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Invited review article

Exacerbating factors of itch in atopic dermatitis

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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 hypersensitivity, 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.

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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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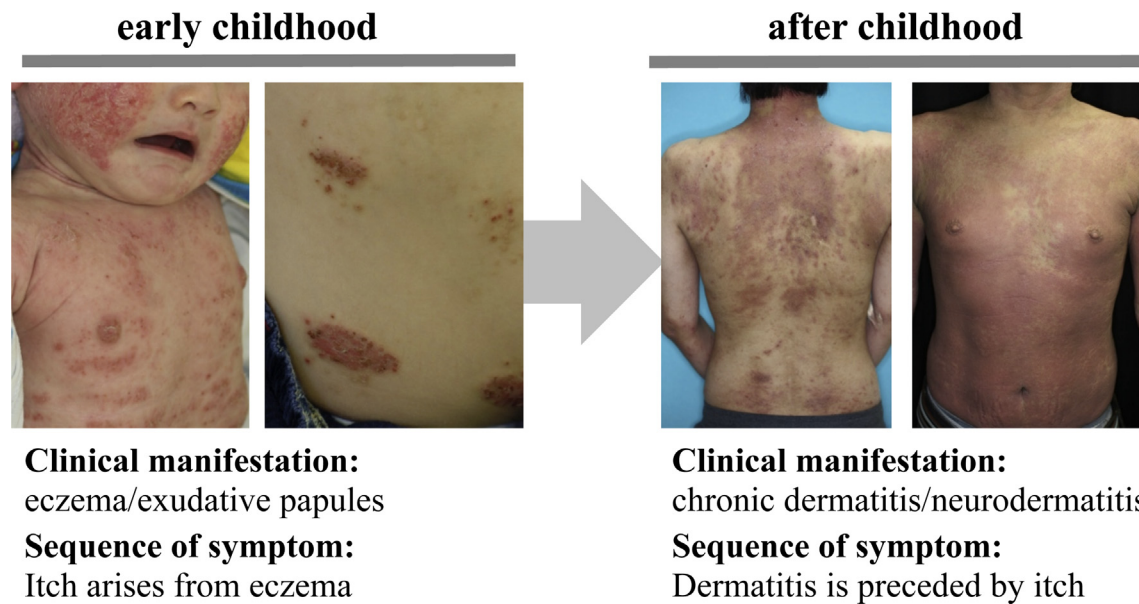


Fig. 1. Clinical characteristics of AD change with both age and disease duration. During early childhood, clinical manifestation is characterized with aggregated exudative papules or small vesicles, so called eczematous change, accompanied by strong itch (left). These clinical features undergo age-related 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

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, 12-HPETE	TRPA1	38,39
Artemin	TRPV1	40
IL-2	GFR α 3	41
GRP	IL-2 receptor	42
β -endorphin	GRP receptor	43,44
Acetylcholine	μ opioid receptor	45,46
CGRP	Acetylcholine receptor	47
	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.

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

in the central nervous system, and converted into information such as localization, quality, scratch, impact, pain, and pleasure.^{17,18} Processing of itch signals in the central nervous system was found to differ in AD patients compared to healthy subjects.¹⁹ Up to now, although the circuit in the central nerve has not been sufficiently clarified, central nerves may contribute to control itch. The descending noradrenergic system suppresses itch signaling by action mediated by $\alpha(2)$ -adrenoceptor.^{20,21} Noradrenaline, which is secreted in the process of the descending nerve system due to excitability of the sympathetic neuron of the medulla or midbrain, can exert tonic inhibition of itch.^{20,22} Hence, itch is controlled in the significant condition of the sympathetic nerve, such as daytime, or when concentrating on something. Also, in AD subjects, itch can be controlled when the attention of the patient is captured by something other than the itch. Further understanding of the descending anti-pruritic nerve system is expected to contribute to improved treatment of itch from AD.

Itch due to dry skin or inflammation in AD

In skin symptoms such as eczema and dry skin, various substances which cause itch (pruritogens) such as cytokine and chemical messengers are released from the affected area^{23,24} (Table 1, Fig. 2). Pruritogens induce itch mainly by acting on the nerve, and the affected area is then scratched.²⁴ However, skin lesions cannot be peeled from the skin, and such scratching aggravates dermatitis. This vicious cycle is called the “itch–scratch cycle”. In chronic inflammation such as AD, skin hyperesthesia occurs. Elongation of the sensory nerve in the epidermis up to right under the stratum corneum due to drying and inflammation is also considered to be a cause of skin hyperesthesia⁴⁹ (Fig. 2). NGF, semaphoring 3A, IL-31, and artemin are related to this aberrant nerve elongation and sprouting in AD.^{41,50,51} Histamine derived from degranulation of mast cells, and substance P which is released from the nerve ending, act directly or indirectly on the aberrantly

elongated nerve, and cause itch. In addition, the role of inflammatory mediators, such as thymic stromal lymphopoietin (TSLP) derived from epidermal keratinocytes and IL-31 derived from infiltrated lymphocytes, on itch has been a recent topic. TSLP and IL-31 were found to induce itch by acting directly on nerve fibers.^{32,33} In hepatic disorders, increase in autotaxins (lysophospholipase) due to cholestasis has been found to cause itch.⁵² Furthermore, a correlation between autotaxin concentration in the blood and itch intensity in subjects with AD has been reported.⁵³

Itch is sometimes induced, not from the skin, but from visual or auditory information. For example, when a person sees an image suggestive of itch, such as being bitten by a mosquito, or hears the sound of somebody else scratching their skin, he may have the urge to scratch himself^{54,55} (Fig. 2). This phenomenon is known as “contagious itch”.⁵⁶ In AD, “contagious itch” has been proven to be stronger than that in healthy subjects.⁵⁶ Psychological and mental factors are also thought to influence itch. Although actual conditions remain unclear, insomnia is also thought to contribute to the onset and worsening of itch. The impact of insufficient sleep and the influence of the circadian rhythm on itch due to AD will be described later.

Temperature and itch

Patients with AD often complain that “itchiness increases when it gets warm”.^{5,57} While “heat” has been known as major inducer of itch in AD,⁵ there are still many uncertainties in its mechanism. Furthermore, thermally-provoked itch frequently shows poor treatment response.⁵⁷ We can experience the relationship between temperature and itch in daily life. For example, ordinarily, itch can be relieved by a painful hot shower or cooling the itchy area with ice. This phenomenon has been validated by scientific methods, and suppression of histamine-evoked itch could be achieved by heat or cold stimulation on healthy skin.^{19,58,59} However, itch in AD

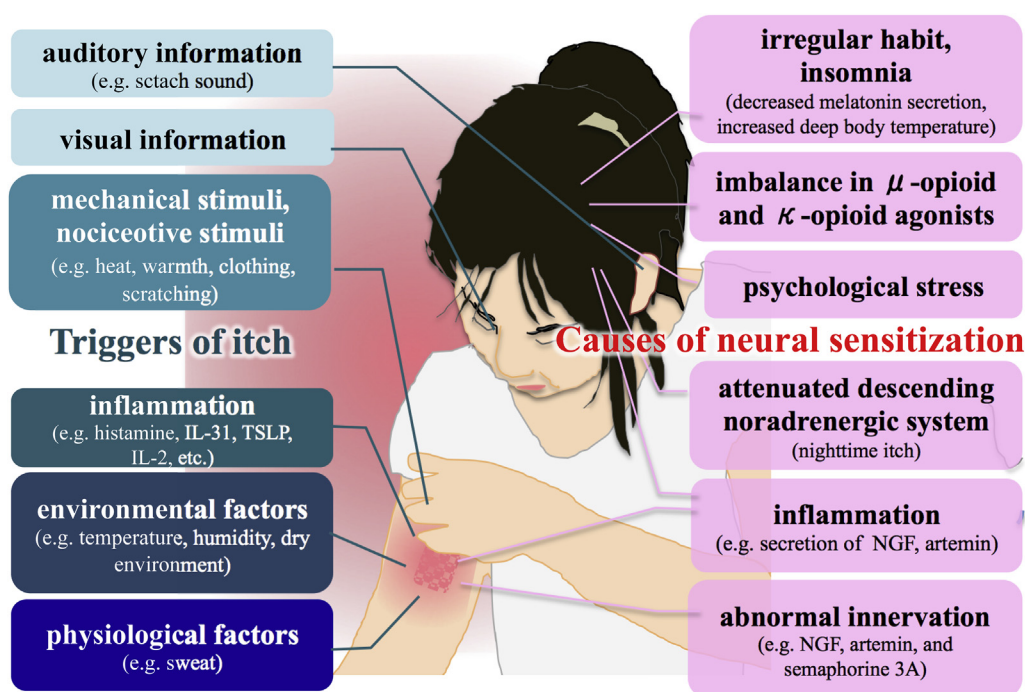


Fig. 2. Illustrating both trigger of itch and causes of neural sensitization schematically. Presumably, memories from repeated experiences of itch may promote neural plasticity, and may augment the susceptibility to these exacerbating factors for itch.

can be suppressed by painful cold stimulation, but increased by painful heat stimulation.^{19,58,60} In other words, AD may promote abnormal hyperesthesia causing patients to feel thermal stimulation as itch. This phenomenon is thought to occur due to sensitization of the peripheral or central nerve, and its molecular mechanism has been slowly revealed.

Skin peripheral nerve fibers are normally distributed in the dermis surrounded with abundant fibroblasts. From this, nerve fibers are assumed to be affected by factors secreted from dermal fibroblasts, and sensitized to cause allodynia. Thus, we comprehensively analyzed genes expressed from dermal fibroblasts which were stimulated by factors related to allergic inflammation and itch. As a result, we focused on artemin, a neurotrophic factor, induced from dermal fibroblast which was stimulated with substance P.⁴¹ Although, artemin is considered to be important mainly in the development of sympathetic innervation, its function in skin was unknown. Expression of artemin is not observed in normal human skin, but is strongly deposited in dermal lesions of AD and nummular eczema.⁴¹ Mice administered artemin showed an increased number of peripheral sensory nerves in the skin, and developed skin thermal hypersensitivity. Furthermore, mice administered artemin on their back skin displayed abnormal behavior such as rubbing the skin of their whole body skin in warm temperature conditions at 38 °C. This phenomenon was not observed in the artemin receptor (GFR α 3) knock out mice. Abnormal accumulation of artemin in the local skin was thought to cause systemic thermally-provoked itch. Now, the question remains as to why accumulation of localized artemin affects skin sensation of the whole body. Administration of capsazepine, a selective antagonist of temperature receptor TRPV1, did not suppress the abnormal behavior caused by artemin in a warm environment. Thus, this reaction is currently thought to be caused by a mechanism independent to TRPV1.⁴¹

In AD, even the temperature setting of the bathwater or of the air conditioner should be considered. Actually, events in everyday life and clinical practice provide us with opportunities to consider the importance of temperature setting. For example, patients with AD scratch an itch developed right after taking a hot bath, or scratch their body right after taking off their clothes. These phenomena are assumed to be related to rapid temperature change of the surface of the skin. In fact, rapid change in skin surface temperature has been experimentally confirmed to increase itch. Pfaff *et al.* stimulated skin administered histamine by repeatedly alternating temperature between warm (32 °C) and comparatively cold (25 °C) at 20 s intervals, and found that itch was heightened by rapid change in skin surface temperature.⁶¹ These results indicate that even within the familiar temperature range of our daily life, rapid change in temperature can intensify itch. AD patients should be instructed to avoid extreme temperature settings for both the air conditioner and bathwater. The Japanese guideline for AD recommends an appropriate temperature of bathwater as 38–40 °C.⁶²

Perspiration and itch

Body temperature adjustment activity: Mammals are homeothermic with a stable body temperature. When body temperature increases, thermal control mechanisms, such as perspiration, expiration, and heat transfer are activated.⁶³ Humans have eccrine sweat glands throughout the body and perspire to regulate body temperature effectively. Perspiration is an important physiological function to adjust body temperature in human activities.⁶³

Sweat contains components to maintain skin homeostasis, such as natural moisture-retaining factors (urea and sodium lactate), bactericidal peptides (dermcidin, cathelicidin, β -defensin), and secretory IgA to protect against infection.⁶⁴ In addition, sweat has

an inhibiting effect on both cysteine protease activity and serine protease activity, and contributes to the prevention of a proinflammatory response against allergens with cysteine protease activity, and to the formation of mature stratum corneum.^{65–68} Furthermore, it has been reported that sweat attenuates experimentally induced itch intensity.⁶⁹

On the other hand, sweat is known as an aggravating factor in AD. Evidence in this regard, the mechanism of exacerbation of AD by sweat can be largely divided to three categories, 1) leaving excess sweat on the skin without rinsing off, 2) abnormality in the components of sweat, 3) abnormal decrease in perspiration. Perspiration itself has been regarded as an aggravating factor due to the fact that many patients with AD view sweating as an aggravating factor, as seen in many large-scale self-completed questionnaires.⁷⁰ In addition, in a report indicating the existence of “sweat allergy”, patient-derived basophils showed positive reaction in a histamine release test for semipurified antigens extracted from sweat derived from healthy subjects.⁷¹ On the other hand, Adachi *et al.* reported that no positive reaction by sweat patch test was observed.⁷² According to the above reports, sweat itself is not considered to be related to delayed allergic reaction, although it may be related in an acute phase allergic reaction. It has been reported that the antigen derived *Malassezia globosa*, an indigenous fungus involved in the normal inhabitants of the skin, contaminated sweat, and may be related to “sweat allergy”.⁷³ Since fungal antigens are not primary components of sweat, the merits and demerits of sweat on AD should be discussed carefully. On the other hand, the possibility of decreased antimicrobial components in perspiration is related to a decrease in the ability to defend against infection of AD.⁶⁴

In addition, abnormal decrease in perspiration ability with AD has been indicated. Regarding its mechanism, A) perspiration is produced but not discharged to the skin surface due to obstruction, and B) abnormality occurs in the production and secretion of sweat itself, etc., have been considered.⁶⁴ One theory on the cause of obstruction is the formation of a horny plug in the sweat pore.⁷⁴ However, whether this is due to keratosis accompanied with inflammation, or drying due to less sweating, is not conclusive. Shiohara *et al.* confirmed a leak image of dermcidin, a bactericidal peptide contained in sweat, surrounding the sweat duct in the lesion area of AD.⁷⁵ As a result of sweat leaking outside the sweat duct, the volume of sweat discharged to the skin surface decreases. Next, in AD, decreased sweat secretion has been confirmed by a perspiration test using acetylcholine load and temperature load.^{75–78} Regarding the mechanism, influence of autonomic dysfunction, and tendency of anxiogenic personality can be considered.⁷⁷ In addition, we have recently discovered that histamine suppresses perspiration by affecting the sweat gland.⁷⁹ In other words, allergic inflammation can be a cause of decreased perspiration in AD. Decreased sweating in AD can be improved by treating the skin symptoms. Therefore, improvement of impaired sweating should be an important therapeutic outcome when determining management of AD.

Leaving excess sweat on the skin surface contributes to aggravation of AD symptoms. One factor causing aggravation is a higher pH level of skin surface due to neglected excess sweat.⁶⁴ Ordinarily, pH of insensible sweat, remains sufficiently low because sodium-bicarbonate (HCO $_3^-$), and alkali ion, in sweat is reduced by reabsorption from the sweat duct.⁶³ However, as the amount of sweat increases with higher body temperature, reabsorption of HCO $_3^-$ from the sweat duct fails, and sweat pH increases. If excess sweat with higher pH remains on the skin, this may easily lead to detachment of the horny cell layer, and increased susceptibility to inflammation.⁶⁴ Contamination or antigens (*Malassezia*-derived antigens, etc.) contained in the sweat on the surface of the skin, and may cause itch. Moreover, the merits of perspiration, such as

proteinase inhibition etc., may be lost as the time of neglect of excess sweat increases. Hence, in cases of itch accompanying perspiration, old excess sweat should be washed or wiped off with a wet towel.

The argument that sweat is an aggravating factor for AD can easily lead to the short-sighted interpretation that “patients with AD should not sweat.” However, there is no evidence that skin symptoms improve under the guidance of “do not sweat”.⁸⁰ Thus, as mentioned above, improvement of impaired perspiration function can be a better treatment goal.

Life rhythm and itch

Irregular habits lead to fluctuation in the skin homeostasis. The complaint “itch increases at night” is often heard from patients with AD. In fact, deep body temperature shows diurnal variation, increasing from the evening into the night, and is lowered by dilatation of skin peripheral vessels during sleep.⁸¹ As a result, skin temperature increases during sleep, and itch can easily occur. Melatonin produced by the pineal gland is considered to be related to decreased body temperature after sleeping. The habit of staying up late reduces melatonin production, and inhibits the decrease of deep body temperature⁸¹ (Fig. 2). Trans Epidermal Water Loss (TEWL) is an indicator of skin barrier function and also increases at night. As a result, in high-temperature and high-humidity (TEWL) environments, the skin surface is susceptible to itch. Furthermore, reduced cortisol production and increased IL-2 production, which is related to inflammation, are observed during nighttime.⁸¹ Irregular habits will also cause imbalance in agonists for μ -opioid and κ -opioid receptors, skewing toward susceptibility of itch.⁸¹

Conclusion

Recent knowledge regarding factors related to the exacerbation of itch, the mechanism of worsening conditions, and countermeasures of AD, have contributed to the management of AD. AD can be aggravated by natural human physiological phenomena and our living environment. Thus, providing a guidance policy for the patient is sometimes difficult. Some problems still remain unresolved, but we hope that the recent accumulation of evidence can be utilized as much as possible in the guidance of patients.

Conflict of interest

The authors have no conflict of interest to declare.

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