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INVESTIGATIVE REPORT

Association of Stress with Symptoms of Atopic Dermatitis

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Psychological stress and atopic dermatitis (AD) symptoms appear to form a vicious cycle. This study compared the degree of stress and impairment of dermatology life quality between patients with AD and healthy controls, and examined for neuropeptides and neurotrophins associated with stress in AD. Questionnaires, comprising five tests evaluating depression, anxiety, interaction anxiousness, private body consciousness, and dermatology life quality, were examined in age- and sex-matched patients with AD ($n=28$) and healthy controls ($n=28$). Immunohistochemical staining of nerve growth factor, substance P, corticotrophin-releasing factor receptor and neuropeptide Y was performed in the AD-involved and normal skin. Patients with AD showed high scores on all of the questionnaires, including Beck Depression Inventory, state anxiety, trait anxiety, Interaction Anxiousness Scale, Private Body Consciousness subscale, and Dermatology Life Quality Index. All of the parameters, except for Beck Depression Inventory, showed higher values in AD than healthy controls ($p<0.001$). Statistically significant correlations were observed between each psychological parameter and Dermatology Life Quality Index. Among the clinical parameters, only pruritus was positively correlated with state anxiety ($R=0.573$, $p<0.05$) and trait anxiety ($R=0.525$, $p<0.05$). The Eczema Area and Severity Index score did not show any significant correlations with psychological parameters. Nerve growth factor-reactive cells were observed more abundantly and intensely in both epidermis and dermis of AD involved skin ($n=4$) than in healthy controls ($n=3$) ($p=0.022$ and 0.029, respectively). Also, the number and intensity of neuropeptide Y-positive cells was significantly greater in the entire epidermis of patients with AD than in healthy controls ($n=3$) ($p=0.029$ and 0.026, respectively). We conclude that anxiety may be associated with the induction of pruritus through neuropeptide Y and nerve growth factor. ***Key words: stress; questionnaire; atopic dermatitis; neuropeptide Y; nerve growth factor.***

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Atopic dermatitis (AD) is a chronic relapsing skin disease, characterized by pruritic and eczematous skin lesions. AD can lead to psychological disturbances, such as stigmatization, social isolation, and discrimination (1). Both children and adults with AD have been reported to exhibit anxiety, depression, and emotional excitability (2, 3). Psychological interventions and programmes are reported to be more effective than conventional treatments alone, in terms of severity of eczema, subjective severity, and effect on quality of life (4).

Psychological stress and AD symptoms seem to form a vicious cycle (5). However, it remains unclear how stress affects AD. Evidence suggests that stress stimulates the hypothalamic-pituitary-adrenal (HPA) axis to induce shifting toward a T helper type 2 (Th2) cell phenotype, releases neuropeptide and neurotrophin, which influence the development and course of AD, induces epidermal barrier dysfunction, and lowers the itch threshold (6). Among the neuropeptides and neurotrophins, substance P (SP) and nerve growth factor (NGF) may be useful markers of disease activity in patients with AD (7). Neuropeptide Y (NPY) is released from sympathetic nerve endings, together with noradrenalin, and enhances synergistically adrenergic action (8). Vascular instability that is observed in patients with AD, such as white dermographism, lower basic temperature of acral parts of the body, and a strong tendency to vasoconstriction after exposure to cold temperature, may be partially caused by NPY (9).

In our study, we compared the degree of stress and impairment of dermatology life quality between patients with AD and healthy individuals without a history of AD using questionnaires. In addition, to evaluate the relationship between stress and neuropeptide/neurotrophin in the development of AD skin lesions, we analysed the expression of various neuropeptides and neurotrophin in the skin through immunohistochemical staining.

MATERIALS AND METHODS

Subjects

Thirty-four patients (20 males, 14 females; mean age 24.1 years, range 13–41 years), with a confirmed diagnosis of AD according to the criteria of Hanifin & Rajka (10), and 32 healthy controls (HCs) (18 males, 14 females; mean age 25.2 years, range 12–43 years) with no history of atopic diseases, were enrolled in this

study. None of the subjects had any other concomitant dermatological disorders or medical disorders including psychological disorders. This study was approved by the institutional review board and informed consent was obtained from each patient, and from parents in the cases of paediatric patients, before they participated in the study.

Questionnaires

The questionnaires consisted of five tests, four of which evaluated psychological stress; depression, anxiety, interaction anxiousness, private body consciousness, and one for assessing quality of life.

Assessment of degree of stress in the subjects

The Beck Depression Inventory (BDI) is a 21-item test presented in multiple choice format that measures the presence and degree of depression in adolescents and adults (11). The Korean version of the BDI demonstrated good psychometric properties (12). Each item is evaluated using scores 0–3. The severity increases with the score.

The Spielberger State-Trait Anxiety Index (STAI) comprises 40 questions; 20 regarding state anxiety (SA) and 20 regarding trait anxiety (TA) (13). SA refers to the level of anxiety felt when the person completes the questionnaires. Trait anxiety refers to the anxiety felt in general by that person. The Korean version of the STAI was previously shown to exhibit excellent psychometric properties (14). Each question is evaluated using scores 1–4.

Interaction Anxiousness Scale (IAS) was constructed to measure the tendency to feel nervous in social encounters independent of patterns of inhibited, reticent, or avoidant behaviour (15). It consists of 15 items that span a broad range of anxiety-evoking situations, including interactions with strangers, parties, dealings with authority figures, cross-sexed encounters, and casual conversation. Each item is evaluated using scores 0–4.

Private body consciousness (PBC) subscale is one of three subscales of the body consciousness questionnaire (16). Its five questions assess attention to internal physical sensations, such as dry mouth, hunger, and body temperature. Questions are rated on a 6-point scale, with 0 representing an "extremely uncharacteristic" quality, and 5 representing an "extremely characteristic" quality.

Assessment of dermatology quality of life in the subjects

The Dermatology Life Quality Index (DLQI) is a 10-question, self-administered questionnaire rating the life quality of daily functioning on a four-point scale from 0 to 3 (17). Patients are asked to recall, for the past week, symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment.

Assessment of clinical severity

Clinical severity was quantified using the Eczema Area and Severity Index (EASI). Two horizontal visual analogue scales (VASs) were used to assess patients with regards to subjective measures of pruritus and loss of sleep (LOS), with the anchors of no pruritus/no LOS at 0 and most severe at 10.

Immunohistochemistry

Formalin-fixed, paraffin-embedded skin sections were deparaffinized with xylene and graded ethanol. After washing with phosphate-buffered saline (PBS), sections were incubated in normal goat serum. Sections were then incubated at 4ºC overnight with polyclonal rabbit antibodies against NPY (Chemicon, Billerica, MA, USA), polyclonal rabbit antibodies against NGF (Abcam plc., Cambridge, UK), polyclonal guinea pig antibodies against SP (Abcam plc., Cambridge, UK), and polyclonal goat antibodies against corticotrophin releasing factor (CRF) receptor 1 (Santa Cruz Biotechnology Inc., CA, USA). The sections were washed with PBS and then incubated with biotinylated goat anti-rabbit IgG antibody. Slides were washed with PBS and then incubated with an avidin–biotinylated peroxidase complex. Peroxidase activity was visualized using stable diaminobenzidine. Staining was monitored under a brightfield microscope, and sections were washed with distilled water to stop the reaction. Sections were then counterstained with methyl green, washed, and mounted.

In the epidermis and dermis, NGF and NPY reactive cells were semi-quantitatively estimated using two scores; intensity score from 0 to 3 (0 = no staining, 1 = weak, 2 = moderate, 3 = high) and positive score from 0 to 3 (0 = no staining, 1 = positive cells < 25%, 2 = positive cells 25–50%, 3 = positive cells > 50%).

Data analysis

Statistical analyses were performed using the Statistical Product and Service Solutions program (SPSS Inc., Chicago, Ill, USA) for Windows (version 12). Results are reported as mean ± standard deviation (SD). Mann-Whitney *U* test was used to determine the statistical significance of differences in degree of stress and dermatology life quality between patients with AD and control subjects. The correlation between degree of stress and DLQI and clinical conditions were analysed via Pearson's correlation test. Mann-Whitney *U* test was used to determine the statistical significance of differences of expression level of NGF

Table I. *Demographics and characteristics of study populations*

			After matching age and sex	
	AD group (n = 34)	Control group (n = 32)	AD group (n = 28)	Control group (n = 28)
Age (years), mean ± SD (range)	24.8 ± 8.1 (13–41)	26.1 ± 9.3 (13–46)	24.6 ± 7.8 (13–41)	24.8 ± 8.0 (13–41)
Gender, *n*				
Male	21	20	18	18
Female	13	12	10	10
EASI score, mean ± SD (range)	21.9 ± 12.7 (5.6–58)		23 ± 13.3 (5.6–58)	
Pruritus (0–10), mean ± SD (range)	6.8 ± 1.7 (4–10)		7.1 ± 1.5 (5–10)	
Loss of sleep (0–10), mean ± SD (range)	5.7 ± 2.9 (0–10)		5.3 ± 3.2 (0–10)	
Peripheral blood eosinophil count (number/μl), mean ± SD	436.5 ± 315.2		405.8 ± 335.1	
Total serum IgE level (IU/ml), mean ± SD	2450.8 ± 1800.6		2461.1 ± 1930.6	

AD: atopic dermatitis; EASI: Eczema Area and Severity Index; IgE: immunoglobulin E.

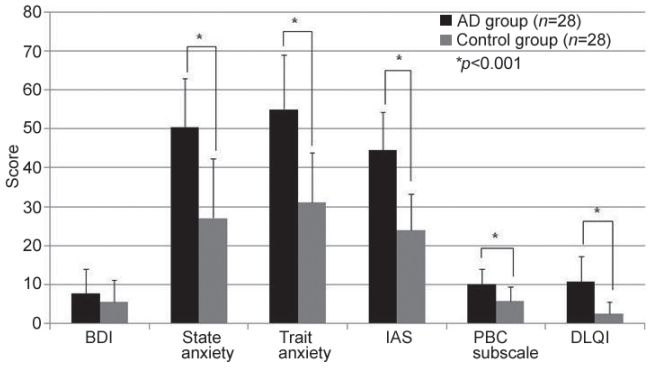

Fig. 1. Comparison of Beck Depression Inventory (BDI), Spielberger State-Trait Anxiety Index (STAI), Interaction Anxiousness Scale (IAS), Private Body Consciousness (PBC) subscale, and Dermatology Life Quality Index (DLQI) between atopic dermatitis group and control group. Except for BDI, all of the parameters showed higher scores in patients with atopic dermatitis than in normal individuals ($p < 0.001$).

and NPY through immunohistochemistry. A difference with a p-value < 0.05 was considered statistically significant.

RESULTS

For the 34 patients with AD, the mean EASI score was 21.9 ± 12.7 (5.6–58) and the mean pruritus and LOS scores were 6.8 ± 1.7 (4–10) and 5.7 ± 2.9 (0–10). Peripheral blood eosinophil count was $436.5 \pm 315.2/\mu l$ and total serum IgE level was 2450.8 ± 1800.6 IU/ml. In excluding the effect of age and sex on the scales of stress and quality of life, we selected 28 patients with AD and 28 normal subjects among 66 participants after matching these variables. After matching age and sex, the mean EASI score was 23.3 ± 13.3 (5.6–58) and the mean pruritus and LOS scores were 7.1 ± 1.5 (5–10) and 5.3 ± 3.2 (0–10), respectively. Peripheral blood eosinophil count was $405.8 \pm 335.1/\mu l$ and total serum IgE level was 2461.1 ± 1930.6 IU/ml (Table I).

Analysis of psychological parameters, quality of life and atopic dermatitis symptoms

As shown in Fig. 1, patients with AD showed high scores on all of the questionnaires including BDI, SA, TA, IAS, PBC subscale, and DLQI. And all of the parameters except for BDI showed higher values in AD compared with HCs ($p < 0.001$). Statistically significant positive correlations were observed between each psychological parameter (BDI, SA, TA, IAS, and PBS subscale) and DLQI. In particular, the PBC subscale showed the most significantly positive correlation with DLQI ($R = 0.662$, $p < 0.01$). IAS showed significantly positive correlations with both SA ($R = 0.714$, $p < 0.01$) and TA ($R = 0.785$, $p < 0.01$).

Among clinical parameters, only pruritus was positively correlated with SA ($R = 0.573$, $p < 0.05$) and TA ($R = 0.525$, $p < 0.05$) (Fig. 2). The EASI score did not show any significant correlations with psychological parameters. Furthermore, even when patients with AD were classified into three groups (< 15, 15–30, > 30) according to the EASI scores, the values of the BDI, SA, TA, IAS, and PBC subscale were not correlated with the severity of AD. LOS, peripheral blood eosinophil count, and total serum IgE level were not correlated with the psychological parameters and DLQI.

Analysis of immunohistochemistry

The expression of substance P and CRF receptor between AD and HC skins was not significantly different. NGF-reactive cells were observed more abundantly and more densely in both the epidermis and dermis of the AD-involved skins ($n = 4$) than in HCs ($n = 3$) ($p = 0.022$ and 0.029, respectively) (Fig. 3a, b; Table II). In the epidermis, strong immune reactive cells were observed in the basal layers. Most of the NGF-reactive cells in the dermis were small and rounded, and some were spindle-like or dendritic in appearance. Also, the number of NPY-positive cells and intensity of NPY were significantly greater in the entire epidermis of AD-involved skins than in HCs ($n = 3$) ($p = 0.029$ and 0.026, respectively) (Fig. 4a, b; Table III). However, NPY was not stained in the dermis of either AD-involved and HCs skins. The difference in intensity and positivity between both AD-involved and HCs skins was slightly larger for NPY staining than for NGF staining, but without statistical significance.

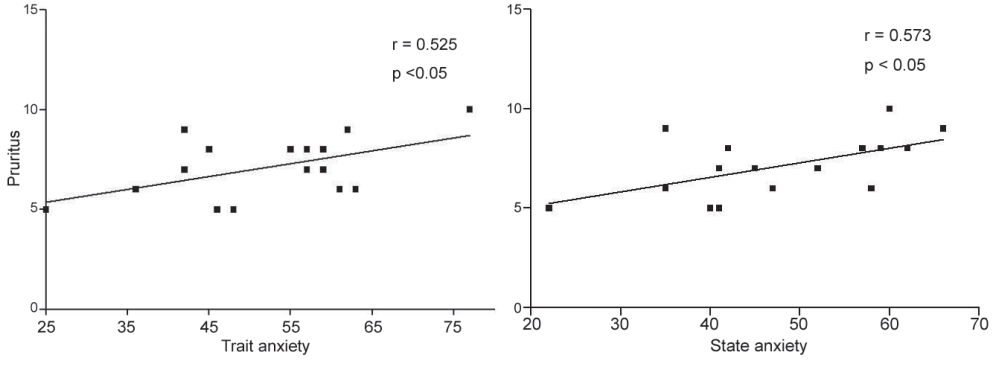

Fig. 2. Correlations between degree of pruritus and state–trait anxiety index in patients with atopic dermatitis.

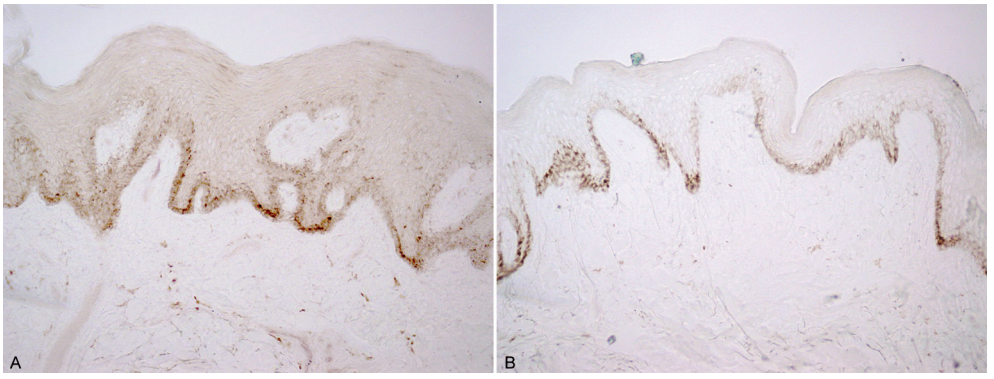

Fig. 3. Immunohistochemical staining of nerve growth factor in atopic dermatitis-involved skin (A; original magnification ×200) and normal skin (B; original magnification ×200). NGF immunoreactive cells were observed to be more numerous and dense in the epidermis and dermis of AD-involved skin than in controls. Basal layers of epidermis showed strong reaction to NGF.

DISCUSSION

It is important to measure the degree of various psychological parameters in patients with AD in order to investigate the role of psychological stress in AD. Psychological stress can include many components, such as depression, social interaction and anxiety. In our study, we tried to determine psychological indices that were closely associated with symptoms of AD. It is widely accepted that anxiety and depression are important components. These components have been dealt with in many articles about psychological stress in AD. Additionally, we took IAS and PBC subscales into account in our questionnaires.

In our study, a diagnosis of AD was performed through Hanifin and Rajka's criteria. Minor diagnostic features of the criteria, which may be less frequent in a community setting where mild or moderate cases predominate, cause their lack of simplicity and validation. Although not suitable for community studies, the criteria would be better in hospital-based settings, in our study also, due to their high sensitivity.

Regarding the unfavourable appearance of AD lesions, adult patients with AD usually felt anxiety, especially in social activities relating to other people. Since STAI can assess only present and general anxiety, it was needed to assess anxiety in interacting with other people; the IAS scale was used. Additionally, many patients with AD seemed to have features of hypochondriasis. They not only worry about their AD, but also other numerous physical problems, such as adverse effects of the long-term application of topical steroids. We therefore used the PBC subscale to assess patients with AD and hypochondriatic features.

In our study, both scores of IAS and PBC subscale were higher in AD compared with HCs, and were positively correlated with DLQI ($R = 0.660$, $p < 0.01$; $R = 0.662$, $p < 0.01$, respectively). High IAS scores mean social avoidance and inactivity in personal relationships. Unfavourable appearance, such as red face and severe lichenification caused by AD, might account for this. In addition, high scores on the PBS subscale in patients with AD might originate from the chronicity and intractable features of AD, which can make patients with AD worry about their body and become very sensitive to their internal physical sensation. Therefore, these two stress profiles were closely correlated with dermatological quality of life, and might be considered to be important profiles that reflect the quality of life in patients with AD.

Arima et al. (18) reported that depression was observed more commonly in patients with AD than in healthy individuals. In our study, the BDI score, which displays the status of depression, was slightly higher in AD than in healthy individuals, and there was no statistical significance between AD and HCs. When it comes to anxiety in AD, most studies found that both children and adults with AD have a higher anxiety level than controls (19–21). Hashizume et al. (22) reported that both TA and SA are significantly higher in adult patients with AD than in controls, and the score of TA was significantly higher than that of SA in their AD patient group. Our study also demonstrated that both scores of TA and SA were significantly higher in patients with AD and the score of TA was significantly higher than that of SA ($p = 0.004$, 55.1 ± 14.1 vs. 50.5 ± 12.6).

In our data, TA and SA were not correlated with EASI score. It is still controversial whether anxiety

Table II. *Examination of nerve growth factor (NGF) expression in atopic dermatitis and normal skins through immunohistochemical staining*

	Epidermis		Dermis	
	Intensity score	NGF-positive score	Intensity score	NGF-positive score
Healthy control ($n=3$), mean (SD)	1 ± 0	1 ± 0	0.67 ± 0.58	0.67 ± 0.58
Atopic dermatitis ($n=4$), mean (SD)	2.75 ± 0.5	2.75 ± 0.5	2.5 ± 0.58	2.5 ± 0.58
p-value	0.022		0.029	

Intensity score: no staining (0), weak (1), moderate (2), high (3).
NGF-positive score: no staining (0), positive cells <25% (1), 25–50% (2), >50% (3).

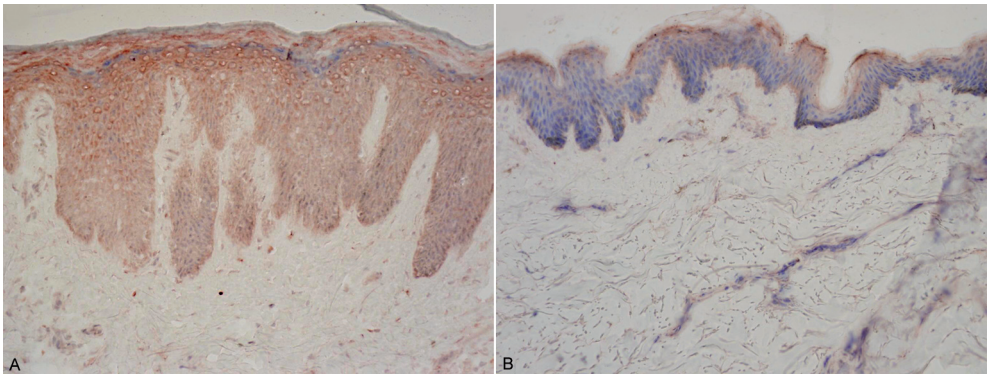

Fig. 4. Immunohistochemical staining of neuropeptide Y (NPY) in atopic dermatitis (AD)-involved skin (A; original magnification ×200) and normal skin (B; original magnification ×200). NPY immunoreactive cells were observed to be more numerous and dense in the entire epidermis of AD-involved skin than in control skin. NPY immune reactivity was not observed in the dermis of either AD-involved or control skin.

levels are correlated with the severity of AD (23). Since various immune and non-immune factors participate in the pathogenesis of AD, anxiety cannot be attributed solely to increased disease activity. However, TA and SA were positively correlated with pruritus. It has long been recognized that stress triggers or enhances pruritus through lowering the itching threshold (24, 25). The mechanism of how stress lowers the itch threshold is not clear. However, neuropeptides and neurotrophins are recognized as a crucial mediator associated with the mechanism of itching (26–28). Therefore, we investigated the expression of neuropeptides and neurotrophins in atopic skin that have been known to be associated with itching and anxiety. Although substance P is regarded as a useful marker of disease activity in AD, the difference in the expression of substance P between AD and HC skins was not remarkable in our study. We investigated the expression of NGF and NPY, which have been reported to be strongly associated with anxiety.

Besides function as a trophic factor of neuropeptidergic and sympathetic neurons, NGF is now increasingly regarded as a potent immunomodulator, promoting interactions between neuronal and immune cells (27). It has been reported that the most likely psychological substrate in anxiogenic stimuli could be NGF (29–32). Research investigating NGF in soldiers experiencing parachute jumping for the first time suggested that anticipatory anxiety might be responsible for NGF release (33). Additionally, NGF is particularly considered as one of the most important mediators lowering the itching threshold. Recently, Peter et al. (34) reported the relationships between stress and peptidergic innervation and mast cell degranulation in murine skin. Increased contact between nerve fibre and mast cells induced by stress may account for a lowered itching threshold. Our findings that the epidermis of AD lesions showed a higher expression of NGF compared with HCs were consistent with previous studies (35). Given the findings that the presence of intraepidermal mast cells is a characteristic of AD (36, 37), NGF expression in the epidermis of AD lesions is expected to induce activation of mast cells and exacerbate itching. In addition, it has been reported that fibroblasts and inflammatory cells, such as mast cells, lymphocytes, and eosinophils, can release NGF (38–40). In our study, inflammatory cells and fibroblasts in the dermis of AD lesions showed a higher expression of NGF.

Table III. *Examination of neuropeptide Y (NPY) expression in atopic dermatitis and normal skin through immunohistochemical staining*

	Epidermis	
	Intensity score	NPY-positive score
Healthy control ($n=3$)	0.67 ± 0.58	0.67 ± 0.58
Atopic dermatitis ($n=4$)	2.25 ± 0.5	2.5 ± 0.58
p-value	0.026	0.029

Intensity score: no staining (0), weak (1), moderate (2), high (3)
NPY-positive score: no staining (0), positive cells < 25% (1), 25–50% (2), > 50% (3).

NPY have been reported to have an anxiolytic effect via Y1 receptor in mice brains (41). Mutant mice lacking NPY show increased anxiety-like behaviour on various tests (42). In addition, low levels of NPY in plasma and cerebrospinal fluid have been found in patients with anxiety disorders (43). Altogether, it is considered that secretion of NPY has a protective role toward anxiety. Additionally, NPY in the central nervous system plays multiple roles in increasing food intake and decreasing physical activity (44). However, the reports regarding the role of NPY in AD have been limited. One report showed that AD skin lesions appeared in higher expressions of NPY (45). Another study demonstrated that the level of NPY in the plasma of patients with AD was elevated during exacerbation of the disease and further increased during remission (9). It was assumed that a lower plasma level of NPY during exacerbation rather than during remission originated from a selective uptake of NPY in the lesional skin. In our study, NPY-staining cells were observed more abundantly in the entire epidermis of AD lesions than in normal skins and NPY-staining was quite sparse in the dermis. *In vitro*, NPY have been reported to activate mast cell and stimulate angiogenesis (46, 47).

The present cross-sectional study has limitations in confirming whether anxiety is premorbid to pruritus with sufficient aetiological significance. However, as mentioned above, stress including anxiety has been reported to trigger and enhance pruritus. Furthermore,

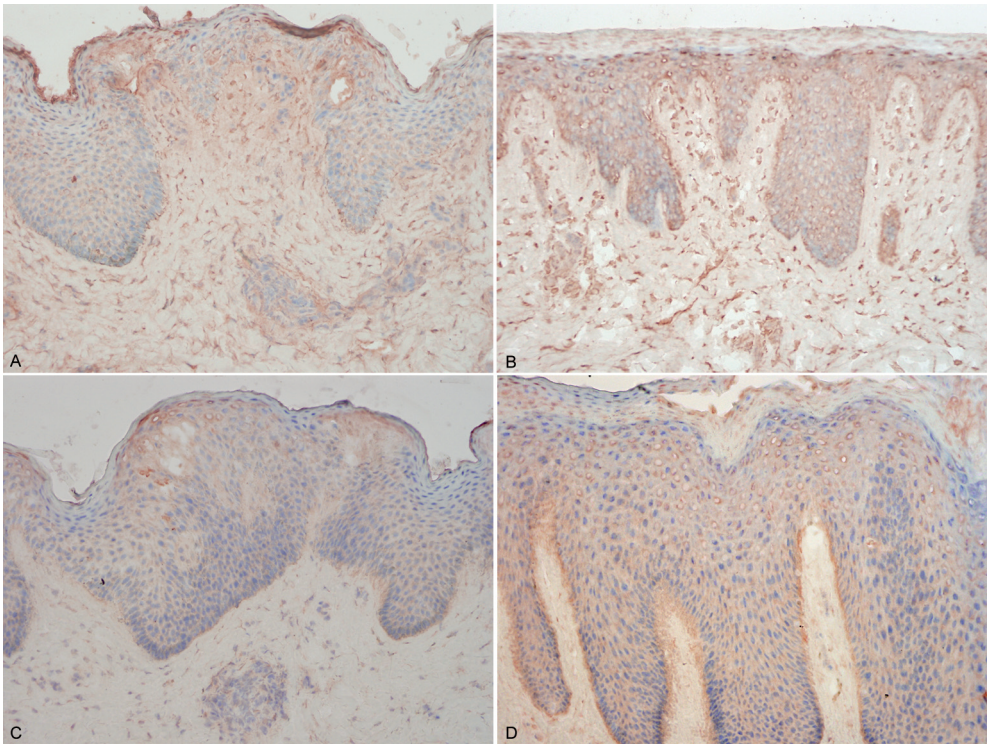

Fig. 5. Difference in expression of nerve growth factor (NGF) and neuropeptide Y in atopic dermatitis lesional skin. Immunohistochemical staining of NGF; (A) Eczema Area and Severity Index (EASI) score: 24.2, trait anxiety (TA): 40, state anxiety (SA): 47, pruritus: 6, (B) EASI score: 25, TA: 47, SA: 61, pruritus: 10 (original magnification ×200). Immunohistochemical staining of NPY; (C) EASI score: 24.2, TA: 40, SA: 47, pruritus: 6, (D) EASI score: 17.8, TA: 53, SA: 51, pruritus: 9 (original magnification ×200).

neuro-immune mediators, including NGF and NPY induced by anxiety, have been reported to be associated with pruritus. In our study, patients with AD who had high scores of SA, TA, and pruritus showed more intense NPY/NGF reactivity in the skin, although these were not statistically confirmed due to the limited numbers of specimens and there might be variation according to the severity of obtained skin lesions (Fig. 5a–d). These results suggested that anxiety may upregulate the expression of NGF and release NPY, both of which could contribute to pruritus. Thus, our study suggested that anxiety might be associated with the induction of pruritus through NGF and NPY. In addition, our results supported the necessity of management to reduce anxiety, such as relaxation therapy, educational programmes, and anxiolytics.

Besides BDI and STAI, which have been evaluated frequently in various psychosomatic studies, new scales such as IAS and PBC subscale, were also confirmed to be higher in patients with AD compared with healthy individuals. In addition, as anxiety among psychological profiles was closely correlated with pruritus, psychological approaches that can reduce anxiety might be considered in cases of patients with AD who do not respond to anti-histamines in the management of pruritus of AD. However, further studies that can support the relevance of psychological aspects in the pathogenesis of AD and the association between anxiety and pruritus are required. Moreover, as the effects of psychological management have been estimated only through severity of eczema and/or psychological parameters until now, studies to discover key molecules linking stress and severity of AD symptoms are necessary. In conclusion, dermatologists should understand the psychological characteristics of patients with AD and be aware of necessary treatment methods to help patients regulate stress conditions according to individual psychological characteristics.

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The authors declare no conflicts of interest.

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