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Atopic Dermatitis: a Systemic Disease

Ana Clara Oliveira

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Autora

Ana Clara Marques Oliveira

Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Correio eletrónico: anaclara.m.oliveira@gmail.com

Orientador

Prof. Doutor Tiago Torres

Assistente de Dermatologia e Venereologia – Centro Hospitalar do Porto

Professor Auxiliar Convidado de Dermatologia do Mestrado Integrado de Medicina do Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

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Autora

Ana Clara Marques Oliveira

Orientador

Prof. Doutor Tiago Torres

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Abstract

Atopic dermatitis is a worldwide prevalent chronic inflammatory skin disease, affecting predominantly children, although it may persist into adulthood. Pruritic eczematous lesions with age-related morphology and distribution are a central feature of the disease which, along with other symptoms, seriously affect patients' quality of life. Both immune dysregulation and cutaneous barrier dysfunction are involved in the pathophysiology of the disease, although the exact mechanisms are still unclear. The concept of atopic dermatitis as a biphasic Th1-Th2 disease is changing, as recent evidence supports systemic activation of multiple other Th-cells subsets.

Atopic dermatitis has been associated with an increasing number of comorbidities, possibly sharing some common pathological mechanisms. The atopic march is well known and represents the natural progression of atopic diseases in a considerable number of patients, usually starting with the development of atopic dermatitis followed by other atopic conditions, such as asthma and allergic rhinitis. Association of atopic dermatitis with cardiovascular disease, autoimmune diseases, as well as cutaneous and extracutaneous infections have been increasingly reported, although the link is not yet clear, requiring more research. Furthermore, the association between atopic dermatitis and neuropsychiatric conditions has also been widely studied, with the increased risk of mental health disorders being strongly influenced by sleep disorders, which are also prevalent among these individuals.

Altogether, these associations contribute to the burden of atopic dermatitis, which increases the need of a closer and multidisciplinary approach of the patients, regarding the best control of their skin disease, along with prevention or early diagnosis and treatment of the comorbidities that may arise.

This review explores the recent associations with atopic dermatitis and the possible underlying mechanisms involved, which supports the concept of atopic dermatitis as a systemic disease.

Key-words: atopic dermatitis; comorbidity; autoimmune diseases; cardiovascular diseases; infection; mental disorders.

Resumo

A dermatite atópica trata-se de uma doença cutânea inflamatória crónica prevalente em todo o mundo, que afeta principalmente crianças mas que pode persistir na idade adulta. As lesões eczematosas pruriginosas são uma característica central da doença que, juntamente com os outros sintomas, afetam gravemente a qualidade de vida dos pacientes. A fisiopatologia da doença envolve uma desregulação imune e uma disfunção da barreira cutânea, no entanto os mecanismos exatos ainda não estão totalmente claros. O conceito de dermatite atópica como uma doença bifásica Th1-Th2 tem sido desafiado, uma vez que evidências recentes enfatizam uma ativação sistémica de múltiplos grupos de células Th.

A dermatite atópica tem sido associada a um número crescente de comorbilidades que possivelmente partilham alguns mecanismos patológicos. A marcha atópica é bem conhecida e representa a progressão natural das doenças atópicas num número significativo de pacientes, geralmente sendo iniciada pelo desenvolvimento da dermatite atópica, seguida por outras condições atópicas, como a asma e a rinite alérgica. A associação da dermatite atópica com doenças cardiovasculares, autoimunes, assim como com infeções cutâneas e extracutâneas tem sido cada vez mais demonstrada, apesar da sua relação ainda não ser clara, exigindo mais estudos. Além disso, a associação entre dermatite atópica e distúrbios neuropsiquiátricos também tem sido largamente estudada, sendo que o risco aumentado de doença mental é fortemente influenciado pelas perturbações do sono, que também são prevalentes nestes indivíduos.

No seu conjunto, estas associações contribuem para o impacto negativo da dermatite atópica, aumentando a necessidade de uma abordagem mais próxima e multidisciplinar dos pacientes, tendo em vista o melhor controlo da sua doença cutânea, assim como a prevenção ou diagnóstico precoce e tratamento das comorbilidades que possam surgir.

Esta revisão bibliográfica explora as associações mais recentes da dermatite atópica e os possíveis mecanismos subjacentes envolvidos, que apoiam o conceito de dermatite atópica como uma doença sistémica.

Palavras-chave: dermatite atópica; comorbilidade; doenças autoimunes; doenças cardiovasculares; infeção; doenças mentais.

Abbreviations list

AA – Alopecia areata
AD – Atopic dermatitis
ADEH – Atopic dermatitis complicated with eczema herpeticum
ADHD – Attention Deficit/Hyperactivity Disorder
aOR – adjusted odd ratio
ASD – Autism Spectrum Disorders
CAD – Coronary artery disease
CD – Crohn's disease
CI – Confidence interval
CRP – C-reactive protein
CVD – Cardiovascular disease
CVRF – Cardiovascular risk factors
EASI – Eczema Area and Severity Index
EH – Eczema herpeticum
FLG – Filaggrin
HPV – Human papilloma virus
HR – Hazard ratio
HSV – Herpes virus simplex
IBD – Inflammatory bowel disease
IC – Impetigo contagiosum
Ig – Immunoglobulin
MCV – Molluscum contagiosum virus
MI – Myocardial infarction
MRSA – Methicillin-resistant Staphylococcus aureus
OR – Odd ratio
PR – Prevalence ratio
RR – Risk ratio
SA – Staphylococcus aureus
SCORAD – Scoring of Atopic Dermatitis
SLE – Systemic lupus erythematosus
Th – T-helper
UC – Ulcerative colitis
US – United States

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Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin disorder affecting up to a fifth of the population in developed countries.[1] The prevalence of the disease is higher among children, but many continue to be affected during adulthood.[2]

AD has a complex pathogenesis which includes barrier dysfunction and immune dysregulation that is driven by interactions of genetic and environmental factors.[3] The abnormal cutaneous barrier facilitates the exposure to environmental allergens, with the subsequent activation of the immune system, resulting in the development of the inflammatory cascade of atopic disease.[3] The immune profile in AD is complex and, although it has been considered a biphasic T helper (Th) 2/Th1 mediated disease, recent studies have suggested that patients with AD also show Th22 and Th17 activation.[4] Filaggrin (FLG) is a structural protein of the cutaneous barrier and mutations in the FLG gene are associated with an increased risk of AD (with more than 40% of all carriers affected), asthma, allergic rhinitis, contact allergy and peanut allergy.[5] FLG deficiency is associated with early AD onset, severe disease, greater allergic sensitization and higher incidence of skin infections with herpes virus.[6] FLG mutations also seem to play a role for disease persistence, as well as early onset of AD and the existence of atopic comorbidities.[7,8]

The diagnosis of AD relies on clinical features. Essential features are pruritus and eczematous lesions, with age-related morphology and distribution, usually affecting extensor surfaces of the body and face during the infantile phase, shifting to flexural surfaces in childhood and later to the hands, head and neck in adults.[1,8] Other dermatological signs and symptoms of AD include xerosis, lichenification and prurigo-like nodules.[1] Altogether, the AD manifestations contribute toward deep disturbances on the physical and psychosocial wellbeing of patients, negatively affecting their quality of life.[8]

AD has long been closely associated with other atopic disorders, however recent studies have suggested multiple other associations, such as cardiovascular diseases (CVD), autoimmunity/inflammatory diseases, infections, neuro-psychiatric disorders, among others, some of which are more controversial than the rest. For this reason, the concept of AD as a systemic disease is gaining strength, along with a greater need for data on the comorbidity profile of patients with AD.

Objectives and Methods

The purpose of this review is to explore the recent developments in the immune profile and comorbidities of AD which suggest that it is not only a dermatological condition but also a systemic disease.

The research for this review included studies published from 2007 to 2017 and written in English, searched through PubMed and Science Direct using the keywords *atopic dermatitis/atopic eczema* exclusively and combined with *comorbidity*, *autoimmunity*, *inflammatory diseases*, *cardiovascular*, *infection* and *mental health disorders*.

Only original studies were considered, with the exception of two review articles that were used to assess solid concepts related to AD prevalence, pathophysiology, signs and symptoms, and one metaanalysis due to its relevance. Studies were included based on the title or abstract if they were investigating the immune alterations of AD, the association between AD and other diseases/comorbidities or the possibility of AD being a systemic disease. Furthermore, some studies were rejected after their full-text analysis in case they did not meet the objective of this review, if not yet excluded based on the above-mentioned criteria. Additionally, some articles cited in the selected publications were included in the analysis.

The atopic march

AD is often accompanied by other atopic diseases, and it is usually the first step of the so-called atopic march[9], given that the dysregulated epidermal barrier facilitates allergenic sensitization[10], with the subsequent onset of other conditions such as allergic rhinitis and asthma or even food allergy and allergic conjunctivitis.[9]

AD is traditionally divided in extrinsic and intrinsic sub-types, comprising approximately 80% and 20% of atopic patients, respectively.[11] The first form of AD is usually characterized by elevated serum immunoglobulin (Ig) E, often with a positive personal and familial history of atopy and specific IgEs to allergens; the second and less common form, although phenotypically identical, does not show high serum IgE, sensitization to specific allergens or other atopic comorbidities.[11] Nevertheless, those definitions have been challenged by recent findings. Pinart et al.[12] used data from a large network of longitudinal birth cohorts in 8 European countries, the Mechanisms of the Development of ALLergy (MeDALL) project, to investigate the excess atopic comorbidity of eczema, allergic rhinitis and asthma and its modification by IgE sensitization, in children at 4 and 8 years of age. The comorbidity of two or three of those atopic conditions exceeded the expected by chance alone (if the diseases were independent). They found a greater absolute excess comorbidity in children with IgE sensitization than in those without, however the excess comorbidity was also demonstrated in children without IgE sensitization. Also, the presence of IgE sensitization at age 4 years independently increased the relative risk of comorbidity at age 8 years, which supports the role of IgE sensitization in comorbidity. On the other hand, stratifying by IgE sensitization, the relative risk of comorbidity was stronger in children without serum-specific IgE, questioning the dominant role of IgE sensitization in atopic comorbidity. Ultimately, the researchers showed that only 38% of the incidence of comorbidity at age 8 years was due to IgE sensitization, so additional studies should be warranted to assess the mechanisms involved in this excess of comorbidity.

Since it is unclear why only a part of patients with AD develop other atopic diseases, Wan and colleagues[13] aimed to assess the role of the age of AD onset on the risk for asthma and seasonal allergies in a cohort study. They found a higher prevalence of both atopic diseases in patients in the early AD onset group (before 2 years of age) than in mid- and late-onset groups (3 to 7 and 8 to 17 years, respectively). The risk for development of seasonal allergies significantly decreased as the age of AD onset increased, but the same was not true to asthma. Hence, the timing of AD onset may explain the variation in the atopic march, but only partially. Furthermore, FLG mutations

also play a role in the AD associated atopic diseases, as AD carriers of those mutations have an increased risk of asthma.[10]

The AD onset before 2 years of age also appears to be an important factor on the persistence of the disease in adulthood, along with childhood hand eczema and comorbid allergic rhinitis, in contrast with asthma and allergic contact dermatitis during childhood, which were not significant risk factors for the maintenance of the disease in a study conducted by Mortz et al.[8]

Although atopic comorbidities are the most established associations of AD, the study of these associations in order to find the underlying causal mechanisms appears to be far from over.

Systemic immune activation in Atopic Dermatitis

There are increasing evidences for systemic immune activation in AD. Cytometry studies have shown that moderate-to-severe AD patients have increased activated T-cell subsets in blood compared to controls,[14,15] and at even higher frequencies than in patients with psoriasis.[14] Also, pathologic T-cell activation extends into skin-homing and central memory populations.[14]

A recent study[16] involving moderate-to-severe AD patients looked for new biomarkers that would correlate with AD severity, assessed with Scoring of AD (SCORAD), and with an epidermal hyperplasia score (thickness and K16 mRNA), before and after Cyclosporine A treatment. These researchers found that AD patients had increased serum cytokines and chemokines compared to controls, which were reduced with treatment, and they also found that SCORAD correlated with immune and epidermal measures in lesional, and even more strongly in non-lesional skin.

Another study[17] compared the AD profile of serum inflammatory mediators to patients with psoriasis and there were large differences between AD and psoriasis blood signature, with more immune pathways showing stronger activation in AD patients (e.g. cytokine-cytokine receptor interaction, chemokine signaling pathway, cytokines and inflammatory response, dendritic cell pathway, Th1/Th2 differentiation). It was found increased Th1, Th2, Th17/Th22 and Th1/Th17/Th22 products in the blood of AD patients and, additionally, several inflammatory mediators from all T-helper-cells axes correlated with lesional and non-lesional skin. Indeed, in another recent study,[11] both intrinsic and extrinsic forms of AD showed significant increases in gene expression levels of Th2 and Th1 cytokines in lesional and non-lesional skin, although lesional skin in intrinsic AD

showed significantly more robust Th22 and Th17 immune responses compared to extrinsic AD.

Vekaria et al.[18] conducted a retrospective study and showed that AD patients had significantly increased blood C-reactive protein (CRP) levels, an acute phase reactant whose levels rise in response to systemic inflammation, compared to controls. Even after they excluded all patients with a history of asthma, a disease associated with increased CRP serum levels, differences remained significantly higher. Interestingly, in this study, they also demonstrated a correlation between AD severity and CRP levels.

Altogether, these findings reflect the strong immune activation in AD and highlights the systemic abnormalities of AD beyond the skin and allergic associations.

Autoimmune and inflammatory diseases

Accumulating evidence suggests an association between AD and a variety of autoimmune diseases. Andersen et al.[19] examined the co-occurrence of 22 autoimmune diseases in adults with AD and showed that AD was significantly associated with 11 of those diseases, wherein patients with a history of smoking had a significantly higher risk.

Vitiligo and alopecia areata (AA) are autoimmune disorders that have been associated with AD. Vitiligo is characterized by melanocyte destruction which leads to loss of pigmentation. Silverberg and Silverberg[20] found a significantly increased prevalence of AD in patients with vitiligo involving a body surface area of at least 76% and itching or burning of skin, compared to the general population. The authors suggested that the pro-inflammatory status of AD may lead to melanocyte destruction and that there may be a common genetic mutation which predisposes to both AD and vitiligo. Furthermore, Augustin et al.[21] reported that vitiligo was seen 3.3 times as often in children with AD than in control subjects, and as well that the prevalence of AA was significantly higher in children with AD than in non-AD children.

A self-reported history of atopy, particularly AD, was associated with an increased risk of AA in a case-control study with 2055 patients with AA and 558 controls.[22] Moreover, FLG mutations are more frequent among AA patients with a history of AD and, in that case, the clinical presentation of AA may be more severe, which suggests that an epidermal barrier defect contributes to a severe course of AA.[23]

Systemic lupus erythematosus (SLE) is another autoimmune disease that has been associated with AD.[19,24-26] A Taiwanese study[24] found that patients with AD have a significantly higher risk of SLE compared to healthy controls. The researchers also found that female AD patients and juvenile patients with AD younger than 18 years old had an

increased risk of SLE in relation to male AD patients and adult patients with AD, respectively. Th2 response is predominant in SLE and is also part of the AD pathogenesis, therefore SLE and AD share similar immune dysfunction, suggesting that these dysregulations and the overproduction of inflammatory mediators may have a role for the increased risk of SLE in patients with AD.[24]

Using The National Health Insurance Research Database of Taiwan, Wei et al.[25] conducted a retrospective cohort study in which they compared 192,357 AD patients with 769,428 non-AD controls aged under 18. The incidence of juvenile SLE was 2.90-fold greater in the AD group than in the non-AD subjects and the incidence rates of SLE were higher for girls than for boys. In addition, a study[26] showed that SLE subjects had more atopic disease comorbidities compared to the control group, especially AD but also allergic rhinitis, allergic conjunctivitis and asthma and, again, this was particularly observed for female patients.

Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract caused by an abnormal activity of the immune system, with its main forms being Crohn's disease (CD) and ulcerative colitis (UC).[27] A recent Danish study[19] comparing 8,112 adults with a diagnosis of AD with 40,560 age- and sex-matched controls reported that AD was significantly associated with both CD (aOR 2.09; 95% CI: 1.52-2.85) and UC (aOR 1.64; 95% CI: 1.31-2.05). Additionally, another study[21] demonstrated that the prevalence of UC among children affected with AD is significantly higher than among controls, however, even though they found a greater prevalence of CD in the patients group, this association was not statistically significant.

A retrospective cohort study[28] used data from German National Health Insurance beneficiaries aged 40 or younger, including 49,847 individuals classified as having prevalent AD and 605,968 non-AD subjects. The researchers found that patients with AD were at increased risk for incident IBD, including CD (RR 1.34; 95% CI: 1.11-1.61) and UC (RR 1.25; 95% CI: 1.03-1.53). They also explored established IBD loci in high-density genotyping data from 2,425 patients with AD and 5,449 controls, but they did not find a higher proportion of risk alleles for IBD associated with AD in a consistent directionality more frequently than the 50% expected by chance. Nevertheless, one UC locus and four CD risk loci were significantly associated with AD, including important genes for adaptive immune regulation and tissue response.

A South Korean cross-sectional study[27] assessed the risk of patients with IBD developing inflammatory skin diseases, comprising AD, psoriasis and rosacea. After adjusting for age and sex, the authors reported that patients with IBD were at an increased risk of AD, compared to control subjects. Th17-mediated inflammation is

important in the pathogenesis of IBD[27] and increasing evidences suggest that Th17 cells are also involved in the pathogenesis of AD.[17,27]

Celiac disease is a childhood immune-mediated disease of the small intestine in which the ingestion of products with gluten causes chronic inflammation and damage of the mucosa.[29] Atopy has been found frequently in individuals with celiac disease in previous studies so, recently, Ress et al.[29] studied a sample of 351 Estonian children with active AD and found a 4-times greater prevalence of celiac disease than in randomly selected schoolchildren. They also found that AD patients can present an atypical or silent celiac disease, although with important histological features.

This apparent increased risk of autoimmune/inflammatory diseases in AD patients may be due to similarities in the genetic susceptibilities and immune activation, yet it is not possible to make conclusions about causality based on observational data. In any case, physicians accompanying AD patients should increase awareness of autoimmune comorbidities in those patients.

Cardiovascular risk and disease

Recent studies have suggested an association between AD and cardiovascular risk factors (CVRF) and disease. Patients with AD are more likely to have CVRF such as sedentary lifestyle, performing less vigorous physical activity, increased alcohol and cigarette consumption[30,31], obesity[30,32,33], high blood pressure[30,33] and high cholesterol[30].

Zhang and Silverberg[32] performed a meta-analysis of 30 observational studies to examine the relationship between AD and overweight/obesity and they concluded that there is a significant association in North America and Asia, where children and adults with AD present a higher prevalence of overweight and obesity than the general population, but the same was not observed in Europe. Also, a case-control study[33] performed in multicenter pediatric dermatology practices in the United States (US) suggests that moderate to severe AD in children may be associated with central obesity and increased systolic blood pressure.

A Taiwanese study[34] using a national database demonstrated that patients with AD had a higher risk of ischemic stroke and, even after adjusting for age, sex, comorbidities, and medications, patients with AD had a 1.33-fold increased incidence, suggesting that AD is an independent risk factor for ischemic stroke. Additionally, they showed a correlation between the severity of the disease and the risk of ischemic stroke, with severe forms of the skin condition presenting a higher risk than mild or moderate forms.

Using Cardiac Computed Tomography Angiography, Hjuler et al.[35] showed an increased coronary artery calcium score of the coronary vessels and mild single-vessel disease in adults with AD without known CVD. Moreover, the prevalence of coronary artery disease (CAD) appears to increase in subjects with severe and persistent AD, so these findings indicate that AD might be associated with a higher risk of CAD.[35]

In a US National Health and Nutrition Examination Survey (2005-2006), using multi-variate models that controlled for socio-demographic factors, asthma and allergic rhinitis, flexural eczema was associated with significantly increased odds of CAD, heart attack and congestive heart failure, although the same association was not found with stroke.[36] In models that controlled for CVRF, only the association between eczema and CAD remained significant. Likewise, in two US National Health Interview Surveys (2010 and 2012), 1-year history of eczema was associated with significantly higher odds of CAD, angina, heart attack, other heart disease, stroke and peripheral vascular disease in multivariate models.[36]

Nevertheless, contradictory findings about the association between AD and CVD are rising. A Danish study[37] comprising a total of 26,898 mild and 2,527 severe cases of AD and 145,372 control subjects, initially found an increased risk of CVD in AD patients, however, after adjusting for socioeconomic status, smoking, medication, and comorbidities the increased risk was no longer present. So, this higher incidence of adverse cardiovascular outcomes seems to be explained by an increased burden of comorbidities and harmful life behaviors. Indeed, a study that assessed the major comorbidities[38], and not only CVD, in adults with AD using the Charlson comorbidity index, showed that the risk for important comorbidities was significantly increased in patients with AD compared to non-AD controls and this risk difference was especially found in subjects with severe disease and, again, among smokers.

Although Silverberg and Greenland[30] found that adults with eczema had higher rates of prediabetes and diabetes, another study[31] demonstrated a lower prevalence of type 2 diabetes in patients with AD than in psoriasis patients, as well as in controls.

In fact, newer studies are suggesting that AD is not an independent risk factor for CVD. Drucker et al.[39] conducted a cross-sectional analysis from a large Canadian cohort and, in contrast to the above-mentioned studies, found that AD was inversely associated with hypertension (OR 0.87; 95% CI: 0.83-0.90), type 2 diabetes (OR 0.78; 95% CI: 0.71-0.84), myocardial infarction (MI) (OR 0.87; 95% CI: 0.75-1.00) and stroke (OR 0.79; 95% CI: 0.66-0.95). Besides that, in a cohort of American women[40], AD was not independently associated with non-fatal MI or stroke, after controlling for important mediators of CVD.

Longitudinal analysis of AD patients in the German AOK PLUS cohort[41] showed a weak association between AD and the development of hypertension, angina pectoris

and peripheral arterial disease, but not for MI and stroke. Furthermore, in the same study, the authors did not find robust evidence for shared genetic risk variants of AD and CVD.

Marshal et al.[42] aimed to determine whether three major inflammatory dermatologic diseases, namely AD, psoriasis and rosacea, were independent risk factors for CVD 1-year following diagnosis. Comparing with controls, the adjusted odds of cardiovascular outcomes were not higher in patients with any of the three conditions.

Although there are contradictory results, altogether these findings suggest that rather than the systemic inflammation associated with AD, it is possible that increased CVRF and poor health behaviors, such as smoking, drinking alcohol or being sedentary, are important factors for cardiovascular events. Patients should be encouraged to modify those habits and acquiring a healthier lifestyle.

Cutaneous and extra-cutaneous infections

Patients with AD are more susceptible to multiple cutaneous bacterial, viral and fungal infections than the general population.[43] The infection with Staphylococcus aureus (SA) is one of the most common complications of AD[43] because this bacteria, which is a colonizer of the skin microbiota, can become pathogenic under certain conditions, such as the loss of integrity of the skin barrier.[44] Healthy individuals show SA colonization prevalence of 5–30%[44], which are lower than those observed in AD patients. Suh et al.[45] performed a cross-sectional study comprising 54 patients with AD aged from 3 months to 17 years, and reported that 80% of those patients were colonized with SA, while 13% of the total number, or 16% of those colonized with SA, were carriers of Methicillin-Resistant SA (MRSA), with previous hospitalization being independently associated with MRSA colonization. The concomitant use of topical calcineurin inhibitors and topical steroids was associated with SA and MRSA colonization, with the patients who used that combination being significantly more likely to be colonized than patients who used exclusively topical steroids. On the other hand, the use of topical antibiotics was associated with reduced SA colonization, whereby its use appears to be a protective factor.

A high rate of SA colonization was also reported in a Canadian cross-sectional study[43] of lesional skin and nares swabs from 200 pediatric patients with AD, in which 61.5% were carriers, represented by 43.7% of skin swabs and 48% of nares swabs. In this study, SA colonization was more frequent in older patients and in those with higher disease severity scores. Although, in contrast to the last mentioned study, only one of the isolations represented MRSA. Furthermore, the results of a Brazilian study[44] confirm

a high rate of SA colonization in children with AD and suggest an important association between colonization and severity of the disease, in this case assessed using the Eczema Area and Severity Index (EASI) score. Of the patients sampled, 73.6% were carriers of SA, nasal swabs were positive in 60.4%, lesional skin swabs were positive in 48.4%, and both lesional skin and nasal swabs were positive in 35.2%. However, no MRSA was found in cultures from any of the subjects.

The loss of integrity of the cutaneous barrier seen in AD leads to a greater susceptibility of the stratum corneum to the SA colonization, which explains the observed high rates of carriers.[43] This bacteria produces toxins that act as superantigens and maintains skin inflammation, eliciting a strong immune response.[43]

Impetigo contagiosum (IC) is caused by the inoculation of SA or group A streptococci into superficial sites of minor trauma, instead of intact skin, and it is a common infection in children with AD.[46] Hayashida et al.[46] reported a greater prevalence of personal and familial AD history in pediatric patients with IC compared with children without this infection, with the odds of a history of IC being 1.8 times higher in AD patients than in non-AD patients. The authors suggested the dysfunction of the skin barrier, small traumas due to scratching, bacterial colonization of the skin, especially SA, and decreased levels of antimicrobial peptides in the skin as possible responsible factors for the high lifetime prevalence of IC in AD.

A subgroup of patients with AD are also susceptible to serious viral infections. The most frequent viral complication in subjects with AD is eczema herpeticum (EH), which is a severe and extensive viral superinfection caused by herpes simplex virus (HSV) on eczematous skin lesions, occurring most frequently in the second and third decade of life.[47] This condition is designated as AD complicated by EH (ADEH) and sometimes it can be complicated by keratoconjunctivitis, which can result in blindness, viremia and multiple organ involvement with meningoencephalitis.[48,49]

Beck et al.[48] compared AD patients with history of EH (ADEH+) with AD patients without history of EH (ADEH-) and healthy controls to characterize those patients who are more prone to develop EH. The ADEH+ subjects had greater severity of AD (evaluated using EASI and Rajka-Langeland scores), a higher affected body surface area, were more likely to have a history of other allergic conditions, were more often sensitized to many common allergens than ADEH- patients and presented higher levels of serum IgE. Additionally, the ADEH+ group more often had a history of cutaneous infections with SA and Molluscum contagiosum virus (MCV) and also a history of HSV infection of the eye than both the ADEH- and control groups. Besides the more pronounced sensitization to aeroallergens and higher levels of serum IgE in the ADEH+

patients, Peng et al.[47] also found that the ADEH+ group had a greater prevalence of early age onset of AD along with a persistent and recurrent course of AD until adulthood.

A feature of ADEH+ patients is their Th2 predominance and relative Th1 deficiency.[47,48] AD patients with EH have more Th2-polarized disease demonstrated by their higher serum levels of the Th2 chemokine TARC/CCL17, their greater peripheral eosinophilia and greater allergen sensitization compared to ADEH-.[48] This Th2/Th1 imbalance leads to the decreased production of antimicrobial factors and reduced cutaneous barrier proteins,[48] and the defect in epidermal barrier and immune responses to pathogens may be important for viral and bacterial infections of the skin. Moreover, IFN-γ-producing cells are important cytotoxic effectors of immune system against viruses, however the ADEH+ patients present reduced IFN-γ production and downregulation of IFN-γ receptor compared to ADEH- and non-atopic control subjects.[50]

Loss-of-function null mutations R501X and 2282del4 in the FLG gene have been consistently associated with risk of AD, representing the strongest genetic risk factors for AD.[49] The R501X mutation confers an added risk of ADEH among European American patients and African American patients, however the association between the 2282del4 mutation and ADEH was only significant among European American patients, while it was absent in the ADEH+ African American patients.[49] Moreover, the combined R501X and 2282del4 mutations further increased the association for AD and ADEH.

MCV belongs to the poxvirus family and replicates in keratinocytes leading to a disruption in the keratinization process.[51] An Italian study[51] involving 100 children with AD and 97 controls revealed that the presence of mutations in the FLG gene was also associated with a significantly increased risk of MCV skin infection, as well with an early onset of AD and more severe clinical course of the disease, given that AD patients with specific FLG variants were predisposed to moderate and severe SCORAD scores. Therefore, the loss of FLG gene function leads to a defective skin barrier, allowing the penetration of antigens and increasing the susceptibility to skin infection.

Beck and colleagues[48] reported that Human papilloma virus (HPV) infections were more frequent in AD patients compared with the non-AD control group. Likewise, Silverberg and Silverberg[52] performed a study using the US 2007 National Health Interview Survey and found higher odds of warts (cutaneous infection with HPV) in children with AD and other concomitant atopic disease. In the same study, the researchers demonstrated that AD children with or without atopic comorbidities were associated with higher odds of various extracutaneous infections, namely strep throat, other sore throat, head or chest cold, influenza/pneumonia, sinus infections, recurrent ear infections, varicella and urinary tract infections. Moreover, Strom and Silverberg[53] used the US 2012 National Health Interview Survey to analyze whether adult AD was

also associated with diverse extra-cutaneous infections. In fact, they showed that adult AD was significantly associated with increased odds of infectious diseases/immune conditions, fever lasting more than 24 hours as well as all the same extracutaneous infections abovementioned for children with AD, with the exception of recurrent ear infections and urinary tract infections. Adult AD alone was significantly associated with one, two, three and even more strongly with four or more infections; AD with atopic disease was associated with even higher risk of two, three and four or more infections compared to AD alone.

Frankowska et al.[54] conducted a retrospective analysis of the medical documentation of a group of children born between 2005 and 2008 treated in the Outpatient Clinic of the Polish Mother's Memorial Hospital in Lodz, consisting in 116 infants and small children with AD and 136 children without atopy included in the control group, and showed that lower respiratory infections (pneumonia and bronchitis) were significantly more frequent in the AD group. Additionally, children with AD were more often hospitalized, especially due to pneumonia and spastic bronchitis. Using the same sample as the last-mentioned study, Rotsztejn et al.[55] reported a higher occurrence of episodes of diarrheas and/or vomiting in children with AD, with a total percentage of positive stool culture significantly higher in children with AD compared to the control group (34.6% vs 17.6%, respectively, $p<0.001$). SA was the most common pathogen cultured in stools, with every fifth child with AD having positive cultures for SA, but Candida strains were also frequent in the group of AD children. Also, children with AD more often manifested chronic diarrhea and required antibiotic therapy.

Hence, the association between AD and multiple cutaneous and extracutaneous infections supports the potential role of immune dysregulation in pathogenesis of AD. Since these infections can be serious, fatal or cause sequelae for the rest of patients' lives, physicians should be aware of them and provide educational information to patients in order to prevent those infections.

Sleep disturbances and mental health disorders

AD has long been associated with sleeping problems and poor quality of sleep, as well as with a variety of mental health disorders.

Pruritus is a central symptom in this inflammatory cutaneous disease and has an important impact on sleep.[56-58] Using polysomnography and actigraphy, Bender et al.[56] demonstrated that sleep quality decreased as the severity of the disease increased in adult patients with AD, with greater disease severity being highly associated with more

scratching and poorer sleep. These researchers suggested that the psychologic distress related to AD may result from the impaired sleep, which in turn impairs daytime functionality. Indeed, in another study,[57] adults with eczema had a higher prevalence of fatigue, regular daytime sleepiness and regular insomnia, which are significant mediators of poorer overall health status, higher number of sick days and doctor visits.

Sleep impairment due to pruritus is also an important problem in children suffering from AD, predicting emotional and conduct disorders.[58] On the other hand, eczema without concurrent sleeping problems did not increase the risk of mental health disorders, suggesting that sleeping problems play a central role for the development of the psychopathologies associated with AD.[58]

A case-control German study[59] with 3769 AD patients aged 15 or older found that adult eczema was independently associated with major psychiatric and psychosomatic disorders, namely schizophrenic, affective, neurotic, stress-related, somatoform, personality and behaviour disorders. Besides that, the likelihood of being affected by any of those conditions significantly increased with each physician visit due to AD.

Yaghmaie et al.[60] also found a strong association between multiple mental health disorders and AD, this time in the US pediatric population, and this association is further enhanced as the severity of the AD increases. Furthermore, a more recent population-based longitudinal cohort study in South Korea[61] demonstrated that subjects with AD diagnosis aged 20 or younger were significantly more likely of visiting a psychiatrist for all psychiatric disorders and this risk increased as the complexity of their treatment regimen raised.

The prevalence of both moderate and severe depression was higher in US adults with AD compared to controls, in a study using data from the US 2005-2006 National Health and Nutrition Examination Survey and 2012 National Health Interview Survey.[62] This results are in line with a previous large Korean study[63] which showed a greater prevalence of depressive symptoms in adults with AD relatively to that of control subjects.

A Taiwanese prospective cohort study reported that both adults and adolescents suffering from AD were more prone to developing major depression, any depressive disorder and anxiety disorders than the non-AD group during the follow-up period, even after adjusting for other atopic comorbidities[64], which are also associated with sleep disturbance and cognitive dysfunction[65]. Adolescents with AD are more likely to experience depressive feelings, suicide ideation, suicide planning and suicide attempts than non-AD subjects.[66] Moreover, the results from a study conducted by Halvorsen et al.[67] revealed that 15.5% of the adolescents with AD reported suicidal ideation, contrasting with only 9.1% of the control group. The prevalence was even greater when they analyzed the patients with both eczema and pruritus, reaching 23.8%.

Atopic diseases have been associated with Attention Deficit/Hyperactivity Disorder (ADHD),[65,68-72] the most frequent psychiatric disorder in childhood[68], and Autism Spectrum Disorders (ASD)[69,72], however contradictory results have been found. Chen et al.[69] conducted a prospective longitudinal study involving an atopic cohort, aged under 3 and born between 1997 and 2000, comprising 14,812 atopic patients with any atopic disease diagnosis without a proper discrimination (asthma, AD, allergic rhinitis or allergic conjunctivitis), and a non-atopic cohort with 6944 subjects. The participants were followed until the end of 2010 to compare the development of ADHD and ASD, which achieved a significant superior risk in the atopic group, with hazard ratios (HR) of 1.97 (95% CI: 1.69–2.29) and 3.40 (95% CI: 1.95–5.93), for ADHD and ASD, respectively. The risk of developing any of these psychiatric disorders showed a dose-dependent relationship, increasing with the number of concurrent atopic diseases in early childhood. Being a longitudinal follow-up study design, it can help to clarify the temporal association between atopic disorders and the referred mental disorders.

A previous study[65] had found that allergic rhinitis and asthma showed higher risks of being associated with ADHD, but the same was not true to AD. Nevertheless, more recent evidence enhances the potential relation between AD and ADHD[70-72] and ASD[72]. Tsai et al.[70] reported higher odds of ADHD for children with AD, allergic rhinitis, asthma and allergic conjunctivitis, for both boys and girls, and they also found a correlation between the risk of ADHD and the number of atopic disorders. In a Danish nationwide population-based cohort study,[71] the subjects with a hospital AD diagnosis before the age of 15 years presented an HR of 1.3 (95% CI: 1.2-1.5) for an ADHD medication requirement and a HR of 1.3 (95% CI: 1.1-1.6) for an ADHD-related admission or outpatient clinic visit, comparing to general population controls. Furthermore, receiving an AD diagnosis before 2 years of age was associated with an increased HR for ASD by 10% and for ADHD by 16% in Taiwanese children, wherein the risk of those mental conditions increased in case of severe AD and comorbid atopic respiratory diseases.[72]

Several studies have shown an impairment in the quality of life of patients living with AD, which present more psychological/psychiatric conditions[73-75], higher level of stress[74] and lower productivity[73,75]. The impact of AD and the associated psychological conditions in the overall health of patients is also reflected by the higher prevalence of injuries requiring medical attention compared to healthy subjects, which is partly mediated by comorbid psychiatric and behavioral disorders.[76]

The vast majority of authors propose two main hypotheses to explain the higher risk of mental health conditions observed in AD patients. First, the association between AD and psychological dysfunction appears to be modified by chronic sleep impairment/deprivation[59-61,66,70-72,76], which in turn seems closely related with pruritus and

consequently scratching overnight. Second, AD and psychiatric diseases may have in common some pathogenic factors related to inflammation, with pro-inflammatory cytokines being capable of penetrating the blood–brain barrier and activate neuropathogenic mechanisms related to emotional control, thus contributing to the development of mental health pathology.[60,61,69-72,76] Moreover, some researchers also suggest the contribution of the negative esthetic aspects of AD lesions and consequent stigmatization, which can be significant factors of stress in patients' social lives.[61,64]

Thus, an effective treatment of AD and pruritus may be important measures and may have a positive impact in the quality of life of patients. Furthermore, collaboration between dermatologists and mental health specialists, as well as treatments targeting sleep disturbances, are likely to improve the global health of individuals with AD in general, and even more of those with greater risk of developing psychological or psychiatric conditions in particular.

Conclusions

The growing evidence of potential comorbidities of AD and its systemic immune activation reflects the burden of the disease on affected individuals and supports the concept of AD as a systemic disease, reinforcing the importance of looking at the patient's overall health, and not only to their skin disease. While various of the referred comorbid associations still seem to be unclear and need to be further explored, perhaps the immediate main focus should be the improvement of the overall health status of AD patients and not only to prove a causality relation between AD and each of those presumed associated conditions.

Patients' quality of life can be severely compromised by its signs and symptoms, so it is important to control the skin disease with the most appropriate treatments. After all, it appears that the severity of AD can influence the emergence of various comorbidities. Health professionals should work on measures that allow a closer surveillance of these patients and should be vigilant in order to prevent and early diagnose their comorbidities and their harmful life behaviors. It is fundamental to give educational information to the patients and, of course, their families, which are of special importance in this disease since it often begins during childhood. Physicians and other health professionals who follow these patients should be available to tend to any of their needs by caring or referring them to another specialist, given that it is now clear that AD is not just a dermatological disease, and that a multidisciplinary approach is essential.

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