

## CLINICAL REPORT

# Progressive Muscle Relaxation Therapy for Atopic Dermatitis: Objective Assessment of Efficacy

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The aims of this study were to validate the efficacy of progressive muscle relaxation (PMR) in patients with atopic dermatitis and to evaluate the serological parameters that may serve as objective measures of the efficacy of PMR. A total of 25 patients with atopic dermatitis were randomly assigned to either a PMR group ( $n=15$ ) or a control group ( $n=10$ ). Serum levels of nerve growth, neuropeptide Y, and Th2 cytokines (IL-4, IL-5, and IL-13) were measured at baseline and after one month. At baseline, only anxiety was positively correlated with pruritus score (state anxiety:  $R=0.496$ ,  $p=0.014$ ; trait anxiety:  $R=0.423$ ,  $p=0.04$ ). Serum levels of neuropeptide Y were inversely related to the State-Trait Anxiety Inventory (STAI) (state anxiety:  $R=-0.475$ ,  $p=0.019$ ; trait anxiety:  $R=-0.418$ ,  $p=0.042$ ) and pruritus scores ( $R=-0.451$ ,  $p=0.035$ ). After one month of PMR therapy, the degree of pruritus and loss of sleep was significantly decreased in the PMR group ( $p<0.001$ ), but not among controls. State anxiety scores showed significant improvement after treatment only in the PMR group ( $p=0.005$ ). There were no significant changes in the serological parameters in either group. Reductions in Eczema Area and Severity Index (EASI) scores were significant, but similar, in both groups. PMR may be a useful adjunctive modality for the management of atopic dermatitis through the reduction of anxiety. No change was found in biological parameters, but it was observed that neuropeptide Y may be related to high levels of anxiety in atopic dermatitis at baseline. **Key words:** anxiety; atopic dermatitis; neuropeptide Y; nerve growth factor; progressive muscle relaxation.

(Accepted April 12, 2011.)

Acta Derm Venereol 2012; 92: 57–61.

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Historically, many clinicians have considered allergic diseases to be closely related to psychosomatic symptoms (1). Furthermore, recent epidemiological studies have demonstrated the detrimental effects of several psychosocial stressors, such as caregiver stress, certain personality

types, poor family relationships, and negative life events, on the symptoms of allergic disease (2, 3). Anxiety, assessed by the State-Trait Anxiety Inventory (STAI), is strongly related to atopic dermatitis (AD) (4–7).

Psychological intervention including cognitive behavioural therapy, dynamic psychotherapy, autogenic training, relaxation therapy, and structured educational programmes have an additive effect compared with conventional treatments alone in terms of severity of eczema, subjective severity, itching intensity, and scratching after intervention (8). According to one review, relaxation therapy is one of the most effective psychological interventions for AD (8). Among several relaxation techniques, progressive muscle relaxation (PMR) has been found to be effective in disorders with a strong psychological component (9). Although there have been many studies with regard to the effects of psychological interventions on the management of AD, there remains a need for well-designed studies that utilize objective assessments of psychological parameters (10). Therefore, the aims of this study were to validate the efficacy of PMR in patients with AD and to evaluate the relevant serological parameters among T-helper type 2 (Th2) cytokines, neuropeptides, and neurotrophins that could correlate with changes in AD symptoms and psychological parameters after PMR (6).

## MATERIALS AND METHODS

### Subjects

A total of 25 patients (14 men, 11 women; mean age 23.5 years, range 12–40 years) with confirmed diagnoses of AD according to the criteria of Hanifin & Rajka (11) and at least moderate severity (Eczema Area and Severity Index (EASI) score  $>10$ ), were enrolled in this study. All had extrinsic AD. None of the subjects had other concomitant dermatological, medical, or psychological disorders, except atopic manifestations, including allergic asthma, allergic rhinitis, and allergic keratoconjunctivitis. 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. Enrolled patients were randomly assigned into two groups: (i) the PMR group, receiving PMR together with conventional treatments, including topical glucocorticoids, topical calcineurin inhibitors, topical emollients, and anti-histamines and; (ii) the control group, which only received conventional treatment. In both groups, systemic immunosuppressant and immunomodulating drugs were prohibited. This study was carried out from September–

October 2009, for the purpose of excluding seasonal differences in the skin condition. Patients who experienced stressful life events during the study period, such as severe disease, death of a family member, conflicts in personal or parental relationships, or other self-reported severe stressful life events, were excluded from this study. One patient in the PMR group was excluded due to a self-reported stressful event.

#### Treatment protocol

Participants in the PMR group received one month of PMR therapy, developed by the American physician Edmund Jacobson (12). PMR comprises both a physical and a mental component. The physical component involves tensing and relaxing muscle groups over the arms, legs, face, abdomen and chest. With eyes closed, the target muscle group is intentionally tensed for about 10 s and then relaxed for 20 s. The mental component involves concentrating on the sensation of tension and relaxation. In this study, the entire procedure was supervised by a psychologist using video and audio programs, which were modified for the patients with AD by a psychologist. The patients were asked to perform PMR using video and audio programs at home twice a day for 4 weeks under controlled room temperature and light conditions without eating or drinking (only water was allowed). In addition, abstinence from drinking alcohol and caffeine-containing beverages was recommended during the study period. Patient compliance was assessed via checklists regarding their performance of PMR, which were completed during the study and returned. In addition, we telephoned the patients once a week to determine if they were following the instructions and to address any issues regarding PMR.

#### Measurements

**Assessment of psychological parameters.** Psychological parameters were evaluated using various types of questionnaires, which assessed the patients for levels of depression, anxiety, interaction anxiousness, and private body consciousness.

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 (13). The Korean version of the BDI demonstrated good psychometric properties (14). Each item is evaluated using scores 0–3. The severity of depression increases with the overall score, which ranges from 0 to 63.

The STAI consists of 40 questions divided into 20 questions regarding state anxiety (SA) and 20 questions regarding trait anxiety (TA) (15). SA refers to the level of anxiety felt at the time that the subject completes the questionnaires. Trait anxiety refers to anxiety felt in general. The Korean version of the STAI was previously shown to exhibit excellent psychometric properties (16). Each question is evaluated using scores 1–4. Both of the total scores for SA and TA range from 20 to 80.

The 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 (17). It consists of 15 items that span a broad range of anxiety-evoking situations, including interactions with strangers, parties, dealing with authority figures, cross-sexed encounters, and casual conversation. Each item is evaluated using scores 0–4. The total score ranges from 0 to 60.

The Private Body Consciousness (PBC) subscale is one of three subscales of the body consciousness questionnaire (18). Its 5 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 clinical severity.** Clinical severity was quantified using EASI (19). The EASI score ranges from 0 to 72.

Two horizontal visual analogue scales (VAS) were used for the subjective assessment of pruritus and loss of sleep (LOS), with the anchors of 0 = no pruritus/no LOS, 10 = the most severe symptoms.

**Serum levels of NGF, NPY, IL-4, IL-5 and IL-13.** All blood samples were drawn in the morning, between 08:00 h and 10:00 h, to control diurnal variation. Serum levels of nerve growth factor (NGF), neuropeptide Y (NPY), and Th2 cytokines (IL-4, IL-5, and IL-13) were evaluated at baseline and after one month of treatment. Peripheral venous blood samples were drawn and allowed to clot at room temperature (20–24°C) for 30 min. The tubes were centrifuged at 1000×g for 10 min. The serum was aliquoted and stored at –70°C until they were tested. NGF was measured using NGF enzyme-linked immunoassay (ELISA) kit (R&D Systems, Minneapolis, MN, USA). NPY was measured using NPY ELISA kit (RayBiotech, Norcross, GA, USA). IL-4, 5, 13 were measured using IL-4 ELISA kit (eBioscience, San Diego, CA, USA), IL-5 ELISA kit (eBioscience) and IL-13 ELISA kit (R&D Systems). All parameters were measured according to the manufacturer’s instructions. All serum samples were assayed in duplicate.

#### Statistical analysis

Statistical analyses were performed using SPSS (SPSS Inc, Chicago, IL, USA) for Windows (version 12). Results were described as means ± standard deviations (SD). At baseline, the differences in the EASI score, pruritus, LOS, the degree of stress, and the serum levels of NPY, NGF, IL-4, IL-5 and IL-13 between the PMR and control groups were analysed with the Mann–Whitney *U* test. Differences in clinical parameters and the serological parameters between baseline and one month after treatment in both groups were analysed with Wilcoxon signed-ranks test. Additionally, the degree of difference, which was calculated by subtracting the value at the one-month follow-up from the baseline value for the EASI score, pruritus, and LOS, was compared between the PMR and control groups using the Mann–Whitney *U* test. Pearson’s correlation analysis of these parameters was performed to elucidate how the psychological and serological parameters related to the severity of AD symptoms and clinical improvement. A *p*-value < 0.05 was considered statistically significant.

## RESULTS

### Characteristics of the enrolled patients with atopic dermatitis

The PMR group (7 males and 7 females; mean age ± SD: 24.6 ± 9.3 years) and the control group (6 males and 4 females; mean age ± SD: 22.5 ± 7.7 years) did not differ in gender or age. For the PMR group, the mean EASI score was 15.7 ± 4.9 (9–27.3) and the mean pruritus and LOS scores were 7.2 ± 1.3 (5–9) and 6.1 ± 2.5 (2–10), respectively. For the control group, the mean EASI score was 13.3 ± 4.1 (10.1–22.9) and the mean pruritus and LOS scores were 5.9 ± 1.1 (5–8) and 3.4 ± 0.7 (2–7), respectively. With the exception of IL-13 being slightly higher in the PMR group, there were no significant differences in Th2 cytokines and neuropeptides, including NGF and NPY in the two groups (Table I). Likewise, total serum IgE and eosinophils did not differ.

*Baseline psychological parameters and their associations with AD symptoms and serum parameters*

Before randomization, the STAI was the only psychological parameter that was positively correlated with pruritus in all enrolled patients with AD (state anxiety (SA):  $R=0.496, p=0.014$ ; trait anxiety (TA):  $R=0.423, p=0.04$ ), but not with the EASI or LOS scores. Both pruritus and LOS were not significantly correlated with total serum IgE level, peripheral blood eosinophil count, or the EASI score.

The serum level of NGF was not correlated with the four psychological parameters at baseline nor with clinical scoring. Among Th2 cytokines, only IL-13 was positively correlated with NGF ( $R=0.414, p=0.04$ ). The serum level of NPY was inversely related to the anxiety score, STAI (SA:  $R=-0.475, p=0.019$ ; TA:  $R=-0.418, p=0.042$ ) and pruritus scores ( $R=-0.451, p=0.035$ ) at baseline, but NPY did not show significant correlation with other psychological parameters nor Th2 cytokines.

*Effect of PMR on clinical symptoms, psychological parameters and serological parameters*

Following one month of PMR therapy, EASI score improved (baseline:  $16.5 \pm 5.6$ , after one month:  $7.2 \pm 7.1$ ). The control group improved similarly (baseline:  $13.3 \pm 4.1$ , after one month:  $7 \pm 1.9$ ) (Fig. 1). The degree of pruritus and LOS were significantly decreased in the PMR group ( $p=0.001$  and  $p=0.007$ , respectively), but not in the control group (Fig. 2).

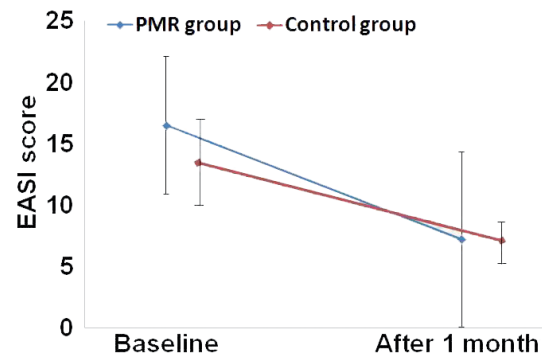


Fig. 1. Improvement in Eczema Area and Severity Index (EASI) score in both groups. The degree of improvement was significant in both groups, but more remarkable in the progressive muscle relaxation (PMR) group.

Among the psychological parameters, the BDI and SA scores showed significant improvement after treatment only in the PMR group ( $p=0.016$  and  $0.04$ , respectively) (Fig. 3).

Compared with baseline, post-treatment serum levels of NGF, NPY and IL-4, IL-5 and IL-13 remained unchanged in both groups (data not shown).

DISCUSSION

In a previous study, we have shown that anxiety is positively correlated with the degree of pruritus in patients with AD (7). Anxiety has also been reported to be an important psychological factor that contributes to the aggravation of AD (20). Psychotherapy may improve both the psychological and dermatological condition of

Table I. Demographics and characteristics of the study sample at baseline

Variables	PMR group (n=14) Mean ± SD (range)	Control group (n=10) Mean ± SD (range)	<sup>a</sup> p-value
Sex, n			
Male	7	6	
Female	7	4	
Age, years	24.6 ± 9.3 (12–40)	22.5 ± 7.7 (16–37)	0.57
EASI score	15.7 ± 4.9 (9–27.3)	13.3 ± 4.1 (10.1–22.9)	0.18
Degree of pruritus (0–10)	7.2 ± 1.3 (5–9)	5.9 ± 1.1 (5–8)	0.1
Loss of sleep (0–10)	6.1 ± 2.5 (2–10)	5.0 ± 1.3 (2–7)	0.1
Peripheral blood eosinophil count (number/ $\mu$ l)	445.7 ± 270.8	548 ± 364.3	0.89
Total serum IgE level (IU/ml)	1,701.8 ± 1366.3	2,685.4 ± 2108.4	0.16
IL-4 (pg/ml)	135.7 ± 355.7 (5.7–1,800)	121.4 ± 266.7 (8.3–124.8)	0.48
IL-5 (pg/ml)	722.5 ± 224.2 (306.1–1,369.9)	676.9 ± 323.6 (259.2–1,116.8)	0.18
IL-13 (pg/ml)	101 ± 45.7 (39.3–157.5)	79.5 ± 69.2 (3.8–252.1)	0.04
NGF (pg/ml)	406.9 ± 111.8 (201.2–714.7)	445.5 ± 290.7 (256.6–1,199.4)	0.36
NPY (pg/ml)	47.2 ± 7.8 (27.0–71.9)	45.3 ± 9.2 (31.6–61.3)	0.83
Psychological parameters			
Depression (0–63)	12.7 ± 6.2 (0–26)	9 ± 4 (4–15)	0.07
State anxiety (20–80)	44.7 ± 11.9 (21–61)	45.3 ± 12 (24–60)	1
Trait anxiety (20–80)	52.4 ± 11.6 (21–61)	49.3 ± 10.2 (31–64)	0.32
Interaction anxiousness scale (0–60)	26 ± 9.8 (15–48)	27.3 ± 7.7 (9–35)	0.32
Private body consciousness subscale (0–25)	11 ± 3.2 (8–19)	10.1 ± 2.7 (6–14)	0.48

<sup>a</sup>Mann-Whitney U test.

EASI: Eczema Area and Severity Index; PMR: progressive muscle relaxation; SD: standard deviation; NPY: neuropeptide Y; NGF: nerve growth factor; IU: International Units; IgE: immunoglobulin E; IL: interleukin.

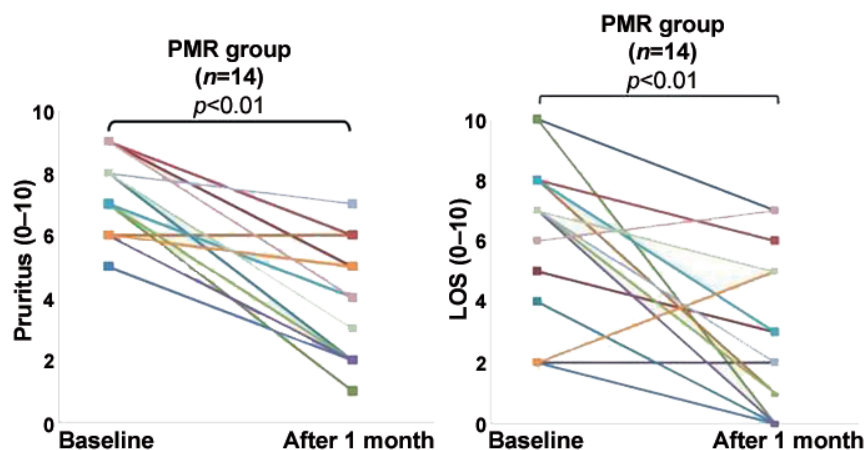


Fig. 2. Effect of progressive muscle relaxation (PMR) on clinical parameters. Significant decrease of pruritus ( $p=0.001$ ) and loss of sleep (LOS) ( $p=0.007$ ) was shown in the PMR group but not in the control group (data not shown).

these patients, especially those with high levels of anxiety (21). Tando spirone, a 5-hydroxytryptamine 1A receptor agonist with anxiolytic effects, has been reported to attenuate itching by controlling emotional response (22).

PMR is a muscle relaxation therapy introduced in 1934 (12). It is effective in treating anxiety disorders, including panic disorder and generalized anxiety disorder (23). Gaylord et al. (24) reported that anxiety assessed by STAI was significantly reduced in healthy individuals who received PMR. PMR therapy is regarded as one of the most effective psychological interventions for AD (8).

Most studies assessing psychological interventions in AD have shown clinical improvement (10). NGF and NPY have been reported to be strongly associated with anxiety, including anxiety in relation to AD (5, 25–30). NGF may participate in the response to anxiogenic stimuli (25). NGF is considered as a potent immunomodulator, the functions of which include mast cell activation, increase in vascular permeability, and cross-action between neuronal and immune cells (5, 26). NPY has an anxiolytic effect via the Y1 receptor in the amygdala and is induced by stress (27, 28). Mutant mice lacking NPY show increased anxiety-like behaviour on various tests (29). In addition, low levels of NPY in plasma and cerebrospinal fluid have been found in patients with anxiety disorders (30). NPY *in vitro* activates mast cells and stimulates angiogenesis (31, 32).

In our study, the serum level of NGF was found not to reflect the degree of anxiety in AD. Toyoda et al. (33) reported that the serum level of NGF in patients with AD is positively related to the EASI score and could be a useful plasma marker of disease activity in AD. Sin et al. (34) reported that NGF induces more IL-13 production from basophils of allergic subjects than from the basophils of non-allergic subjects. Although our study provided evidence of a correlation between IL-13 and NGF, neither were related to AD disease activity.

In our study, the serum level of NPY was inversely correlated with the anxiety scores; SA and TA. To our knowledge, this is the first report to show an inverse correlation between NPY levels and anxiety scores in patients with AD. Previously, Zhou et al. (35) reported that plasma levels of NPY are inversely correlated with trait anxiety in healthy individuals. We did not observe any significant changes in NPY levels following PMR, despite improvement in clinical parameters and anxiety scores. It is possible that the restoration of NPY levels following PMR may take longer. In conclusion, PMR may be a useful adjunctive modality for the management of pruritus and sleep disturbances in patients with AD, through the reduction in SA. However, limitations of our study include the small number of patients, which may cause sampling bias, the short duration of PMR therapy, and the short follow-up period.

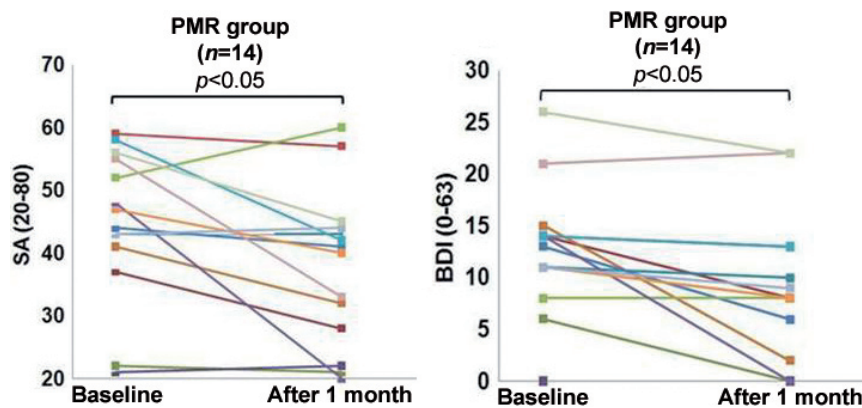


Fig. 3. Effect of progressive muscle relaxation (PMR) on psychological parameters. Among the four psychological parameters, significant decrease of depression, assessed by Beck Depression Inventory (BDI) ( $p=0.02$ ), and state anxiety (SA) ( $p=0.016$ ) was shown in the PMR group, but not in the control group (data not shown).

## ACKNOWLEDGEMENTS

The authors have no relevant financial interests in the research presented in this article.

This study was supported by a grant from the Korea Health 21 R&D Project (Ministry of Health & Welfare and Family Affairs, Republic of Korea, A080892).

*The authors declare no conflicts of interest.*

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