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ECZEMA AND DERMATITIS: TYPES AND PATHOPHYSIOLOGY-AN UPDATED REVIEW

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ABSTRACT

Background: Atopic eczema (AE), or atopic dermatitis, is a common inflammatory skin condition influenced by various environmental factors. Understanding these influences is crucial for addressing prevalence variations across populations. **Aim:** This study investigates the environmental factors affecting AE, including climate, urban versus rural living conditions, diet, breastfeeding practices, obesity, pollution, and microbial exposure. **Methods:** An ecological analysis utilizing data from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase 1 examined correlations between AE symptoms and environmental variables such as climate, urbanization, dietary habits, and more. Systematic reviews and meta-analyses of various studies were also employed to gather comprehensive insights. **Results:** The analysis revealed that AE symptoms are positively correlated with latitude and negatively correlated with average annual outdoor temperature. Urban areas exhibited higher AE prevalence than rural settings, attributed to environmental pollution and hygiene-related exposures. Dietary shifts towards a Western diet showed increased AE risks, while high fish intake appeared protective. Limited evidence supported breastfeeding's role in AE prevention. Obesity rates were linked to increased AE risk, and pollution exposure, though associated with AE, showed only weak correlations. The hygiene hypothesis suggests that reduced microbial exposure may contribute to AE development. **Conclusion:** Environmental factors play a significant role in the prevalence and severity of AE. Further research is needed to elucidate these relationships and the mechanisms behind them, with an emphasis on prevention and management strategies.

KEYWORDS: Atopic eczema, environmental factors, climate, urbanization, diet, breastfeeding, obesity, pollution, hygiene hypothesis.

INTRODUCTION

Atopic eczema (AE), also known as atopic dermatitis, is challenging to define due to the absence of a definitive diagnostic test and the variability of its clinical presentation. A widely accepted definition aligns with most consensus groups: AE is described as an itchy, chronic or chronically relapsing inflammatory skin condition that often begins in early childhood, typically before the age of two.[1,2] The clinical manifestation of AE is characterized by erythema, itchy papules or papulovesicles (with occasional vesicles in infants), which can become excoriated and lichenified. The rash commonly exhibits a flexural distribution. Additionally, AE is frequently associated with other atopic conditions, either in the affected individual or among family members.[1–3] Notably, patients with filaggrin mutations may present with associated clinical features such as ichthyosis vulgaris, keratosis pilaris, and hyperlinear palms.

Atopic and Non-Atopic Eczema

A significant challenge in defining atopic eczema (AE) stems from the ambiguous nature of its association with atopy and the concept of atopy itself. AE, along with disorders that induce anaphylaxis, such as those triggered by insect stings and food allergies, may be linked with immunoglobulin E (IgE) antibodies, thus categorizing them within atopic diseases. However, this categorization is not optimal, as individuals with AE can exhibit normal total IgE levels[4], and AE is infrequently connected to a specific allergic reaction. There remains ongoing debate about whether the subset of dermatitis cases with normal IgE levels, referred to as intrinsic atopic eczema or non-atopic eczema, can be clinically and prognostically differentiated from extrinsic AE. Positive skin tests indicating allergen-specific IgE responses or elevated levels of allergen-specific IgE titers in serum are observed in 40–90% of patients (extrinsic AE).[5,6] While sensitization to allergens is important, not all AE cases

demonstrate high total IgE levels. Some studies suggest that 'non-atopic' eczema may constitute the majority of cases during early childhood.[6–8] Over time, however, atopic characteristics become increasingly prominent, with the intrinsic form appearing in only 5.4% of adult patients.[9] Given the current understanding of the epidermis's principal role in the pathogenesis of the disease, some experts have questioned the inclusion of the term 'atopic' in the designation. The European Academy of Allergy and Clinical Immunology has proposed a definition stating that "atopy is a personal or familial predisposition to produce IgE antibodies in response to low doses of allergens, typically proteins, and to exhibit typical symptoms of asthma, rhinoconjunctivitis, or eczema/dermatitis".[10] Following this, the World Allergy Organization has recommended that "eczema" be utilized as an overarching term, divided into atopic eczema and non-atopic eczema.[11]

Diagnostic Criteria

Hanifin and Rajka[12] established major and minor diagnostic criteria derived from their clinical experiences. These criteria facilitate uniformity in diagnosis across hospital-based and experimental studies; however, they have been deemed inadequate for population-based research.[13] In response to this limitation, Williams et al. convened a working party in the UK aimed at refining Hanifin and Rajka's criteria into a reproducible and validated set of diagnostic standards for atopic eczema (AE). This refined set demonstrated an 80% positive predictive value and a 97% negative predictive value.[14,15] These diagnostic guidelines appear to be applicable for adults, children, and non-white ethnic groups affected by AE[16] and have been validated within a population context. While primarily developed for epidemiological research, the criteria necessarily exclude certain signs that may be diagnostically relevant for individuals but are not sufficiently prevalent for assessment in large populations. More recently, additional modifications to the diagnostic criteria have been suggested; however, these revisions have undergone less rigorous validation.[17,18]

Epidemiology

Incidence and Prevalence

Significant prevalence and trend data for atopic eczema (AE) have been derived from the International Study of Asthma and Allergies in Childhood (ISAAC).[19,20,21,22] Involving nearly 2 million children across 106 countries, ISAAC represents the largest and only allergy study with a genuinely global perspective. Findings indicated that the prevalence of AE at ages 6–7 years varied markedly, ranging from less than 2% in Iran to over 16% in Japan. The reliance on questionnaire-based studies introduced certain uncertainties, such as discrepancies in the reported versus symptomatic prevalence of eczema. For instance, 13% of children in Sunderland, UK, exhibited symptoms of AE, while 27% reported suffering from the condition. ISAAC Phases 1 and 3 were established to assess temporal trends, revealing that AE was common among 13- to 14-year-olds in Phase 1, predominantly in high-income settings. However, prevalences did not significantly increase or even declined, while the burden of AE continued to escalate in many developing regions.[23] Among 6- to 7-year-olds, most centers indicated an increase in AE symptoms, irrespective of national per capita income. Additionally, a recent systematic review of 69 cross-sectional and cohort studies confirmed that AE has become a global phenomenon, with lifetime prevalences exceeding 20% in numerous affluent countries.[24] There is also compelling evidence of rising prevalence in low-income countries, particularly in Africa and East Asia.[24] The prevalence of AE among adults has been less extensively studied but has been reported to gradually decline in a Japanese population, from 10% at ages 20–29 to less than 5% after 50 years of age.[25] A study involving European and North American adults aged 20–44 revealed prevalence rates ranging from 2.2% in Switzerland to 17.6% in Estonia, yielding an overall prevalence of 7.1% (95% confidence interval [CI] 6.6–7.7%).[26]

Disease Severity: In public health discourse, the distribution of severity in atopic eczema (AE) holds greater significance than its overall prevalence, which may encompass numerous mild and asymptomatic cases. Severity likely influences individuals' usage of, or necessity for, healthcare services. Limited studies have thoroughly assessed the severity distribution of AE within communities, but evidence suggests that severe cases are rare, affecting less than 5% of those diagnosed with AE.[27,28]

Age and Sex: Typically, AE manifests during infancy, usually before the age of 2[14], although milder community cases may present later, extending into adulthood.[29] Minor gender differences in AE prevalence have been observed, with a slightly higher occurrence in females; however, this finding is not universally consistent.[30]

Morbidity and Cost: Globally, AE, with a prevalence of approximately 229,761,000, ranks among the top eight skin conditions and is the leading cause of disability-adjusted life years (DALYs) lost.[31] AE often registers the highest morbidity scores on generic disability measures when compared to other skin disorders, with the health state utilities of severe AE paralleling those of rheumatoid arthritis, multiple sclerosis, and ischemic heart disease.[32,33] Additionally, the impairment of quality of life is directly correlated with the severity of AE.[34] The psychological morbidity stemming from chronic scratching, sleep disturbances, and the stigma associated with a visible skin condition significantly impacts families, with emerging links to attention deficit hyperactivity disorder (ADHD).[35,36] Economically, AE is a costly condition, with an average annual expense of $338 per affected individual, which increases 2.5-fold when atopic comorbidities are present.[37]

Insights from Prevalence Surveys: Population-based surveys reveal notable differences in AE prevalence not only between countries but also within them, indicating that environmental factors, rather than genetic ones, are likely the primary drivers of changes in disease burden.[38] Significant fluctuations in disease burden over brief periods, such as those observed before and after German reunification, present opportunities to identify environmental risk factors. For instance, while the incidence of AE remained stable among preschoolers in West Germany post-reunification, East Germany experienced a more than doubling in newly diagnosed cases of AE among children under six, rising from 9.6% in 1991 to 23.4% in 1997.[39] Similar patterns emerge in relation to urbanization in developing nations and among migrant populations transitioning from low-prevalence to high-prevalence regions, typically adopting the AE risk profile of their new environments.[21,40] These variations in disease risk, identified through standardized methodologies and diagnostic criteria, have been attributed to the adoption of a 'Western' lifestyle.[39,41] However, the specific lifestyle factors and environmental conditions responsible for these changes remain to be elucidated.

Pathophysiology

Recent insights reveal that atopic eczema (AE), akin to asthma and bronchial epithelial dysfunction, encompasses not only immune regulation abnormalities but also a range of primary epidermal functions. A critical factor is filaggrin insufficiency, which predisposes individuals to barrier dysfunction. Additionally, T helper 2 (Th2) cytokines, particularly interleukin (IL)-4 and IL-13, can down-regulate filaggrin expression.[42] This indicates a complex interplay where epithelial function and immune responses mutually regulate each other.

Genetics

Genetic influences play a substantial role in expressing the atopic phenotype, as evidenced by twin studies. Monozygotic twins exhibit a concordance rate of 0.72, while dizygotic twins show a significantly lower rate of 0.23.[43–45] Although a clear genetic impact is evident, environmental factors account for nearly one-third of cases. Genome-wide linkage studies have identified various susceptibility loci across multiple populations, including German/Scandinavian (n = 839)[46], British (n = 383)[47], Swedish (n = 470)[48], Danish (n = 424)[49], Japanese (n = 287)[50], and French (n = 1317).[51] These studies have pinpointed numerous loci, particularly on chromosomes 1q21, 1q24, 3p24, and others. Notably, the 1q21 locus, associated with the filaggrin protein (FLG), was identified in one study[47], and only 3p24 has shown consistent reproducibility across cohorts.[48,49]

Genome-wide association studies (GWAS) further examine genetic associations by comparing individuals with the disease to control populations, utilizing DNA chip analysis to evaluate up to 2.4 million single nucleotide polymorphisms (SNPs). Four GWAS focusing on AE have confirmed the association with the FLG gene and identified additional loci, including 2q12, 3p21.33, and 5q22.1, among others.[52,53,54] While exploration of these associations continues, most GWAS loci arise from non-coding sequences, complicating our understanding of their causal roles. Analysis of inflammatory diseases indicates that AE-associated loci are strongly linked to Th2 cell function, likely through modifications of non-canonical regulatory sequences rather than direct transcription factor expression.[57] Interestingly, Cookson et al. first reported in 2001 that genetic susceptibility loci for AE overlap more significantly with psoriasis than with asthma, a finding unexpected given the clinical exclusivity of these conditions.[47] Recent GWAS studies corroborate this, revealing that of the 62 reported SNP markers for psoriasis, 13 also achieved significant P values in AE, with eight demonstrating opposing risk associations between the two diseases.[54] For instance, the IL13 gene exhibits SNPs that show significant associations with both conditions but with opposing effects. While over 200 reports indicate a positive association between AE and candidate genes, few negative associations suggest a potential reporting bias. Many studies are underpowered or suffer from heterogeneity in studied populations.[58] A recent review identified only 13 genes consistently associated across independent studies, including FLG, IL4, and IL13, of which most relate to immune function. Notably, the positive association with FLG has been replicated four times more than any other gene.[58] Furthermore, many of these candidate genes are linked to other diseases, notably asthma and allergic rhinitis. For example, DEFB1 has associations with AE, asthma, chronic obstructive pulmonary disease (COPD), HIV, and sepsis, while NOD2 polymorphisms relate to AE, Crohn's disease, and sarcoidosis.[58] Using ingenuity pathway analysis, candidate genes associated with AE predominantly cluster within pathways related to antigen presentation and immune response or cell signaling and movement.[58]

Environmental Factors Influencing Atopic Eczema

Atopic eczema (AE), or atopic dermatitis, is influenced by various environmental factors, including climate, urban versus rural living conditions, diet, breastfeeding practices, obesity, pollution, and microbial exposure. Understanding these factors can help elucidate the prevalence differences observed in various populations.

Climate

Climate plays a significant role in the prevalence of AE, yet it has been an underexplored area. An ecological analysis utilizing the International Study of Asthma and Allergies in Childhood (ISAAC) Phase 1 data revealed that AE symptoms correlate positively with latitude and negatively with average annual outdoor temperature. This analysis, which adjusted for gross national income (GNP), indicated that areas with higher latitudes and lower temperatures might have increased AE symptoms.

Supporting this, studies in Spain and Taiwan have shown similar patterns, potentially linked to climatic influences like UV radiation, known for its immunosuppressive properties. UV exposure can convert trans-urocanic acid, a filaggrin breakdown product, into the immunosuppressive cis-urocanic acid. While lower outdoor temperatures combined with skin irritants can exacerbate AE, the relationship between outdoor climate and flare-ups is complex; some children report worsening in summer while others do so in winter. This complexity suggests that additional factors, such as humidity and seasonal pollen counts, may interact with climate to influence AE.

Urban Versus Rural Living

Epidemiological studies indicate a higher burden of eczema in urban areas compared to rural settings, particularly in less affluent regions. A systematic review encompassing 26 studies has demonstrated this trend. Environmental risk factors linked to urbanization include differences in hygiene-related exposures (e.g., infections, vaccination, antibiotic use), environmental pollution, and dietary practices. Urban environments often expose individuals to more allergens and pollutants, contributing to the increased prevalence of AE.

Diet

The shift towards a "Western" diet, characterized by high consumption of refined grains, red and cured meats, and saturated fats, raises questions about its impact on AE risk. Data from ISAAC Phase 3 indicated a protective effect of frequent fresh fruit consumption against AE, while high fast food intake was associated with an increased risk. Ecological analyses further revealed that greater vegetable and fish consumption correlated inversely with AE prevalence, even after adjusting for GNP. Notably, studies have suggested that high fish intake during pregnancy may lower AE risk in offspring significantly. This has been attributed to the anti-inflammatory properties of n-3 polyunsaturated fatty acids (PUFAs) found in fish. Conversely, the Western diet has seen a decline in these beneficial fatty acids and an increase in pro-inflammatory n-6 PUFAs. A Cochrane review indicated that dietary interventions during pregnancy had little impact on reducing atopic disease risk in children, and no strong evidence supported dietary modifications during breastfeeding to lower AE risk.

Breastfeeding and Delayed Weaning

Breastfeeding is often promoted as a preventive measure against allergies, including AE. The WHO recommends exclusive breastfeeding for six months. However, cross-sectional studies and meta-analyses provide limited support for the idea that breastfeeding duration or timing of introducing solid foods significantly affects AE prevalence. For instance, a meta-analysis involving 27 cohort studies showed no substantial benefit of exclusive breastfeeding on reducing AE risk.

Obesity and Physical Exercise

The increasing rates of childhood obesity in affluent societies have been linked to AE. Studies suggest a positive correlation between obesity and the prevalence of AE, with overweight and obese children showing higher odds of developing the condition. The ISAAC analysis indicated that prolonged television viewing was associated with increased AE risk, particularly in obese children. It remains unclear whether this association is causal, potentially involving inflammatory processes mediated by adipokines or related to dietary patterns that exclude antioxidant-rich foods.

Pollution and Tobacco Smoke

Recent studies indicate a weak association between air pollution and AE risk. A Taiwanese study found that exposure to traffic-related air pollutants, such as nitrogen oxides, had a slight correlation with AE. Similar associations were noted in German and French studies, linking air pollutants to diagnosed cases of AE. However, the evidence regarding the impact of maternal smoking during pregnancy or postnatal exposure to tobacco smoke on AE risk remains inconclusive.

The Hygiene Hypothesis

The hygiene hypothesis posits that reduced microbial exposure may influence AE development, with observations suggesting an inverse relationship between the risk of disease and sibling size. Systematic reviews on microbial exposure and AE have indicated that certain risk factors, such as pet ownership and exposure to farm animals, could influence AE risk due to their potential for endotoxin exposure. Overall, environmental factors, including climate, urbanization, diet, breastfeeding practices, obesity, pollution, and microbial exposure, significantly influence the prevalence and severity of atopic eczema. Future research is necessary to clarify these relationships and understand the underlying mechanisms, particularly as they pertain to the interactions between genetic predisposition and environmental exposures. Addressing these factors can provide insights into prevention and management strategies for AE, ultimately improving outcomes for affected individuals.

CONCLUSION

Environmental factors significantly influence the prevalence and severity of atopic eczema (AE), revealing complex interactions that warrant further exploration. Climate emerges as a critical factor, with data suggesting that higher latitudes and lower average temperatures correlate with increased AE symptoms. This association is potentially linked to factors such as UV radiation, which has immunosuppressive effects that may exacerbate skin conditions. The urbanization effect is notable, as studies consistently demonstrate a higher burden of AE in urban populations compared to rural counterparts, especially in less affluent regions. Urban environments expose individuals to more allergens, pollutants, and differing hygiene practices, which may

contribute to the higher prevalence of AE. Dietary patterns also play a crucial role. The rise of a "Western" diet, characterized by high refined grain and fast food consumption, correlates with increased AE risk. Conversely, a diet rich in fresh fruits, vegetables, and fish appears protective. Interestingly, high fish consumption during pregnancy is linked to a reduced risk of AE in offspring, likely due to the anti-inflammatory properties of n-3 polyunsaturated fatty acids. While breastfeeding is commonly advocated for allergy prevention, current research indicates limited impact on AE prevalence, suggesting that other factors may be more significant. Moreover, the increasing rates of obesity in affluent societies are associated with heightened AE risk, although the mechanisms underlying this relationship require further investigation. Pollution and exposure to tobacco smoke have also been implicated in AE risk, although the evidence remains mixed. Lastly, the hygiene hypothesis offers an intriguing perspective, positing that reduced microbial exposure may contribute to the development of AE. In conclusion, a multifaceted approach considering these various environmental influences is essential for understanding AE's etiology and for developing effective prevention and management strategies. Future research should continue to investigate the intricate relationships between genetic predisposition and environmental exposures, aiming to improve outcomes for individuals affected by atopic eczema.

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الإكزيما والتهاب الجلد: الأنواع والفيزيولوجيا المرضية - مراجعة محدثة

الملخص:

الخلفية :الإكزيما التأتبية (AE) أو التهاب الجلد التأتبي هي حالة جلدية التهابية شائعة تتأثر بعدة عوامل بيئية. فهم هذه التأثيرات ضروري لمعالجة تفاوت الانتشار عبر السكان.

الهدف :تهدف هذه الدراسة إلى التحقيق في العوامل البيئية التي تؤثر على الإكزيما التأتبية، بما في ذلك المناخ، وظروف المعيشة الحضرية مقابل الريفية، والنظام الغذائي، وممارسات الرضاعة الطبيعية، والسمنة، والتلوث، والتعرض للميكروبات.

الطرق :تم إجراء تحليل بيئي باستخدام بيانات من الدراسة الدولية للربو والحساسية في الطفولة (ISAAC) المرحلة 1، والتي فحصت العلاقة بين أعراض الإكزيما التأتبية والمتغيرات البيئية مثل المناخ، والتحضر، والعادات الغذائية، وغيرها. كما تم استخدام مراجعات منهجية وتحليلات ميتا لعدة دراسات لجمع رؤى شاملة.

النتائج :كشفت التحليلات أن أعراض الإكزيما التأتبية مرتبطة إيجابيًا مع خط العرض ومرتبط سلبًا مع متوسط درجة الحرارة الخارجية السنوية. أظهرت المناطق الحضرية معدل انتشار أعلى للإكزيما التأتبية مقارنة بالمناطق الريفية، مما يُعزى إلى التلوث البيئي والتعرضات المتعلقة بالنظافة. أظهرت التحولات الغذائية نحو النظام الغذائي الغربي زيادة في مخاطر الإكزيما التأتبية، بينما بدا أن تناول السمك بكميات كبيرة يوفر حماية. كانت الأدلة المحدودة تدعم دور الرضاعة الطبيعية في الوقاية من الإكزيما التأتبية. ارتبطت معدلات السمنة بزيادة خطر الإكزيما التأتبية، على الرغم من أن التعرض للتلوث، رغم ارتباطه بالإكزيما، أظهر فقط ارتباطات ضعيفة. تشير فرضية النظافة إلى أن تقليل التعرض للميكروبات قد يساهم في تطوير الإكزيما التأتبية.

الخلاصة :تلعب العوامل البيئية دورًا كبيرًا في انتشار وشدة الإكزيما التأتبية. هناك حاجة لمزيد من البحث لتوضيح هذه العلاقات والآليات وراءها، مع التركيز على استراتيجيات الوقاية والإدارة.

الكلمات المفتاحية :الإكزيما التأتبية، العوامل البيئية، المناخ، التحضر، النظام الغذائي، الرضاعة الطبيعية، السمنة، التلوث، فرضية النظافة.