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Selected comorbidities of atopic dermatitis: Atopy, neuropsychiatric, and musculoskeletal associations

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Abstract

Atopic dermatitis (AD) is a chronic pruritic inflammatory skin disease with substantial morbidity and quality of life impairment. There are a number of comorbid health problems that occur in patients with AD, aside from the cutaneous signs and symptoms. Chronic pruritus and inflammation can lead to sleep disturbances and mental health symptoms, which are not mutually exclusive. AD is associated with and may predispose to higher risk of other atopic disorders, including asthma and hay fever. Persons with AD appear to be at higher risk for multiple neuropsychiatric disorders, including depression, attention deficit (hyperactivity) disorder, speech disorders in childhood, headaches, and seizures. There is also a multifactorial association of AD with osteoporosis, injuries, and fractures. Elucidating the comorbidities of AD is important for disease management and improving overall clinical outcomes. This review summarizes recent developments in the atopic and neuropsychiatric comorbidities of AD.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disorder with significant morbidity and quality of life (QoL) impairment. The cutaneous signs and symptoms of AD, include itch, pain, erythema, lichenification, scaling, oozing/weeping, and prurigo nodules. These contribute toward profound functional disturbances that limit the ability to perform activities of daily living, psychosocial distress, and stigma.

Recent studies have found associations between AD a variety of extra-cutaneous manifestations, including atopic and neuropsychiatric disorders, as well as increased risk of musculoskeletal problems including injuries and fractures. Recognizing the comorbidities of

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AD highlights the global burden of this disorder on patients, especially in its moderate to severe form. Factoring the extra-cutaneous comorbidities into evaluation and management of patients with AD may improve therapeutic decision making and overall clinical outcomes. This review will summarize recent developments in the understanding of the atopic, musculoskeletal, and neuropsychiatric comorbidities of AD.

Atopic comorbidities

Epidemiology—AD is associated with a spectrum of atopic comorbidities, including asthma, hay fever, and food allergy. Recent population-based studies (National Survey of Children's Health [NSCH]) found that 19.8% and 34.3% of children¹ and 8.0% and 7.5% of adults² with AD have comorbid asthma and hay fever in the United States (US), respectively. The prevalence and severity of asthma and hay fever were increased in children with more severe AD¹. While these associations are widely recognized, the mechanism of such associations is still highly debated.

Mechanism—Recent evidence suggests that impaired skin-barrier function in patients with AD may allow for transcutaneous penetration of allergens, subsequent activation of the immune system, ultimately resulting in the development of atopic disease³. An elegant study of 619 exclusively-breastfed infants at 3 months of age found that children with AD had dramatically higher rates of positive skin-prick tests to different foods, with even higher rates in more severe AD⁴. Transcutaneous sensitization was theorized to be contributory, given that the children studied had not yet been exposed to food in their diet.

Interventions aimed at optimizing long-term control of inflammation and skin-barrier function early on in the course of AD may actually lower the risk of developing future atopic disease. One promising intervention aimed at primary prevention of AD and subsequent atopic comorbidities employs routine emollient usage in neonates to enhance skin barrier function. An RCT was recently published, showing that at least once daily whole-body use of emollients (SS-free skin care) after the bath starting within the first 3 weeks of life was associated with a 50% relative risk reduction in the incidence of AD at 6 months of age⁵. Studies with longer follow-up and larger cohorts are needed to confirm these findings and the potential length of protective benefit. This approach may prove to be a cost-effective and safe approach to prevent AD and atopic comorbidities⁶. The Study of Atopic March is 6-year RCT following 1,100 infants with AD being treated with either pimecrolimus cream or placebo to determine the effects of topical calcineurin inhibitors on secondary prevention of atopic comorbidities⁷.

For many children, AD may present in the first two years of life, followed by later onset of asthma and even later hay fever⁸. This led some authors to propose the concept of the “atopic march;”⁹ however, several studies have demonstrated varied clinical courses in persons with AD, suggesting that the simplified “atopic march” may not be generalizable to all childhood AD^{10, 11}.

Some have suggested that Immunoglobulin E (IgE) mediated inflammation may be a common mechanism for AD, asthma, and hay fever¹². IgE plays a primary role in asthma and hay fever; however, the pathogenic role of IgE in AD remains controversial, given that

both total and allergen-specific IgE levels are within normal limits in a large subset of AD patients. This subset of patients has been assigned several different names, including intrinsic AD¹³, atopi form dermatitis^{14, 15}, or non-IgE-associated dermatitis or non-atopic eczema¹⁶. Recent evidence-based reviews found that treatment with omalizumab (a monoclonal antibody targeting IgE) is not effective in AD¹⁷ despite showing very good efficacy and effectiveness in asthma^{18, 19}. Activation of T helper 2 inflammatory pathways has been shown to play a primary role in both AD and asthma, irrespective of IgE status²⁰. It is thus possible that Th2 inflammation is a common pathway for AD and atopic disease, with elevated IgE occurring secondarily.

Clinical ramifications—The presence of atopic comorbidities may impact the management of patients with AD. For example, allergic rhinoconjunctivitis or hay fever can lead to worsening of the underlying AD. AD patients with hay fever can present with intense pruritus, severe lichenification and excoriations of the eyelids and periorbital area and madarosis (loss of eyelashes and/or eyebrows) secondary to chronic rubbing and scratching, eyelid edema, and Dennie-Morgan fold (extra transverse infra-orbital crease). The eyelid dermatitis is often refractory to topical therapies secondary to frequent exacerbations from repeated allergen exposure. In this scenario, anti-histamine eye-drops and non-sedating oral anti-histamines can be very effective at treating the underlying hay fever, thereby improving the eyelid dermatitis.

Similarly, some patients with AD have comorbid urticaria and dermatographism, which can independently be pruritic and trigger the itch-scratch cycle. Non-sedating oral anti-histamines can be very effective at controlling the urticaria and associated itch, thereby breaking the itch-scratch cycle. Of note, these are unique scenarios where oral anti-histamines may be effective, whereas they have not proven to be an effective treatment for AD *per se*²¹.

Neuropsychiatric comorbidities

Sleep disturbance

Epidemiology—The intense itch and pain of AD can lead to profound sleep disturbances. A case-control study of 14 AD and 14 control patients without skin disease assessed sleep impairment using the Pittsburgh sleep quality index (patient-reported outcome [PRO]) and actigraphy (an objective assessment of sleep characteristics)²². PRO revealed poor sleep-quality, more frequent and prolonged awakening and daytime dysfunction among AD patients. Similarly, actigraphy revealed that AD patients awoke more often, spent more time awake during waking episodes, with lower overall sleep efficiency²². Another study administered questionnaires, actigraphy, and polysomnography (the gold standard approach to assess sleep characteristics) to 20 adult AD patients and found that more severe AD was associated with poorer sleep²³. A multicenter questionnaire-based study of 1,098 adults from the International Study of Life with Atopic Eczema found that a typical AD flare disrupts sleep for an average of 8.4 nights per flare, which extrapolated to ~81 days per patient-year²⁴. Actigraphy and infrared video evidence reveals fragmented sleep with increased scratch-time and restless nocturnal movement in both pediatric and adult AD²⁵.

Recent studies found that AD is associated with high rates of sleep disturbances in both children and adults in the general US population. A US population study (NSCH) of 79,667 children found that 10.8% of children with AD experienced 4 or more nights of impaired sleep²⁶. A US population-based study of 34,613 adults (National Health and Information Survey [NHIS]) found that approximately 1 in 3 adults with AD reported fatigue and insomnia and 1 in 4 reported regular daytime sleepiness². A US population-based study of 5,563 adults (National Health and Nutrition Examination Survey [NHANES]) found that adults with AD had higher odds of short sleep duration, trouble falling asleep, nighttime awakenings, early morning awakenings, leg jerks and leg cramps during sleep, and were more likely to feel unrested, be overly sleepy during the day and feel as if they did not get enough sleep²⁷. Of note, these studies were not limited to more severe clinical cohorts; rather, they encompassed the entire spectrum of AD severity in the US population, which is predominantly mild^{1, 26}. Even so, the rates of sleep disturbances were remarkably high.

Adults with AD and fatigue or sleep disturbance had dramatically higher rates of reduced overall health (i.e. only fair or poor health) than those with AD alone, as well as more frequent missed workdays, day in bed and doctor visits². In a study of 384 adult AD patients, sleep disturbance was strongly associated with decreased QoL using the Dermatology Life Quality Index (a validated 10-question PRO for QoL)²⁸. Adults with AD (NHANES) had more difficulty with different instrumental activities of daily living when tired, including concentrating, remembering, eating, performing hobbies, doing finances and getting things done due to trouble driving and navigating public transportation²⁷. Adults with AD were also more likely to report being unable to do their finances and hobbies, get things done and work²⁷. Multiple studies showed that sleep disturbance is one of the top contributing factors to poor QOL in childhood AD^{29–31}.

Interestingly, the abovementioned US population-based study (NHIS) found that AD was associated with both short and long sleep durations². Short duration was attributed to difficulty falling asleep and premature awakening secondary to itch, whereas long duration was attributed to poor sleep efficiency, excessive fatigue and sleepiness and perhaps the use of sedating antihistamines. There were two distinct groups of AD that had sleep disturbance: one with other allergic disease that have higher probabilities of insomnia, fatigue and daytime sleepiness and the other without allergic disease and a higher probability of insomnia alone.

Clinical ramifications—Sleep disturbances have important ramifications for the management of AD. Adjunctive treatments should be considered to improve the sleep of children and adults with AD. For example, sedating anti-histamines may improve patients sleep, even though there is insufficient evidence to support their efficacy as a treatment for itch in AD²¹. A recent randomized controlled trial of 48 Taiwanese children with AD found high-dose melatonin (3 gm/day) was well-tolerated and resulted in improved SCORAD (which includes an item for sleeplessness) and decreased sleep-onset latency³².

Sleep disturbances should also be factored into the treatment approach for AD. Profound sleep disturbances despite optimized topical therapy should prompt consideration for adding a systemic agent, e.g. cyclosporine or methotrexate, to reduce inflammation, itch and

associated sleep disturbance. Efforts should also be made to improve the sleep hygiene of patients with AD. Patients with AD can develop poor sleep hygiene over many years of being unable to fall or stay asleep at night, e.g. watching late night movies or infomercials, consumption of large amounts of caffeine or other stimulants to overcome fatigue, etc. Referral to a sleep medicine specialist may be needed in scenarios where sleep disturbances do not improve with optimal control of itch and skin disease or where management of sleep disturbances is deemed outside the scope of dermatology practice. Finally, sleep disturbances may be an important predictor of comorbid mental health and medical conditions as discussed below.

Mental health disorders

Epidemiology—Intense pruritus, high rates of sleep disturbance, stigma, poor QoL and possibly systemic inflammation may all contribute to higher rates of mental health disorders in AD. A US population-based study of 5,555 adults (NHANES) found that 1 in 3 adults with AD reported one or more symptom of depression, including little interest in doing things, feeling down, depressed or hopeless, feeling tired or having little energy, having a poor appetite, feeling bad themselves, having trouble concentrating, moving or speaking slowly or too fast and having thoughts of being better off dead³³. Approximately 1 in 5 adults with AD met the SIGECAPS criteria for major depressive disorder and 1 in 10 had Patient Health Questionnaire (PHQ)-9 scores (a validated PRO to assess the severity of depression) consistent with moderate or severe depression³³. Similarly, another study (NHIS) demonstrated that approximately 1 in 5 adults with AD were diagnosed by healthcare provider with depression in the past year³³. Previous studies found that Taiwanese adolescents and adults and Korean men with AD had higher incidences of major depressive disorder than those without AD³⁴. One study (NSCH) revealed that children with AD were more likely to have depression in their lifetime (6.5%) or currently (3.9%) compared to those without AD (3.4% and 1.8%)³⁵. US children with AD also had significantly higher prevalences of anxiety, ADD/ADHD, conduct, oppositional defiant disorder and autistic spectrum disorders³⁵. Severe AD was associated with even higher rates of these mental health disorders than mild or moderate AD (14.1% for depression, 16.3% for anxiety and 27.7% for ADD/ADHD)³⁵.

A study of 354,416 children age 2–17 years from 19 US population-based cohorts and 34,613 adults from one cohort found that AD was associated with ADD/ADHD³⁶. Among children with AD, sleep disturbance, history of anemia, headaches, and obesity were associated with even higher odds of ADD/ADHD³⁶. Among adults with AD, asthma, insomnia, and headaches were associated with even higher odds of ADHD³⁶. A cross-sectional study of 13,318 German children age 3–17 years demonstrated that AD was associated with higher odds of ADHD. In a subgroup analysis of children ages 3–11 years, AD was only associated with ADHD in children that had sleeping problems³⁷. Many studies found associations between childhood AD and ADD/ADHD, owing in part to sleep disturbance and increased AD severity^{35, 38–44}. A meta-analysis of four studies found 43% higher risk of ADHD symptoms or diagnosis in children with AD⁴³.

Clinical ramifications—Mental health comorbidity is an important consideration in the management of AD patients. First, it is important to recognize that many of these mental health symptoms, e.g. depression, anxiety, impaired concentration, are symptoms of the AD per se, i.e. DSM-IV Axis III disorders (secondary to a medical condition). In many (if not most) instances, these symptoms resolve with improved control of the itch and visual aspects of the disease. Patients experiencing mental health symptoms secondary to their AD may warrant use of a systemic agent to improve disease control. For some chronic AD patients, the mental health symptoms may be indicators of standalone DSM-IV Axis I diagnoses, e.g. major depressive disorders. Either way, patients experiencing mental health symptoms would likely benefit from referral to a mental health specialist. It is important that healthcare providers managing patients with AD screen for mental health symptoms and treat or refer appropriately.

Other neuropsychiatric disorders

Epidemiology—Several studies have reported on associations with other neuropsychiatric disorders. A US-population study (NSCH) found that children with AD were more likely to see a variety of health care providers, including speech therapists and specialists²⁶, suggesting that AD may affect speech, language and other neurocognitive development. Indeed, sleep disturbance^{45, 46} and ADHD⁴⁷ were independently found to be associated with speech and language development. A study of 19 US population-based cohorts found that significantly higher odds of speech disorders in childhood AD in 16 of 19 studies (pooled prevalence 4.7%)⁴⁸. One study (NSCH) found that severe AD was associated with even higher odds of speech disorders than mild AD and that AD was associated with more severe speech disorders⁴⁸. Part of the association between AD and speech disorders was explained by sleep disturbance and ADHD, though AD alone was still associated with speech disorders. This suggests that AD may negatively impact neurocognitive development in children. Of note, AD may have other harmful effects on child development, such as short stature⁴⁹.

I have anecdotally observed that many of my adult patients with AD have higher rates of chronic headaches. This prompted me to examine the association between AD and headaches. In a pooled analysis of 401,002 children across 19 cohorts, AD was associated with higher odds of headaches in all 19 cohorts (pooled prevalence: 11.1%)⁵⁰. One study found that children with severe AD had significantly higher prevalence of headaches than those with mild AD (19.7% vs. 8.4%). Children with AD had even higher odds of headaches when they also had comorbid atopic disease, fatigue, and sleep disturbances⁵⁰. A case-control study of the UK General Practice Research Database showed that patients with migraines had higher rates of AD, asthma and hay fever⁵¹. A study of 1,077 British children from a suburban practice ages 3–11 years found that children with AD, asthma, and hay fever had higher rates of headache, in general, and migraines, in particular⁵².

Previous studies from our laboratory found that a single tonic-clonic seizure in mice induced interleukin-4 (IL4) and immunoglobulin E (IgE) negative T and B cells to infiltrate brain and switch to IL4+ and IgE+ cells⁵³. These animal studies suggest that inflammatory pathways involved in allergic diseases may also be activated in brain and may contribute toward

epilepsy. This prompted me to examine the association between AD and seizures/epilepsy. In a US population-based study (NSCH) of 91,642 children, childhood AD was associated with higher odds of epilepsy ever or in the past year, with even higher odds in severe vs. mild-moderate AD⁵⁴. In a follow-up study of 206,613 children from 17 cohorts (NHIS), AD was associated with higher odds of seizures in the past year⁵⁵. Similarly, a study of the Taiwan National Health Insurance Research database found that AD and allergic rhinitis, but not asthma, were significantly associated with future development of epilepsy in children and adolescents⁵⁶.

Injuries and fractures

Epidemiology—Patients with AD have multiple risk factors for injuries, including the abovementioned sleep disturbances^{57–59}, distraction from chronic itch, sedating antihistamine use, and psychological comorbidity.³⁵ A US population-based study (NSCH) of 27,556 children age 0–5 years found that AD was associated with higher rates of injuries requiring medical attention, particularly injuries in the home; this association was only partially mediated by psychiatric and behavioral disorders⁴⁴. A study of 27,556 US adults (NHIS) found that AD was associated with higher odds of any injury causing limitation, particularly fractures, bone and joint injury; risk peaked at ages 50–69 years, and decreased thereafter. Adults with AD who also reported fatigue, sleep disturbances or psychological or behavioral problems had even higher rates of injuries than those with AD alone⁶⁰.

Patients with AD may independently have increased risk of fractures. A study of 3,049 children and adolescents ages 8–19 (NHANES) found that children with AD had significantly lower overall BMD z-scores for the total femur, including trochanter and femoral neck, and total lumbar spine⁶¹. Children with AD also had higher rates of BMD z-score <−2 of the femur and spine⁶¹. The covariates with the largest effects on low BMD were low parathyroid hormone and albumin, higher basophil count, Hispanic ethnicity and BMI <5th percentile⁶¹. An Australian case-control study of 43 children with severe AD and 73 healthy controls found that AD was associated with low BMD, particularly in those who used cyclosporine⁶². In contrast, a study of 60 Dutch children with moderate to severe AD found no significant differences of BMD, even when oral corticosteroids and/or cyclosporine were used⁶³.

A study of 4,972 US adults found that AD was associated with significantly lower overall BMD t-score for the femur and lumbar spine, as well osteopenia and osteoporosis of the trochanter⁶⁴. In turn, adults with AD had higher odds of any fracture, including hip/spine and other fracture⁶⁴. Osteoporosis was associated with ever using oral corticosteroids daily for a month or longer in AD patients⁶⁴. A study of 29 Finnish adults with AD found no significant differences of BMD in AD compared with reference normal⁶⁵; however, there were some marginal associations with extensive corticosteroid usage⁶⁵. A study of 125 Dutch adults with moderate to severe AD found that 4.8% had osteoporosis and 32.8% had osteopenia, with a predilection for lower BMD z-scores in men; though, there was no control group in that study for comparison⁶⁶. Another study found that approximately one-third of adults with moderate to severe AD had low BMD as measured by dual-energy X-ray absorptiometry⁶⁷.

Mechanism—Diseases characterized by chronic inflammation, e.g. rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease, are associated with bone loss and skeletal remodeling.^{68, 69} It is possible that the chronic inflammation in adult AD similarly predisposes to bone loss and increased fracture risk. Chronic systemic (and perhaps topical) corticosteroid use may contribute toward impaired BMD and increased risk of rib and vertebral fracture⁷⁰. Low serum vitamin D levels occurring in AD^{71–75} might also contribute to low BMD and fracture risk.

Clinical ramifications—The associations between AD, low BMD, fractures and other injuries have a number of important clinical implications. First, use of systemic corticosteroids is not encouraged owing to their harmful effects. Cyclosporine, methotrexate, azathioprine, phototherapy and emerging systemic agents in the pipeline for AD may all be reasonable alternatives for patients with an inadequate response to topical therapy. Use of sedating medications, e.g. diphenhydramine or hydroxyzine, should not be recommended for daytime, especially given their lack of efficacy at improving the signs and symptoms of AD²¹. Patients using sedating medications should be counseled on the risk of injury. Finally, patients with moderate to severe AD might benefit from more aggressive treatment using a systemic agent in order to achieve better long-term disease control, improve sleep, reduce fatigue and day time sleepiness, improve physical activity levels and perhaps reduce systemic inflammation.

Conclusions

AD is associated with multiple comorbid allergic and neuropsychiatric comorbidities, which should be accounted for in clinical decision-making. The occurrence of comorbid sleep and/or mental health symptoms may warrant more aggressive treatment using systemic agents to achieve better long-term AD control. Treatment approaches should be used in AD that will not iatrogenically cause or worsen comorbid health conditions. Finally, recognition of the comorbidities of AD is essential in order to improve their detection and management, thereby improving overall clinical outcomes.

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