

How acute stress impacts the itch–scratch cycle in atopic dermatitis: a clinical lesson

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Dermatology has recently entered a new era of novel, breakthrough therapies for atopic dermatitis (AD). Dupilumab and nemolizumab comprise the first and very promising line of drugs that demonstrate improved management of the signs and symptoms of some patients with severe AD.¹ In this context, it is of high importance to understand the clinically disruptive elements of these therapies and potential reasons for treatment nonresponders. Interestingly, there is still a lack of long-term clinical research on the natural course of AD,² which could address the above-mentioned issues. This is most likely due to the methodological challenges of prospective studies, as AD is a lifelong disease.² A longitudinal data analysis from the Pediatric Eczema Elective Registry of 5798 participants aged 2–26 years concluded that most patients in this cohort had active disease at all ages with only few or no periods of complete control without treatment.³ This impacts our traditional clinical view of AD as a chronic relapsing disease with healing during intervals. Another idea considered for several years is the concept of a subclinical stage of AD.^{4,5} Despite visibly normal skin, microscopic and molecular biological findings in patients with AD are clearly distinct from those found in normal skin of healthy volunteers.⁵ Next to barrier abnormalities, the presence of an inflammatory infiltrate (lymphocytic cells, dendritic cells) and upregulation of T-helper 2 cytokines (for example, interleukin-13) were found in the subclinical stage of AD with visibly normal skin.⁵

A barrier deficiency and immune activation in normal-appearing AD skin has several clinical implications including maintenance of itching.⁶ Ongoing activation of nonhistaminergic sensory nerve fibres by pruritogenic cytokines, chemokines and keratinocyte mediators (released on barrier disturbance) promotes neurogenic inflammation and, finally, neuronal plasticity and sensitization of nerve fibres.⁶ In the long term, this leads to chronicity of the symptom and involvement of the central nervous system (CNS). Signs of this process are alloknesis (pruritus induced by light brushing, such as from clothing) and hyperknesis (pruritus induced by mechanical stimuli such as scratching), which are well-known signs in patients with AD. The involvement of the CNS makes patients with AD vulnerable to mental factors. It was demonstrated previously that patients with AD are sensitive to stress; stress levels correlate with itch intensity and disease severity.^{7,8}

However, the influence of stress on the scratching behaviour in patients with AD has not been investigated until now.

In this issue of the *BJD*, Mochizuki et al.⁹ analysed the effects of acute stress on itching and scratching in patients with AD. Patients with AD with an active disease and moderate itch intensity, as well as a healthy control group, were enrolled and underwent a complex and elaborate experimental design of itch induction on the forearm via cowhage spicules (activation of nonhistaminergic nerve fibres) and induction of acute stress with the Trier Social Stress Test. Itch intensity, urge to scratch and scratching activity outside the test area ('off-site scratching'), which was recorded with a hidden video camera, comprised the assessed parameters. The authors described that acute stress led to a reported reduction of the itch intensity and lower desire to scratch, but also, surprisingly, to an increased off-site scratching behaviour. Accordingly, these data argue for a separation between the perception of symptoms and behavioural response to them. While distraction-induced relief of itch is a common observation in real-world patients in clinical practice, the authors argue that the reduced perception of the itch can most likely not be explained by a distraction, as it occurs with latency. Interestingly, in another experimental itch-induction study involving healthy volunteers, distraction also did not lead to a reduction of itch perception.¹⁰ Together, these two studies suggest that altered itch inhibitory pathways under experimental conditions might be due to social stress.

However, the most interesting and clinically relevant finding of the study is that patients showed an increased off-site scratching behaviour. As it is not related to increased itch intensity, the authors discussed it as an unconscious displacement behaviour towards the acute stress. This is of high relevance, as scratching can subsequently worsen both the itch (via hyperknesis) and the eczema. In fact, the authors found a relation between sensitivity to acute stress and the severity of the eczema in the investigated patients with AD. This finding contributes to our understanding of the maintenance of the itch–scratch cycle in patients with AD (Fig. 1). If this observation can be confirmed in further clinical studies, it might explain why patients do not improve clinically under therapies despite a reported management of itch. They possibly continue scratching due to acutely stressful events. Moreover, the same mechanisms might take place in clinically improved patients but with subclinical AD leading to quick relapses on stress events and subsequent intensive scratching. Considering the complexity of the psychoneuroimmune interactions in AD, it is not surprising that current therapies target only parts of the involved domains and do not always lead to a complete

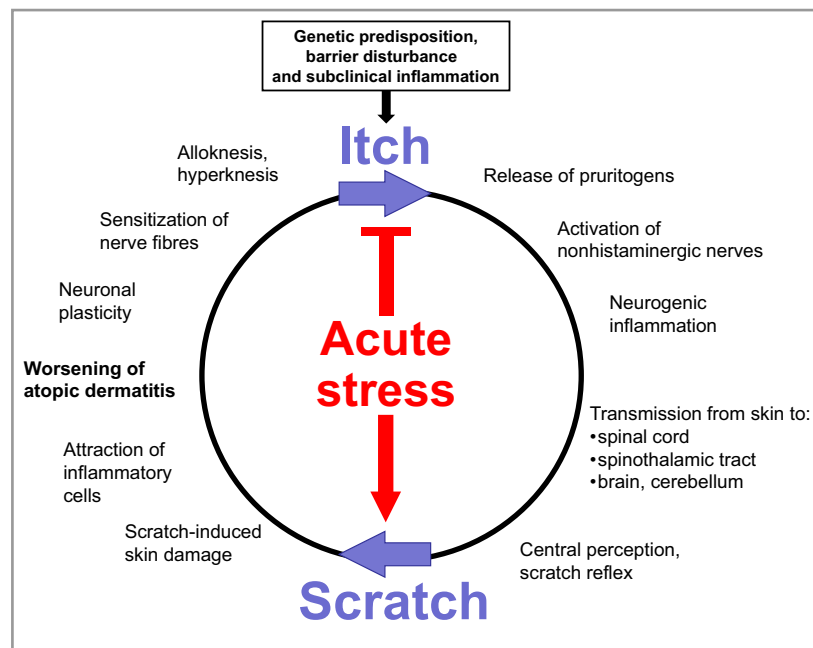


Fig 1. The itch-scratch cycle in atopic dermatitis and role of acute, experimentally induced stress. In the study by Mochizuki et al.,⁹ acute stress reduced the itch intensity but increased the 'off-site' scratching behaviour.

recovery of signs and symptoms. A deeper exploration of the interactions between mental, immune and neuronal mechanisms and their vulnerability to external stressors is needed in order to develop adjunctive therapies that support the disease-modifying properties of the current novel biological drugs.

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Conflicts of interest

None declared.

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