Increasing Comorbidities Suggest that Atopic Dermatitis Is a Systemic Disorder

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Atopic dermatitis comorbidities extend well beyond the march to allergic conditions (food allergy, asthma, allergic rhinitis, allergic conjunctivitis, and eosinophilic esophagitis), suggesting both cutaneous and systemic immune activation. In reviewing atopic dermatitis comorbidities, Councilors of the International Eczema Council found a strong pattern of immune activation in peripheral blood and the propensity to both skin and systemic infections. Associations with cardiovascular, neuropsychiatric, and malignant diseases were increasingly reported, but confirmation of their link with atopic dermatitis requires longitudinal studies. Given the possibility of atopic dermatitis-related systemic immune activation, future investigations of new interventions should concurrently examine the impact on these comorbidities.

Journal of Investigative Dermatology (2017) **137,** 18–25; doi:10.1016/j.jid.2016.08.022

INTRODUCTION

The immune-mediated skin disease atopic dermatitis (AD) has long been recognized as closely associated with other atopic conditions. More recent studies have uncovered multiple previously unrecognized disease associations, further highlighting the possibility that AD is a systemic disorder. Councilors of the International Eczema Council, all leaders in AD research, gathered at the Annual European Society for Dermatological Research meeting in 2015 to review the increasingly recognized comorbidities, including controversial associations, that may contribute to the burden of AD.

Before the meeting, presenters searched for AD/eczema studies from 2000 through 2016 using PubMed, Google scholar, Science direct, and ClinicalTrials.gov using keywords such as *atopic dermatitis* or *eczema* combined with *infection, cardiovascular, neuro-psychiatric,* and *malignant.* Topics were then discussed by the group, and teams of Councilors further reviewed the literature from 2000–2016 literature to describe (i) pathogenic concepts of immune activation leading to both overt inflammation and increased susceptibility to infection in AD and (ii) associations with AD derived from epidemiologic studies, in which pathogenic mechanisms are still largely unclear. Selected effects sizes of disease associations for autoimmune, infectious, cardiovascular, malignant, and neuropsychiatric disorders are summarized in Supplementary Table S1 online.

ATOPIC DERMATITIS AND SYSTEMIC IMMUNE DEVIATION

The atopic march

AD usually begins early in life (Czarnowicki et al., 2015a; Eichenfield et al., 2012), and its onset is often followed by the serial occurrence of allergic diseases that represent the atopic march, especially food allergies, asthma, and allergic rhinoconjunctivitis (Schneider et al., 2016; Simpson et al., 2012). This sequence has recently been challenged, suggesting that developmental profiles might be much more heterogeneous (Belgrave et al., 2014). AD patients, often in adulthood, also suffer from increased frequencies of hand eczema and allergic contact dermatitis (Thyssen et al., 2010, 2014), although these conditions are not classically included as components of the atopic march.

Allergic sensitization may result from skin barrier dysfunction, facilitating cutaneous allergen penetration. Loss-of-function mutations in the gene encoding filaggrin, *FLG,* are associated with an increased risk of AD and asthma (Irvine et al., 2011; McAleer and Irvine, 2013) and are present in 15–46% of AD patients (Brown et al.,

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Abbreviations: AD, atopic dermatitis; CI, confidence interval; OR, odds ratio; Th, T helper

Received 7 April 2016; revised 4 August 2016; accepted 19 August 2016; corrected proof published online 20 October 2016

2008; Carson et al., 2012). However, T helper (Th) 2 (IL-4/IL-13/IL-25) and Th22 (IL-22) cytokines, which are increased in AD, suppress filaggrin expression in keratinocytes (Gutowska-Owsiak et al., 2011; Howell et al., 2007; Hvid et al., 2011; Pellerin et al., 2013) and may contribute to the barrier deficits in vivo. Thus, immune activation in AD may trigger barrier dysfunction and/or aggravate inherited barrier defects through a positive feedback loop (Leung and Guttman-Yassky, 2014). Subsequent migration of sensitized T cells and/or IgE into the nose and airways facilitates upper and lower airway disease (Kubo et al., 2012; Leung, 2013). The important role of barrier defects in AD has further justified vigorous application of emollients, which likely contribute more than barrier substitution, given that petrolatum application increases expression of barrier proteins and antimicrobial peptides and decreases proinflammatory cytokines (Czarnowicki et al., 2016). Furthermore, preliminary studies suggest that proactive application of emollients to infants at risk for AD, beginning as neonates, reduces AD development and/or severity (Horimukai et al., 2014; Simpson et al., 2014). Longitudinal studies are currently addressing the ability of early emollient application to decrease sensitization to antigens and development of the atopic march.

A recent mechanistic study suggested that Th2/Th22 skewing and epidermal hyperplasia, but not the deficiency of barrier proteins of adult AD, are seen in the skin of infants and toddlers with new-onset disease, suggesting an early role for T-cell skewing (Esaki et al., 2016). Nevertheless, the correlation of high transepidermal water loss at 2 days of age and the occurrence of AD at 1 and 2 years of age suggest an early barrier defect as an initial driver (Kelleher et al., 2015; Kelleher et al., 2016). Additional studies in infants and children are warranted to address potential differences between infant/childhood (i.e., early-onset) and adult (i.e., chronic) disease to better understand disease evolution with age and disease heterogeneity (Garmhausen et al., 2013).

Immune activation beyond the skin

Similar to psoriasis, AD skin lesions are accompanied by epidermal hyperplasia, large T-cell and dendritic cell infiltrates, and increased production of inflammatory products (Guttman-Yassky et al., 2011a, 2011b). Psoriasis has been associated with inflammation in several noncutaneous systems, particularly the joints, gastrointestinal, and cardiovascular systems, and elevations in C-reactive protein are associated with disease severity (Beygi et al., 2014). In contrast to psoriasis, however, AD immune abnormalities also profoundly involve nonlesional skin and the blood compartment (Leung and Guttman-Yassky, 2014; Suarez-Farinas et al., 2011; Tang et al., 2014), although acute phase reactants, such as C-reactive protein, do not tend to be elevated. These observations suggest that the mechanisms of the inflammatory component of AD and psoriasis are different. Indeed, blood from individuals with AD has more polar differentiation of central and effector memory T-cell subsets and significantly higher and more persistent T-cell activation than is seen in psoriasis (Czarnowicki et al., 2015b, 2015c). Ongoing blood T-cell activation is a feature of both adults and children with moderate to severe AD. In pediatric AD, Th2 imbalance is confined to skin homing/CLA$^+$ T cells and does not extend to CD8$^+$ T cells, whereas in adults, Th2 activation extends into systemic/CLA$^-$ CD4$^+$ T cells and CD8$^+$ T cells (Czarnowicki et al., 2015a). Consistent with elevated IgE levels in 80% of AD patients (Weidinger and Novak, 2016), AD blood is characterized by a unique peripheral B-cell signature, and subsets of memory B cells correlate with clinical AD severity (Scoring Atopic Dermatitis score/SCORAD) and IgE levels (Czarnowicki et al., 2016). In peripheral blood, several biomarkers were shown to correlate with disease activity, including systemic cytokine activation (Haeck et al., 2011; Hayashida et al., 2011; Jahnz-Rozyk et al., 2005; Raap et al., 2012; Waxweiler et al., 2011). Alarmins (especially IL-33, but also IL-25 and thymic stromal lymphopoietin) have recently been shown to drive the cutaneous expansion of innate lymphoid cells—particularly innate lymphoid cell-2, producing IL-5 and IL-13—in AD skin (Salimi et al., 2013; Soumelis et al., 2002); this recently described mechanism may play a key early role in systemic activation related to AD (Saunders et al., 2016).

AD has been shown to share susceptibility loci with other immune-mediated diseases such as psoriasis, inflammatory bowel disease, and alopecia areata (Ellinghaus et al., 2013; Weidinger et al., 2013). In a German cohort study, AD was associated with a slightly increased risk for rheumatoid arthritis and inflammatory bowel disease and a decreased risk for type 1 diabetes (relative risk = 0.72), independent of known risk alleles (see Supplementary Table S1) (Schmitt et al., 2016). Prominent Th1 and Th17 responses promoting autoimmunity are known to be present in inflammatory bowel disease and rheumatoid arthritis and are also implicated in the transition to chronic inflammation in AD (Gittler et al., 2012). Autoreactivity is most common in severe and persistent AD (Tang et al., 2012). In a Taiwanese study (Wu et al., 2014), AD was associated with lupus erythematosus (odds ratio [OR] = 1.94, 95% confidence interval [CI] = 1.48−2.54) (see Supplementary Table S1), another disease in which not only Th1 and Th2 but also Th17 responses may play a pathogenic role (Martin et al., 2014; Oh et al., 2011). Associations were more prominent in individuals younger than 18 years of age (OR = 3.02, 95% CI = 1.30−7.03) and in female patients (OR = 2.05, 95% CI = 1.53−2.76) (Wu et al., 2014). Future studies will need to identify potential subsets of AD patients at highest risk and elucidate the mechanism underlying these associations.

Infection

The increased association of AD with more frequent and severe bacterial and viral infections is a minor diagnostic criterion (Hanifin and Rajka, 1980). *Staphylococcus aureus* is cultured from up to 90% of AD lesions (Leyden et al., 1974), and methicillin-resistant *S. aureus* predominates in some patients. Skin microbiome and virome research has expanded our view on the role of infections in AD (Belkaid and Segre, 2014; Kong et al., 2012). Bacterial gene sequencing studies found that

AD flares are associated with increased *S. aureus* and decreased microbial diversity (Kong et al., 2012). Moreover, AD treatment (including intermittent bleach baths and anti-inflammatory medications) decreases *S. aureus* and increases microbial diversity (Kong et al., 2012).

The relative role of *S. aureus* dysbiosis as a result versus instigator of AD is unclear. Dysbiosis (microbial imbalance) may directly affect AD skin inflammation (Kobayashi et al., 2015). *S. aureus* has been shown to induce IL-4/IL-13 and IL-22 cytokines, promoting Th2/Th22 inflammation in AD (Brandt and Sivaprasad, 2011; Niebuhr et al., 2010) and might even affect systemic immune deviation such as food allergies (Jones et al., 2016). Experimentally, occurrence of pruritic AD-like dermatitis in keratinocyte-specific Adam17-deficient mice depends on the presence of *S. aureus* and *Corynebacterium bovis* (Blaydon et al., 2011; Kobayashi et al., 2015), suggesting that bacteria might trigger AD in humans as well. Further, sodium hypochlorite (bleach) baths are not just antiseptic but also reduce AD severity (Huang et al., 2009; Huang et al., 2011), although perhaps in part by direct anti-inflammatory effects (Leung et al., 2013). Increasing microbial diversity improves AD severity in mice (Volz et al., 2014), and *Staphylococcus epidermidis* products have anti-*S. aureus* activity (Cogen et al., 2010; Lai et al., 2010; Naik et al., 2012). There is evidence that cutaneous application of extracts from nonpathogenic bacteria (*Vitreoscilla filiformis*) (Gueniche et al., 2008) and even emollients (Seite et al., 2014) restores skin dysbiosis and thereby may reduce AD severity. Greater severity is associated with higher risk of infection, and both topical and systemic anti-inflammatory interventions reduce staphylococcal colonization (Bath-Hextall et al., 2010; Boguniewicz and Leung, 2010).

Eczema herpeticum, a well-recognized infectious complication, appears in a subset of patients with severe Th2-polarized AD, greater allergen sensitization, and more commonly a history of food allergy and/or asthma (Beck et al., 2009). Eczema coxsackium is a newly recognized complication of coxsackie diseases associated with AD, which can be confused with eczema herpeticum (Mathes et al., 2013).

Children with AD also have a higher prevalence of warts and extracutaneous infections, including streptococcal pharyngitis, upper and lower respiratory infections, recurrent otitis, chickenpox, and urinary tract infections (Silverberg and Silverberg, 2014) (see Supplementary Table S1). Recent reports also suggest a relationship between AD and infective endocarditis (Fukunaga et al., 2013; Patel and Jahnke, 2015) (see Supplementary Table S1).

ATOPIC DERMATITIS AND EPIDEMIOLOGIC ASSOCIATIONS

Cardiovascular risks

Analogous to psoriasis, recent studies have suggested an association between AD, obesity, and cardiovascular disease in both adults and pediatric patients. A meta-analysis of 30 studies showed higher odds of overweight and/or obesity in children and adults with AD in studies from North America and Asia but not Europe (Zhang and Silverberg, 2015) (see Supplementary Table S1). In a study using the 2007–2008 National Survey of Children's Health with 45,897 U.S. adolescents, an increased prevalence of overweight and/or obesity was found in adolescents with AD versus healthy control subjects (Silverberg and Simpson, 2014) (see Supplementary Table S1). Increased waist circumference percentiles (85th percentile or greater: OR = 3.92, 95% CI, 1.50–10.26) and waist-to-height ratios (ratio of 0.5 or greater: OR = 2.22, 95% CI = 1.10–4.50) (see Supplementary Table S1) have also been associated with moderate to severe AD in children (Silverberg et al., 2015). The recognition by practitioners of obesity in many patients with psoriasis, but not with AD, may reflect the higher overall body mass indexes among psoriasis versus AD patients with obesity.

Moderate to severe pediatric AD has significantly higher systolic (OR = 2.94, 95% CI = 1.04–8.36) and diastolic (OR = 3.68, 95% CI = 1.19–11.37) blood pressures and significantly higher odds of systolic blood pressure at or above the 90th percentile (OR = 2.06, 95% CI = 1.09–3.90) (Silverberg et al., 2015) (see Supplementary Table S1), unrelated to excess adiposity. Adults with AD have significantly higher odds of a self-reported history of hypertension, adult-onset diabetes, and hypercholesterolemia, even after controlling for body mass index and/or comorbid allergic disease (Silverberg and Greenland, 2015) (see Supplementary Table S1). Cardiovascular risk is further increased when fatigue and sleep disturbances are present.

Patients with AD may have poor health behaviors that increase their cardiovascular risk. In adults, the odds are higher for smoking at least 100 cigarettes in their lifetime, currently smoking, initiating smoking at a younger age, drinking alcohol, and having reduced vigorous physical activity (Silverberg and Greenland, 2015). Children with severe AD have less vigorous physical activity and sports participation and increased hours of daily television and/or video game use (Strom and Silverberg, 2016) (see Supplementary Table S1). The increased cardiovascular risk factors in AD likely play a prominent role in the development of cardiovascular disease.

Hjuler et al. (2015) found evidence of increased coronary artery calcium score in the cardiac computed tomography angiography 18-segment model of the coronary tree, and mild single-vessel disease, in adults with AD compared with both healthy subjects and patients with psoriasis (see Supplementary Table S1). Patients with psoriasis, however, have more coronary stenosis and three-vessel or left main artery disease compared with patients with AD. Cardiovascular events have also been evaluated using the 2005–2006 National Health and Nutrition Examination Survey and the 2010 and 2012 National Health Interview Surveys. Overall, adults with AD in all three cohorts had significantly higher odds of coronary disease, myocardial infarction, and congestive heart disease; odds of angina, stroke, and peripheral vascular disease were also increased in the National Health Interview Surveys (Silverberg, 2015) (see Supplementary Table S1). AD has been reported to be an independent risk factor for ischemic stroke in a large Taiwanese study (Su et al., 2014). After

multivariate adjustment, patients with AD had a 1.33-fold increased incidence of ischemic stroke, and adjusted hazard ratios in patients with mild, moderate, and severe AD were 1.20, 1.64, and 1.71, respectively (see Supplementary Table S1). However, the increased risk of cardiovascular disease in a Danish cohort was no longer present after adjustment for socioeconomic status, smoking, comorbidities, and medication use (Andersen et al., 2016) (see Supplementary Table S1). In addition, nonfatal stroke was significantly increased in female U.S.-based nurses with history of ever having AD when controlling for age (Drucker et al., 2016) but not after controlling for hypertension, hypercholesterolemia, and diabetes; nonfatal myocardial infarction was not increased. These studies suggest that poor health behaviors and increased cardiovascular risk factors are the major drivers of cardiovascular disease and events in patients with AD, rather than systemic inflammation (see Supplementary Table S1). Longitudinal studies are warranted to assess the potential burden of cardiovascular disease in AD.

Cancer

The relationship between AD and cancer is complex and remains controversial. A recent meta-analysis found small but significantly increased odds of any lymphoma in AD in cohort (relative risk = 1.43; 95% CI = 1.12−1.81), but not case-control (OR = 1.18; 95% CI = 0.94−1.47) studies (Legendre et al., 2015) (see Supplementary Table S1). AD severity was a significant risk factor. Although some studies suggest an association of cutaneous T-cell lymphoma with AD (Arellano et al., 2007, 2009) (see Supplementary Table S1), misdiagnosis of cutaneous T-cell lymphoma as AD in many adults may lead to the erroneous overestimation of the association (Tennis et al., 2011). The mechanisms underlying the possible association of AD and lymphoma are poorly understood, but chronic inflammation, perhaps driven by genetic factors, may promote carcinogenesis, and inappropriate Th2 skewing might divert immunity from tumor-protective Th1 responses (Josephs et al., 2013). Systemic immunosuppressive agents used to treat moderate to severe AD, such as cyclosporine and azathioprine, increase the risk of malignancy (Chockalingam et al., 2015; Simon and Bieber, 2014). Although a regional health record database study found an association between topical calcineurin inhibitors and increased risk of lymphoma (Hui et al., 2009), a nested case-control study with a cohort of almost 300,000 AD patients found no association (Arellano et al., 2007, 2009) (see Supplementary Table S1). Furthermore, a longitudinal cohort of 7,457 children treated with pimecrolimus had no increased malignancy (Margolis et al., 2015). A recent consensus report concluded that use of topical calcineurin inhibitors is effective and safe, even in infants as young as 3 months of age, suggesting that warnings of possible carcinogenicity and restrictions regarding their use under 2 years of age are no longer justified (Luger et al., 2015).

In contrast to a possible increased risk of lymphoma, a meta-analysis found an inverse association between AD and acute lymphoblastic leukemia in six studies and no association with acute myelogenous leukemia in two studies (Linabery et al., 2010) (see Supplementary Table S1). No association was found between AD and bladder cancer (Kim et al., 2000). Recent systematic reviews showed either inverse or no association between AD and pancreatic, brain, and skin cancers (Deckert et al., 2014). A prospective adult Dutch cohort study found an inverse association between AD and actinic keratosis but no association with basal cell carcinoma or squamous cell carcinoma (Hajdarbegovic et al., 2016). A recent population-based case-control study found an inverse association between a history of allergy and early-onset basal cell carcinoma but not with squamous cell carcinoma or melanoma (Cheng et al., 2015) (see Supplementary Table S1). Reasons for such inverse associations between AD and cancer may include increased immune surveillance and eradication of dysregulated cells by systemic inflammation (Fu et al., 2008), as well as the reported IgE-facilitated cross-presentation of tumor antigens by dendritic cells (Platzer et al., 2015).

Neuropsychiatric disorders

AD is associated with higher rates of psychological diseases such as depression, anxiety, suicidal ideation, attention deficit/hyperactivity disorder, and autism spectrum disorder (Arima et al., 2005; Buske-Kirschbaum et al., 2013; Dalgard et al., 2015; Dieris-Hirche et al., 2009; Riis et al., 2016; Sanna et al., 2014; Schmitt et al., 2010; Schut et al., 2014; Yaghmaie et al., 2013) (see Supplementary Table S1). Although most studies do not allow conclusions on temporal relationships and thus causality, a longitudinal Taiwanese study found that the presence of any atopic disease in early childhood (i.e., before 3 years of age) increased the risk of developing attention deficit/hyperactivity disorder (hazard ratio = 1.97) and autism spectrum disorder (hazard ratio = 3.40) later in life, with increasing risks with higher numbers of atopic diseases (Chen et al., 2014). The individual contribution of AD, however, was not reported.

The underlying mechanisms of neuropsychiatric disorders in AD are still unclear, but associations are potentially driven by the harmful effects of AD on quality of life (Chrostowska-Plak et al., 2013; Senra and Wollenberg, 2014), unbearable chronic itch, and sleeplessness (Weisshaar et al., 2008). Clinical investigations have associated depression, anxiety, and autism with elevated levels of proinflammatory (although not Th2) cytokines (Kiecolt-Glaser et al., 2011; Pollak and Yirmiya, 2002; Zimmerman et al., 2005), which theoretically could penetrate the blood-brain barrier (Yarlagadda et al., 2009) and modulate behavior and emotions (Buske-Kirschbaum et al., 2013; Ishiuji et al., 2009; Raison et al., 2006; Rosenkranz et al., 2005). Other chronic health conditions of childhood also increase the risk of emotional and behavioral problems, including attention deficit/hyperactivity disorder (Blackman et al., 2011).

Itch is central to the burden of AD and is significantly correlated with sleeplessness. Itch is also associated with coping behavior and poor quality of life in parents of children with AD (Weisshaar et al., 2008), which should be monitored when evaluating the impact of AD treatment (Metz et al.,

2013; Senra and Wollenberg, 2014). Itch mechanisms in AD are complex and involve cutaneous nerves as well as inflammatory cells and keratinocytes (Kim, 2012; Suarez et al., 2012). There is evidence for a direct correlation between the density of peripheral nerves and AD severity (Sugiura et al., 1997; Tominaga et al., 2009). Furthermore, central mechanisms are speculated to contribute to central sensitization, resulting in a loss of inhibitory control and synaptic recruiting of excitatory interneurons (Stander et al., 2015; Suarez et al., 2012).

OUTLOOK

The growing list of potential cutaneous and systemic AD comorbidities reflects the increasing appreciation of its high burden, both on affected individuals and their families, making the development of better interventions even more urgent. Pathophysiological interconnections are complex, because infections and allergies often develop during active disease, but malignancy or cardiovascular disease may be related to longstanding chronic inflammation or may even occur years after disease activity had abated. Although epidemiologic studies aim to reduce discernible bias and confounder effects (Nijsten and Wakkee, 2009; Schmitt and Weidinger, 2014), statistical associations cannot prove causality. As new treatment approaches for AD are being developed, monitoring of patients longitudinally to determine the impact of these approaches on AD-associated comorbidities, in addition to skin manifestations, will likely reveal mechanisms of disease associations and result in the development of more targeted, or even personalized, treatment approaches.

CONFLICT OF INTEREST

JIS is a consultant for AbbVie, GlaxoSmithKline, Lilly, Medimmune, Proctor & Gamble, Regeneron Sanofi, and Anacor. EGY is a board member for Sanofi Aventis, Regeneron, Stiefel/GlaxoSmithKline, MedImmune, Celgene, Anacor, AnaptysBio, Celsus, Dermira, Galderma, Glenmark, Novartis, Pfizer, Vitae, and Leo Pharma; has received consultancy fees from Regeneron, Sanofi, MedImmune, Celgene, Stiefel/GlaxoSmithKline, Celsus, BMS, Amgen, Drais, AbbVie, Anacor, AnaptysBio, Dermira, Galderma, Glenmark, LEO Pharma, Novartis, Pfizer, Vitae, Mitsubishi Tanabe, and Eli Lilly; and has received research support from Janssen, Regeneron, Celgene, Bristol-Myers Squibb, Novartis, Merck, LEO Pharma, and Dermira. ASP is an investigator for Anacor, Astellas, and LEO Pharma and has received honoraria related to atopic dermatitis consulting from Anacor, Galderma, GlaxoSmithKline-Stiefel, Novartis, Regeneron, and Vitae Pharmaceuticals. KK is in an advisory board for Chugai. MD is an advisor for Meda Pharma, Regeneron, Sanofi, and Pierre Fabre and an investigator for AbbVie, Novartis, Pierre Fabre, and Regeneron. The other authors state no conflict of interest.

ACKNOWLEDGMENTS

We acknowledge other Councilors of the International Eczema Council who participated in the original discussion for their valuable input: Martine Bagot, Dirk Jan Hijnen, Michael Ardern-Jones, Nick Reynolds, Phyllis Spuls, and Alain Taieb.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at http://dx.doi.org/10.1016/j.jid.2016.08.022.

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