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Atopic Dermatitis





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Atopic Eczema—Epidemiology and Comorbidities

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ABSTRACT

Atopic dermatitis (AD), also called eczema, is a chronic inflammatory skin disease, with flares of acute pruritic lesions superimposed on underlying dry skin. The disease is often associated with other atopic conditions like allergic rhinitis, asthma, and food allergies and shows a global prevalence of up to 20% in children and up to 3% in adults. Recent evidence suggests AD to be a systemic disorder with significant systemic comorbidities. The artical provides a review of the current epidemiology and risk factors in AD, along with a brief discussion of associated comorbidities.

INTRODUCTION

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease, characterized by episodes of acute pruritic lesions and an underlying dry skin. The epidemiology of AD is complex and ever-evolving. The disease usually begins in childhood, although onset has been reported to occur at any age. The nature of disease and its relapsing-remitting course is associated with significant morbidity, adversely affecting the quality of life in AD patients. This review aims to focus on the recent trends in epidemiology and the associated morbidity.

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EPIDEMIOLOGY

Prevalence Studies

The onset of AD is mostly seen in children, although it can begin at any age.[1] Global prevalence is 15–20% in case of children and 1–3% in adults. In 30–50% patients, there is improvement in adolescence. Most worldwide data and trends regarding AD and other atopic disorders in children have been obtained via the International Study of Asthma and Allergies in Childhood (ISAAC), which has used a uniform validated methodology for comparing results in different pediatric population.[2]

In phase I of ISAAC study, the global prevalence varied between 3 and 20.5%.[3] Williams et al. compared the findings of ISAAC phase I versus ISAAC phase III and found that the prevalence of AD is increasing worldwide. In the 6–7 years group, there was overall rise in prevalence for AD in most centers. In the 13–14 years group, prevalence decreased in previously high-prevalence areas, including New Zealand and United Kingdom, whereas the prevalence increased in the developing countries.

International Study of Asthma and Allergies in Childhood phase III study reported the global variation in prevalence of AD to be highly variable across different countries, ranging from as low as 0.9% in India to as high as 22.5% in Ecuador in 6–7 years age group.[4] In 13–14 years age group, prevalence was similarly variable, ranging from 0.2% in China to 24.6% in Columbia. Highest prevalence in all age groups evaluated were found in Latin American countries and Africa. Active AD (current eczema) was higher in girls than boys.[5] In a systematic review by Deckers et al., AD prevalence in children was found to be more than 20% in developed countries, with rising trends in Africa, West and Northern Europe, and Eastern Asia.[6] The update on phase III ISAAC by Mallol et al. in 2013 has reported the global prevalence of AD to be 7.9% in the 6–7 years age group and 7.3% in 13–14 years age group. This update also established that the prevalence of AD is significantly higher in nonaffluent centers with low socioeconomic conditions.[7]

The previously held opinion that AD is an active disease only affecting children is no longer valid. Older studies have found prevalence of AD in adults ranging from 2.0 to 6.9%. Recent studies have suggested that AD may be more common in adults than previously thought. In the United States, the 1-year prevalence for AD in adults was found to be 10.2% in 2010 and 7.2% in 2012.[8] In the same 2012 study, peak prevalence was seen in early childhood (14%), decreased in adolescents (8%), and was stable in adults (6–8%). A study in Taiwan reported 8% prevalence of adult AD in a medical center.[9] A recent study in China has reported the prevalence of adult AD in outpatient department to be 4.6%. The same study suggested the onset age to be 35 years and the average age to be 40 years for adult AD.[10]

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Regarding gender preference for AD, most studies suggest equal preponderance in males and females before 6 years of age.[11] Beyond 6 years of age, females are more commonly affected than males.[12,13]

Prevalence in India

Among Indian children studied in phase I of ISAAC study, the 12-month prevalence varied between 2.4 and 6%, with Kottayam in Kerala reporting more than 9% prevalence.[3] As per ISAAC phase III, the prevalence of current eczema as well as severe eczema in India in the age groups of 6–7 years as well as 13–14 years was below the global prevalence, being less than 5% at most centers.[4]

In a prospective hospital-based study from Bihar, the prevalence of AD was found to be 7.2% in children from 0 to 15-year age group, with male to female ratio being 1:1.3. Majority of patients (89.4%) had onset of AD before 5 years of age. Infantile AD had statistically significant higher Severity Scoring of Atopic Dermatitis (SCORAD) scores in all three grades of severity. The same study also reported significant increase in total serum immunoglobulin E (IgE) and absolute eosinophil count in 66% patients with AD.[14] Kumar et al. have reported 6.7% point-prevalence of AD in Indian patients across all four zones of India.[15] In a clinico-etiological study conducted in a tertiary health center in Gujarat, the prevalence of AD was found to be 4.3% in children.[16]

RISK FACTORS FOR DEVELOPMENT OF ATOPIC DERMATITIS

Hygiene Hypothesis

Studies have shown inverse relation of AD with overcrowding, large family size, and day care infections, whereas antibiotic use in early life has been suggested to be associated with greater risk of AD.[17] Observations like these have prompted further investigations into role of the so-called "hygiene hypothesis." This hypothesis suggests that with rising hygiene levels, there is reduced exposure to certain viral and bacterial pathogens in young life. Normally, microbial antigens induce anti-inflammatory cytokines like interleukin-10 and transforming growth factor-β. Deprivation of stimulation by microbes induces immune dysregulation and increases risk of sensitization in a genetically predisposed individual, thereby resulting in AD. In a recent cohort-based study, it was shown that antibiotic use within first 2 years of life is a risk factor for current AD, asthma, and allergic rhinitis in 5 year old children.[18] As reported in the recent German Health Interview and Examination Survey for Children and Adolescents (KIGGS) study, vaccination in first year of life was not associated with increased risk of AD.[19]

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Birth Order

Many studies have reported that compared to second or higher birth order, first born children have a higher risk of developing AD and also that AD has inverse relationship with number of siblings in the family. An update on phase III of ISAAC study, as reported by Strachan et al., demonstrated inverse relation of "eczema ever" with increase in total number of siblings ($p < 0.0001$). The inverse association with larger family size was significantly more in developed countries with high socioeconomic status.[20]

SMOKING

Environmental tobacco smoke exposure is one of the most important indoor air pollutants and has been evaluated in multiple studies. Lee et al. have reported association of childhood exposure to environmental tobacco smoke with adult-onset AD.[21] In a systematic review by Saulyte et al., allergic dermatitis was modestly associated with both active smoking and secondhand exposure to smoke, more in children and adolescents than adults.[22] In another recent systematic review and meta-analysis, Kantor et al. have concluded that both active and passive smoking exposure are associated with increased prevalence of AD in both children and adults.[23] Thyssen et al. have recently reported that the risk of major comorbidities is significantly increased in adult AD patients, especially smokers, as assessed by Charlson comorbidity index.[24]

Atopic March

Although AD can develop subsequent to appearance of other atopic lesions,[25] classically, it has often been said to precede the others, including food allergies, allergic rhinitis, and bronchial asthma.[26] This so-called "atopic march" is theorized to represent a sequential chain of epicutaneous sensitization by allergens, development of sensitized immune cells and their subsequent migration to respiratory epithelium.[27,28] Disruption of skin barrier and filaggrin mutations have been found to be consistently associated with atopic disorders. Patients with extrinsic AD (having specific IgE antibodies against environmental allergens) are found to be at higher risk for progressing in the atopic march to allergic rhinitis and asthma than those with intrinsic AD. The severity of AD directly correlates with risk of allergic rhinitis and with increased IgE antibodies.[29]

Breastfeeding and Other Dietary Influences

The effect of breastfeeding on the development of AD is still controversial. While some studies suggest protective effects of breastfeeding on AD,[30] others show

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insignificant or reverse effects.[31] The role of other dietary factors in AD is not clear. A systematic review has reported that a significant number of studies have reported the beneficial effects of fish oil supplementation during pregnancy as well as early childhood in reducing the prevalence of atopic disorders.[32] A recent study found no association between diet quality during pregnancy or in early life with AD or other atopic disorders in later life.[33]

Barrier Care with Prophylactic Emollients

Since impaired skin barrier has been hypothesized to have a key role in development of AD, recent focus has shifted to possible role of prophylactic use of emollients in preventing the development of AD. Simpson et al. reported statistically significant protective effect of daily full-dose emollient application against AD, in a randomized trial on 124 neonates.[34] Recently, the PEBBLES pilot study by Lowe et al. has reported significantly reduced incidence of AD and food allergies in infants treated with twice daily use of ceramide-dominant emollient.[35]

MORBIDITY IN ATOPIC DERMATITIS

Atopic dermatitis is associated with many complications and comorbidities. Atopic dermatitis has been proposed by some authors to be a systemic disease, with skin barrier disruption and immune dysregulation being pivotal in pathogenesis. Ocular disorders found to be associated with AD include allergic blepharoconjunctivitis, keratoconus, and posterior and anterior subcapsular cataracts. Gastrointestinal conditions found to be associated with AD include eosinophilic gastroenteritis and higher risk of inflammatory bowel disease, presumably related to Th2 cytokine pathway involvement as a common factor. Other associations like nephritic syndrome, neuropsychiatric illnesses, and metabolic syndrome have also been reported.[36]

Atopic Dermatitis and Infections

Altered cutaneous flora, with increased colonization by *Staphylococcus aureus* has been demonstrated.[37] The increased staphylococcal carriage produces superinfection of skin lesions in AD. Colonization with methicillin-resistant strains of *S. aureus* is also more common than methicillin-sensitive ones in these patients.[38,39] Studies have shown that *S. aureus* promotes Th2/Th22 inflammation in AD[40] and may even have a role in food allergies.[41] Patients with AD show higher risk for skin infection by herpes simplex virus, resulting in "eczema herpeticum."[42] Mathes et al. have reported increased infection by coxsackieviruses in AD, resulting in "eczema coxsackium."[43] Other infections like warts, streptococcal respiratory infections,

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urinary infections and otitis media have also been reported to be more prevalent in AD patients.[44]

Neuropsychiatric Morbidity

Itching in AD patients adversely affects the quality of life (QOL). Itching and emotional distress have a reinforcing effect on each other. While on one hand, itching produces increased mental stress and even suicidal tendency,[45] emotional stress itself has also been shown to result in increased itching.[46] Itching further results in sleep disturbances and daytime fatigue. Children with AD have a higher risk of learning and behavioral disorders like speech disorders and attention deficit hyperactivity disorder.[47] Even in adults, depression and anxiety disorders are more common in AD patients.[48,49] Recent studies have also reported increased odds of childhood nocturnal enuresis with allergic disorders, including AD.[50] A recent cross-sectional study in adolescents showed a significantly increased prevalence of migraine in AD.[51]

Cardiovascular Morbidity in Atopic Dermatitis

Recent studies have focused on the cardiovascular morbidity in AD patients. Obesity and increased waist circumference have been reported in children and adolescents with AD, as compared to controls.[52,53] Patients with AD have significant elevations in systolic as well as diastolic blood pressures in moderate to severe AD.[53] In a 2014 study by Su et al., AD was reported to be an independent risk factor for ischemic stroke in Taiwanese population.[54] However, some studies have reported that risk of cardiovascular disease and stroke is not increased in AD patients, when adjusted for factors like smoking, medication, and hypertension.[55,56] In a recent cross-sectional analysis from the Canadian Partnership for Tomorrow Project, AD was inversely associated with risk of myocardial infarction, stroke, hypertension, and type 2 diabetes mellitus.[57]

These findings suggest that rather than systemic inflammation, poor health behaviors, smoking, and medication related factors may be the major determinants of cardiovascular disease in AD patients.

Malignancy in Atopic Dermatitis

Many studies have focused on the relation between AD and malignancies. Chronic systemic inflammation, particularly shift from a Th1 type immunity to a Th2 type, as well as use of agents like cyclosporine in severe forms of AD have been postulated to play a role.[58,59] Arellano et al. have reported increased risk of cutaneous T cell lymphoma in AD, with risk more in severe forms.[60] Other studies

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have suggested that this association with lymphomas is overestimated and apparent association might be due to the misdiagnosis of cutaneous T cell lymphomas as AD.[61] Regarding other malignancies, recent studies and systematic reviews have shown inverse or no association between AD and risk of acute leukemia, actinic keratosis, basal cell carcinoma, malignant melanoma, and pancreatic and brain tumors.[62-64] Inverse association may be described by immune surveillance as well as IgE-mediated tumor antigen presentation by dendritic cells.[65]

Atopic Dermatitis and Autoimmunity

A connection between autoimmunity and AD has been suspected. Increased incidence of autoimmune disorders has been reported in atopic children. In a systematic review, Tang et al. reported a strong association between autoreactivity and AD.[66] Although IgE autoreactivity to various human proteins has been reported in AD patients,[67] further studies are needed to define the exact correlation in clinical terms.

Other Comorbidities

Patients with AD are prone to increased risk of fractures, on account of decreased bone mineral density.[68,69] This can be attributed to a variety of factors, including effects of cutaneous inflammation,[70] as well as widespread use of oral corticosteroids in treating even mild exacerbations, despite recommendations to the contrary.[71] Short stature has also been described more frequently in children with AD, with one older study putting prevalence in AD at 22%,[72] although later studies suggest that AD is not significantly associated with short stature.[73,74]

ECONOMIC IMPACT AND QUALITY OF LIFE IN ATOPIC DERMATITIS

In addition to direct health-related effects as described, AD also results in increased burden of costs, both direct and indirect, to the patient and family. Direct costs arise on account of medications, physician-visits, hospitalizations, as well as employing allergen-avoiding measures like dust and mite protectors. Indirect costs include absenteeism in school for children and loss of work hours for adult patients with AD.[75] An Indian study reported significantly high cost of care in AD, comparable to those with chronic diseases like diabetes mellitus.[76]

The QOL is adversely affected in all forms of AD across all ages. Mozaffari et al. have reported significant impact on QOL in both children and adult AD patients using the Dermatology Life Quality Index scores.[77] Holm et al. reported significant impact of AD on QOL in children, using an objective score

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called SCORAD.[78] Another study in AD patients between 4 and 70 years age demonstrated significantly inferior scores in AD patients on social functioning, vitality, and mental health subscales compared to the general population.[79] An international multicenter study has reported significant adverse impact on QOL and family QOL in children with AD.[80]

CONCLUSION

Atopic dermatitis represents a challenging disorder with epidemiological factors still not fully elucidated. The worldwide prevalence is rising with greater prevalence in affluent parts of the world. There is an inverse correlation with family size and birth order and role of environmental and dietary factors is increasingly being appreciated. Atopic dermatitis carries significant comorbidities in the form of infections and various systemic illnesses. Quality of life is significantly affected across all age groups and is an important consideration in deciding management.

Editor's Comment

Studies of disease prevalence of atopic dermatitis gives us an indication of its priority as a disease in that particular community. An increase in prevalence of this disease in the developing world also shows the role of environmental factors, and moving to a more westernized lifestyle. It is a disease with morbidity and decrease in quality of life of the patients, hence, emphasizing the need for newer therapeutic modalities.

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Etiopathogenesis of Atopic Dermatitis

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ABSTRACT

Atopic dermatitis (AD) is one of the most common allergic inflammatory skin disorders usually affecting the pediatric population. It is a chronic, pruritic skin condition, demonstrating a frequently relapsing course. The etiopathogenesis of AD involves complex interplay of genetic, immunological and environmental factors including allergens, irritants, and microbial antigens resulting in skin barrier dysfunction, the hallmark pathological disturbance of this condition. Although the exact pathogenesis is still unclear, newer insights are being gained with each passing day. The recent developments in this aspect are discussed in this article to provide a comprehensive understanding of this subject.

INTRODUCTION

Atopic dermatitis is an inherited skin disorder characterized by the development of pruritic and eczematous lesions in a typical distribution (usually flexural folds) usually affecting the pediatric population.[1] It typically follows a chronic course interspersed with acute and frequent flare-ups and exacerbations. The pathogenesis of this disorder is complex, involving different genetic, immunological, and environmental factors (allergens and microbial antigens). Interaction of these factors result in epidermal barrier dysfunction and immune dysregulation—the two major pathological aberrations of this condition. Recently, new knowledge has been gained regarding these pathological interactions. The etiopathogenesis of AD has been discussed here along with the recent updates and relevant review of literature.

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