Allergology International 66 (2017) 8–13

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Invited review article

Exacerbating factors of itch in atopic dermatitis

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ARTICLE INFO

Article history:
Received 12 September 2016
Received in revised form
11 October 2016
Accepted 12 October 2016
Available online 15 November 2016

Keywords:
Atopic dermatitis
Exacerbating factors
Itch
Life rhythm
Pruritus

Abbreviations:

AD	atopic dermatitis
TSLP	thymic stromal lymphopoietin
TEWL	trans epidermal water loss

ABSTRACT

Atopic dermatitis (AD) displays different clinical symptoms, progress, and response to treatment during early infancy and after childhood. After the childhood period, itch appears first, followed by formation of well-circumscribed plaque or polymorphous dermatoses at the same site. When accompanied with dermatitis and dry skin, treatment of skin lesions should be prioritized. When itch appears first, disease history, such as causes and time of appearance of itch should be obtained by history taking. In many cases, itch increases in the evening when the sympathetic nerve activity decreased. Treatment is provided considering that hypersensitivity to various external stimulations can cause itch. Heat and sweating are thought to especially exacerbate itch. Factors causing itch, such as cytokines and chemical messengers, also induce itch mainly by stimulating the nerve. Scratching further aggravates dermatitis. Skin hypersensibility, where other non-itch senses, such as pain and heat, are felt as itch, sometimes occurs in AD. Abnormal elongation of the sensory nerve into the epidermis, as well as sensitizing of the peripheral/central nerve, are possible causes of hypersensitivity, leading to itch. To control itch induced by environmental factors such as heat, treatment for dermatitis is given priority. In the background of itch exacerbated by sweating, attention should be given to the negative impact of sweat on skin homeostasis due to 1) leaving excess sweat on the skin, and 2) heat retention due to insufficient sweating. Excess sweat on the skin should be properly wiped off, and dermatitis should be controlled so that appropriate amount of sweat can be produced. Not only stimulation from the skin surface, but also visual and auditory stimulation can induce new itch. This “contagious itch” can be notably observed in patients with AD. This article reviews and introduces causes of aggravation of itch and information regarding how to cope with such causes.

Clinical features of itch in atopic dermatitis (AD)

Clinical characteristics of AD change with both age and disease duration. Sulzberger, who first named AD, described patients with AD according to a characteristic clinical picture for each age.[1] Clinical manifestation of AD in the childhood period centers on eczematous change accompanied with serous papules (Fig. 1). Eczema or exudative papules are accompanied by strong itch, and excoriation and new papules develop due to scratching (Fig. 1). Next, as clinical course progresses from childhood to adult, skin lesions begin to change into a different phenotype than that in the childhood period (Fig. 1). Phenotype of dermatitis during this period is more varied, and this condition has been historically referred to as disseminated neurodermatitis, or Besnier's prurigo.[2,3] Disseminated neurodermatitis was proposed by Brocq and Jacquet.[2] Characteristics include, 1) mental nervousness, 2) continuous itch appearing before visible skin abnormality, 3) apparent circumscribed plaque occurring in almost completely same site where the itch first appeared, 4) distribution of skin lesions similar to dermatoses of nervous origin, 5) skin dryness, 6) visible papillae of hypertrophy of skin and pigmented skin, and 7) chronic condition. Besnier's prurigo was proposed by Besnier, and determined as a type of “diathetic prurigo”.[3] Skin manifestation in early infancy is characterized by non-specific skin lesions occurring after the appearance of itch, and in the young adulthood period, it is characterized by “paroxystic and chronic polymorphous and pruriginous dermatoses, Hebra's prurigo type.” Such a detailed description of distribution, nature, clinical course, and response to treatment of a rash can be applied in today's daily clinical practice.[1–4] AD is characterized by itch preceding dermatitis, and symptoms and response to treatment are different in early infancy and after childhood. Thus, elucidation of the distinctive mechanism

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Peer review under responsibility of Japanese Society of Allergology.

http://dx.doi.org/10.1016/j.alit.2016.10.005

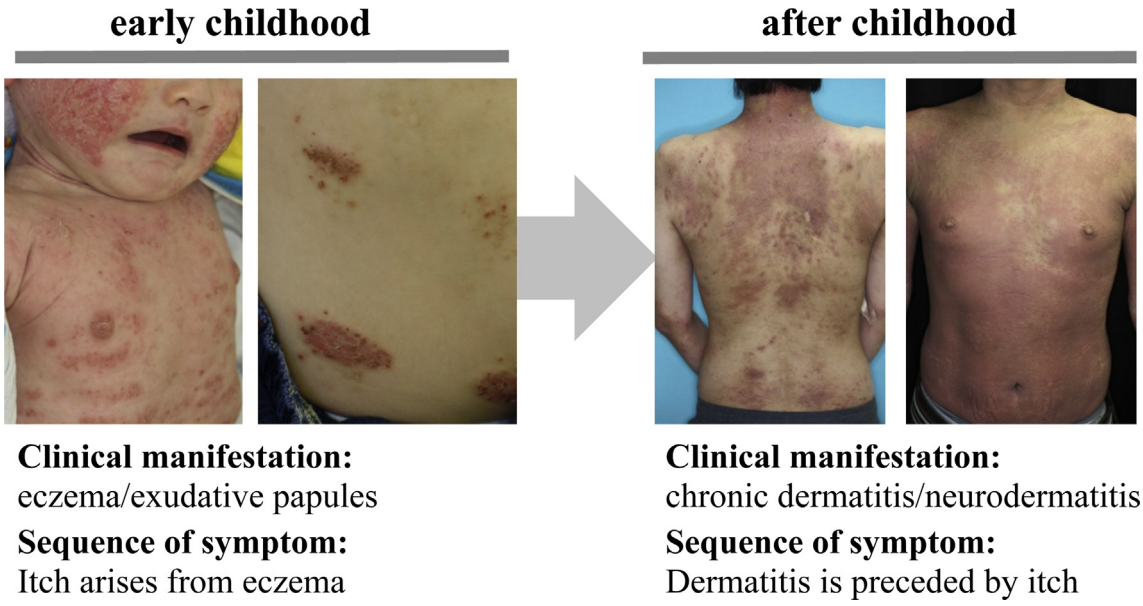

Fig. 1. Clinical characteristics of AD change with both age and disease duration. During early childhood, clinical manifestation is characterized with aggregated exudative papules or small vesicles, so called eczematous change, accompanied by strong itch (left). These clinical features undergo age-related change. After childhood, skin manifestations change into symmetrically localized extensive dermatitis with lichenification (right). This chronic skin condition occurs repeatedly where the itch first appeared, and is referred to as neurodermatitis.

leading to itch related to AD for each age range is required. Furthermore, itch related to AD is aggravated by heat, sweating, wool fibers, emotional stress, certain foods, alcohol, and the common cold.[5] Especially the first three are known to be related to factors that aggravate clinical itch. Countermeasures of these aggravating factors are essential for itch management of AD.

Transmission and processing of itch in AD

Itch is transmitted to the brain by electrical impulses and waves passing through peripheral nerve fibers. The brain receives the information and induces a bodily reaction. Recently, it has been indicated that astrogliosis in spinal dorsal horn influences chronic itch in AD-like animal models, and that the processing of the sense of itch, which is characteristic in AD, occurs in the central nerves.[6] Further clarification of the specific mechanism of transmission of the sense of itch in human AD is required. Here, the overall picture of neuronal transmission of itch is summarized.

The itch-related stimuli from skin are received by the receptor in the free nerve ending of the skin, then converted to electrical current by coexisting ion channel, and is transmitted to the spinal cord. Many receptors and ligands related to itch have been reported previously (Table 1). Itch ligands (pruritogens) activate voltage gated ion channels by exciting TRPV1 (histaminergic) or TRPA1 (non-histaminergic), and subsequently increase action potential leading to an itch sensation.[7–10] In recent years, TRPV1 and TRPA1 have been in the spotlight as targets for drug development because they are keys to peripheral itch transmission.[11] Inhibition of TRPV1 or TRPA1 can attenuate itch in AD-like model animals.[12,13] Electrical current occurring in the free nerve ending is transmitted to the spinal cord. The electrical current from the peripheral nerve of the skin is transmitted to neurons which travel to the central nerve via interneurons in the spinal cord.[7] Strength of the electrical current is adjusted in the spinal cord and sorted by interneurons. The functions of inhibitory interneurons are of particular interest.[14–16] Scratching, heat stimulation, and mechanical stimulation on the skin surface can influence itch-intensity. These stimulations increase inhibitory interneuron activity in the spinal cord via the peripheral nerve which transmits the feeling of pain of the skin. Neurotransmission inhibitors (neurotransmitter gamma-aminobutyric acid (GABA)), glycine, and dynorphins are released from the nerve ending of inhibitory interneurons, and control neuron activity to the central nerve.[15,16] As a result, itch will subside. Controlling inhibitory interneurons is considered to be a strong candidate as a strategy for itch treatment. This processed itch signal is transmitted from the spinal cord through the neurons in the ascending pathway to the amygdala via the thalamus or medulla oblongata of the central nerve. The itch signal is analyzed

Table 1
Major itch-inducing factors and their receptors in atopic dermatitis.

Ligands	Receptors	Ref.
Histamine	Histamine receptors	25
Kallikreins, tryptase, endogenous/ exogenous proteases	PAR-2	26,27
Bradykinin	Bradykinin receptors	28
Serotonin, 5-HT	5-HT receptor	29
Endothelin-1	Endothelin receptors (ETA)	30,31
IL-31	IL-31 receptor A	32
TSLP	TSLP receptor	33
Substance P	NK-1R	34,35
PAF	PAF receptor	36
LTB4 (murine)	LTB4 receptor (murine)	37
Electrophiles, oxidants, pro-inflammatory agents,	TRPA1	38,39
12-HPETE	TRPV1	40
Artemin	GFRα3	41
IL-2	IL-2 receptor	42
GRP	GRP receptor	43,44
β-endorphin	μ opioid receptor	45,46
Acethylcholine	Acethylcholine receptor	47
CGRP	CGRP receptor	48

PAR, protease activated receptor; HT, hydroxytryptamine; TSLP, thymic stromal lymphopoietin; NK-1R, neurokinin-1 receptor; PAF, platelet activating factor; LTB4, leukotriene B4; GFR, glial cell line-derived neurotrophic factor receptor; 12-HPETE, 12-hydroperoxyeicosatetraenoic acid; GRP, gastrin releasing peptide; CGRP, calcitonin gene-related peptide.