IN-DEPTH REVIEWS

Systemic Manifestations of Atopic Dermatitis: A Systematic Review

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ABSTRACT

Background: Atopic dermatitis (AD) is known to be associated with other allergic diseases, which often develop later in life in a serial fashion. This progression is termed the “atopic march” and is considered the classical presentation of atopic disease. However, recent evidence suggests that this paradigm may not hold true for a significant portion of patients with these conditions. Not only is the timing of development likely more complex than previously believed, the comorbidities associated with AD are possibly more numerous and varied.

Methods: This two-step systematic review involved a targeted search of PubMed and EMBASE with an additional hand search of key journals. The terms “atopic dermatitis” and “atopic eczema” were searched in conjunction with multiple keywords representing the concept of systemic nature of disease. All titles and abstracts were subsequently screened for relevance to the research question.

Results: This review’s evidence supports an association between AD and other atopic diseases. However, it also suggests that the classical paradigm of the “atopic march” does not apply to all patients with atopic dermatitis. There appears to be a significant association between AD and multiple neuro-psychiatric comorbidities, particularly ASD and ADHD. Additional themes supported by lower-level evidence are increased risk of cardiovascular disease, decreased risk of type I diabetes, and increased risk of multiple malignancies in patients with AD.

Conclusion: There is likely a diversity of phenotypes for patterns of allergic disease. Both positive and negative associations identified in this systematic review suggest that AD is condition with varied systemic manifestations.

BACKGROUND

Atopic dermatitis (AD) is known to be associated with other allergic diseases. These conditions include asthma, food allergy, and allergic rhinoconjunctivitis[1]. AD typically occurs in early childhood with allergic comorbidities developing later in life in a serial fashion. This progression is termed the “atopic march” and is

considered the classical presentation of atopic disease[2]. However, recent evidence suggests that this paradigm may not hold true for a significant portion of patients with these conditions[3]. Not only is the timing of development likely more complex than previously believed, the comorbidities associated with AD are possibly more numerous and varied[4].

Because AD is an inflammatory disease characterized by ongoing T-cell activation and cytokine production, it stands to reason that its mediators could have an effect on multiple extracutaneous organ systems. If the mechanisms underlying atopic disease do indeed play a role in the development of non-atopic comorbidities, it would support the notion put forth by Brunner et al. (2016) that AD should be regarded as a systemic disease. The body of evidence behind this idea is rapidly expanding, with associations between AD and autoimmune, infectious, cardiovascular, neuro-psychiatric, and gastrointestinal disease becoming more well defined. However, there has not been a systematic review on this topic to date.

METHODS

We conducted a two-part systematic search of the literature on AD and extracutaneous disease. The first part involved a targeted search of PubMed (MEDLINE + Cochrane Library) and EMBASE. In both of these databases “atopic dermatitis” and “atopic eczema” were searched in conjunction with various keywords representing the concept of systemic nature of disease (Table 1). The second part of the systematic search process was a hand search of all recent abstracts accepted by the AAD and EADV and abstracts published in 5 key journals (*Journal of the American Academy of Dermatology, Journal of the European Academy of Dermatology and Venereology, British Journal of Dermatology, American Journal of Clinical Dermatology, and the Journal of Allergy and Clinical Immunology*) within the past 2 years. All hits returned by both parts of the search process were screened for possible inclusion. Narrative reviews, single-case studies, animal studies, editorials, non-English articles, and articles published prior to 1996 (greater than 20 years old) were excluded in a first review. Next, titles and abstracts were screened for relevance to the research question. Finally, all included articles were rated for quality of evidence with a Newcastle-Ottowa score[5]. This scale was chosen because the majority of included articles were case-control or cohort studies.

RESULTS

The numbers of references obtained after each step of the search process are detailed in Table 2. The final yield of the two-step, systematic search was 65 articles. These consisted of 41 case-control studies (63.1%), 19 cohort studies (29.2%), and 5 meta-analyses (7.7%). Mean star ratings on the Newcastle Ottowa scale for case-control studies were: Selection 2.44, Comparability 1.56, and Exposure 2.21. For cohort studies, mean ratings were 3.26, 1.63, and 2.37, respectively. Non-atopic comorbidities identified in these studies included autoimmune disease, cardiovascular disease, gastrointestinal disease, neuro-psychiatric disease, infectious disease, and malignancy. All distinct associated conditions identified during the search process are discussed below; when multiple studies revealed a positive association with a comorbidity, those with the highest Newcastle Ottowa score were cited.

FIGURES/TABLES

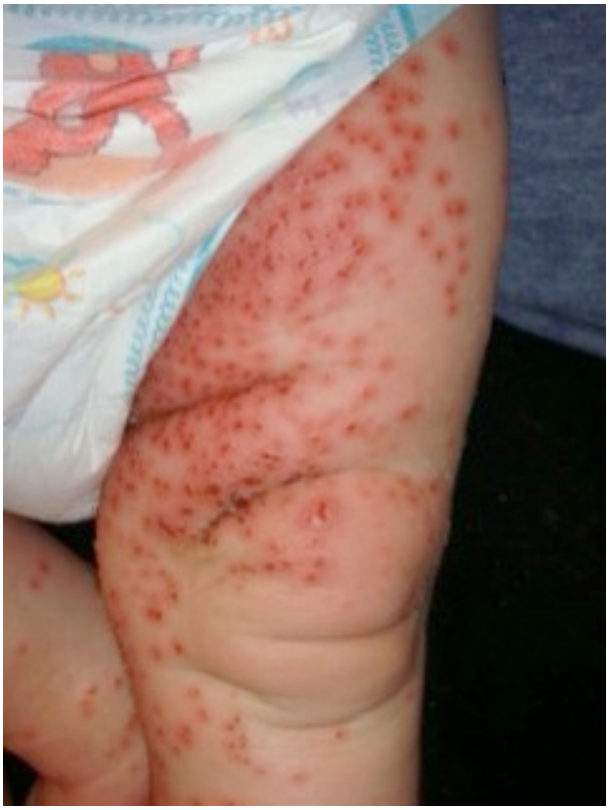

Figure 1. Eczema herpeticum. This vesicular eruption is caused by viral infection, typically HSV, of pre-existing atopic dermatitis.

Concept	Keywords/Phrases
Atopic dermatitis	Atopic dermatitis
	Atopic eczema
Systemic nature of disease	Systemic, inflammat*
	Epidemiology, etiology
	Comorbid*
	Autoimmun*, immun*, cytokine activation
	Atopic march, food allergy, asthma
	Cardiovascular, gastrointestinal, neuro-psychiatric, malignancy

Table 1. Keywords used in systematic search process. Truncation symbols are represented by asterisk.

DISCUSSION

Results obtained in this review support the notion that the development of various allergic diseases is a dynamic process. There are numerous studies that describe the relationship among AD, asthma, food allergy, hay fever, allergic rhinitis, and atopic ophthalmic disease. While the "atopic march" pattern is prevalent, there is evidence that it may represent only one particular phenotype of allergic disease[6]. Additionally, development of one allergic disease does not dictate which additional diseases might develop or when[7]. This apparent variability of phenotypes is worth mentioning before any discussion of non-atopic comorbidities, as it is possible that each one produces distinct extracutanous disease.

Autoimmune Disease: The most well studied autoimmune disease investigated with AD is type I diabetes mellitus. The great majority of the evidence, including the study with the highest Newcastle Ottowa score, supports an inverse relationship between AD and type I diabetes[8]. In other words, children with insulin-dependent diabetes are less likely to suffer from eczema. This is thought to be due to negative interaction between Th1 and Th2 subsets[9]. Interestingly, no association was shown between diabetes and asthma or hay fever. There is less data available on the association between AD and other autoimmune diseases. Two studies provide conflicting evidence on its relationship with lupus erythematosus[10, 11], although the study showing a positive association is both more recent and higher quality by Newcastle Ottowa score. Finally, there is one cohort study suggesting that AD may be a risk factor for rheumatoid arthritis[12].

Cardiovascular Disease: The data on cardiovascular disease and risk factors in the AD population are more heterogeneous. Evidence was mixed on the association between AD and increased BMI or hypertension. However, one study demonstrated an increased prevalence of coronary artery disease in AD patients using CT angiography[13]. The highest-scoring study related to cardiovascular disease demonstrated an increased risk of adverse cardiovascular outcomes in a cohort of 145,372 patients, including myocardial infarction, ischemic stroke, and cardiovascular death[14]. A possibly related comorbidity, erectile dysfunction, was observed in a case-control study to occur more frequently in AD patients[15]. Interestingly, one study showed an association between AD and IgA vasculitis in children[16]. For all of these cardiovascular conditions, further studies are needed to clarify the role of lifestyle and psychosocial factors in their development.

Gastrointestinal Disease: There is extensive literature on the relationship between AD and food allergy, as discussed above. However, less information is available on non-allergic gastrointestinal disease. One case-control study examined various gastrointestinal symptoms in the pediatric AD population and found an increased incidence of vomiting, regurgitation, and diarrhea[17]. There is also emerging evidence supporting the role of the intestinal microbiome in the development of AD and the possibility of probiotic use in therapy[18]. There is one case-control study showing that children with AD are predisposed to develop fatty liver, but further investigation is needed[19]. Finally, the cohort study mentioned above suggests that, in addition to being a risk factor for rheumatoid arthritis, AD might also be a risk factor for inflammatory bowel disease[12].

Neuro-Psychiatric Disease: There is a significant body of evidence supporting an association between AD and autism spectrum and attention deficit hyperactivity disorders (ASD, ADHD). One retrospective cohort study

of 21,756 patients demonstrated that AD occurring before the age of 3 increased the risk of developing both of these conditions[20]. Additionally, increased rates of depression, anxiety, somatization, and injury requiring medical attention have been observed in multiple case-control studies[21-23]. These associations are often positively correlated with severity of AD. One possible explanation for these phenomena is sleep disturbance in AD patients. A case-control study found that inadequate sleep persists even when patients are in clinical remission[24].

Malignancy: Multiple high-quality studies analyze the risk of cancer in patients with AD. There is consistent evidence that AD patients are at increased risk for lymphoma, squamous cell carcinoma, and basal cell carcinoma[25-27]. However, a case-control study of 13,687 patients found that the increased risk of lymphoma was correlated with length of treatment with topical corticosteroids[27]. Further studies are therefore needed to disentangle the effects of disease and the effects of treatment on skin cancer risk. There is conflicting evidence regarding other types of cancer. For instance, there is low-quality evidence of both increased and decreased risk of central nervous system malignancy in the AD population[28, 29]. A meta-analysis focusing on leukemia noted that available data were also quite heterogeneous[30]. It did, however, find a significant inverse relationship between AD and ALL. Future high-quality cohort studies are needed to evaluate the risk of these malignancies.

Infectious Disease: It is well documented that patients with AD are at increased risk for certain cutaneous infections due to the compromised barrier function of the skin. These classically include *Staphylococcus aureus*, herpesvirus (Fig. 1), and cocksackivirus. However, studies identified in this literature review also provided evidence for association with warts, molluscum, otitis media, and dental caries[31-34]. It is worth noting a case series that did not meet inclusion criteria for this review, which described an increased incidence of infectious endocarditis in AD patients[35]. Because of the severity of this possible comorbidity, a case control or cohort study is recommended.

CONCLUSIONS

The results of this systematic review support the notion that atopic dermatitis is strongly associated with other atopic diseases, including asthma, hay fever, and allergic rhinoconjunctivitis. However, it also suggests that the classical paradigm of the “atopic march” does not apply to all patients with atopic dermatitis. There is likely a diversity of phenotypes for patters of allergic disease. Our analysis supports a significant association between AD and multiple neuro-psychiatric comorbidities, particularly ASD and ADHD. Additional themes supported by lower-level evidence are increased risk of cardiovascular disease, decreased risk of type I diabetes, and increased risk of multiple malignancies in patients with AD. In conclusion, the systemic manifestations of AD are likely multifactorial, resulting from both the inflammatory disease itself and associated lifestyle factors.

Conflict of Interest Disclosures:
Dr. Emma Guttman-Yassky has served on advisory boards for AbbVie, Anaco, Celgene, Demira, Galderma, Glenmark, Leo Pharmaceuticals, Medimmune, Novartis, Pfizer, Regeneron, Sanofi, Stiefel/GlaxoSmithKline, Vitae, Mitsubishi Tanabe, Eli Lilly, Asana Biosciences, Kiowa Kirin, and Almirall

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