+ cells.[23,24] Perhaps allergic disease and epilepsy share some common pathways. Overall, as children with epilepsy were found to have a high prevalence of allergic disease (approximately 46%), the authors suggested that children with epilepsy stand to benefit from routine screening for allergic disorders.[20]

Conceptually, all of these data and comorbidities point toward AD being a multisystem inflammatory disorder and not just a cutaneous diathesis. As our conceptualization of the disease shifts to include the whole patient, more effective therapy, prevention of comorbidity, and even partial or total cures are likely to become realities.

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Quick Poll Question

In your practice, what psychological or behavioral comorbidity has presented most often in children with atopic dermatitis?

a. attention deficit hyperactivity disorder
b. autism
c. conduct disorder
d. depression

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