

# Does being easily moved to tears as a response to psychological stress reflect response to treatment and the general prognosis in patients with rheumatoid arthritis ?

H. Ishii, M. Nagashima, M. Tanno, A. Nakajima, S. Yoshino

*Department of Joint Disease and Rheumatism, Nippon Medical School, Tokyo, Japan*

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## Abstract

### Objective

*Psychological stress affects the condition of patients with rheumatoid arthritis (RA). We evaluated the neuroendocrine and immune responses (NEIRs) in the peripheral blood to psychological stress induced by deep emotion with tears in patients with RA.*

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### Methods

*We compared the levels of plasma cortisol and interleukin-6 (IL-6), the CD4/CD8 ratio, and natural killer (NK) cell activity in peripheral blood between the patients with easily controlled RA (CRP < 1.0 mg/dl) and those with difficult-to-control RA (CRP ≥ 1.0 mg/dl) before and after the stress session.*

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### Results

*Psychological stress induced by deep emotion with tears had a greater influence on NEIRs in patients with difficult-to-control RA (CRP ≥ 1.0 mg/dl) than in those with easily controlled RA (CRP < 1.0 mg/dl). The levels of plasma cortisol, IL-6, and the CD4/CD8 ratio were lower, while NK cell activity in the peripheral blood was higher in those who were not moved to tears than in those who were moved to tears. Patients who were moved to tears were apt to obtain good control of RA (CRP < 1.0 mg/dl) within one year.*

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### Conclusion

*The patients with better RA control are easily moved to tears as an emotional expression; shedding tears is considered to suppress the influence of stress on the NEIRs, thus preventing the buildup of stress. Patients who were moved to tears had a more easily controlled RA compared with those who were emotionally affected but not moved to tears.*

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### Key words

Psychological stress, rheumatoid arthritis, neuroendocrine-immune response.

Hiroyasu Ishii, MD, PhD; Masakazu Nagashima, MD, PhD; Makoto Tanno, MD; Atsuo Nakajima, MD, PhD; and Shinichi Yoshino, MD, PhD.

Please address correspondence and reprint requests to: Shinichi Yoshino, MD, PhD, Department of Joint Disease & Rheumatism, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan. E-mail: n7148@nms.ac.jp

Received on December 23, 2002; accepted in revised form on July 1, 2003.

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## Introduction

It is clinically suspected that psychological stress induces the occurrence or causes the progression of various diseases (1). When a stressor that induces psychological stress is applied to an organism, either the secretion of hormones from the adrenal cortex or the stimulation of the sympathetic nervous system is enhanced, resulting in an increased secretion of catecholamines from the adrenal cortex (2, 3). The level of plasma cortisol in the peripheral blood also increases due to psychological stress (4, 5). Humans under psychological stress may express feelings of grief or anger.

Likewise, the act of weeping may be categorized into two types (4); one is weeping induced by agony following physical trauma or unpleasant experiences associated with sadness, the other is weeping induced by happy events. These two types of weeping are categorized into the same group with respect to the expression of feelings. However, since the after-effects of these two types of weeping are different, we empirically consider that the two types are probably different. Thus far, few studies on weeping accompanying deep emotions have been reported. We have also found that both mirthful laughter and general anesthesia influence the neuroendocrine and immune responses (NEIRs) of humans to some extent (6-8). In this study, whether or not weeping accompanying deep emotion is a response to psychological stress in a manner similar to mirthful laughter leading to mental calmness or a sense of relaxation in organisms, was investigated based on NEIRs in the peripheral blood (9).

It has been previously reported that healthy people and patients with autoimmune diseases like rheumatoid arthritis (RA) have different levels of response to psychological stress (10). In view of this understanding we examined if: a) weeping accompanying deep emotion as a response alleviates psychological stress; b) healthy subjects and patients with RA have different NEIRs after experiencing deep emotion; and c) patients with easily controlled RA (CRP < 1.0 mg/dl) or diffi-

cult-to-control RA (CRP = 1.0 mg/dl) have different NEIRs after experiencing deep emotion.

## Patients and methods

### Patients

In this study, 24 patients with RA (all female) were diagnosed based on the criteria of the American College of Rheumatology. The mean age was 58.1 years, range 41-78 years. Healthy subjects (control group) consisted of 21 healthy females whose average age was 59 years (range 46 - 73 years). There was no significant difference in the average age between the RA and healthy subjects. Patients and healthy subjects were instructed to listen to a traditional Japanese sentimental story, told by a professional storyteller for approximately 60 minutes. The time of blood sampling was 11:00-12:00 pm, considering the endocrine circadian rhythm within a day's precision. The patients were instructed to take prednisolone (range 2.5 - 5 mg/day) and anti-rheumatic drugs with the morning dose of their prescribed drug on the day.

### Methods

The levels of plasma cortisol, interleukin-6 (IL-6), the CD4/CD8 ratio, and natural killer (NK) cell activity in the peripheral blood were measured immediately before and after listening to the story. The chemiluminescence enzyme immunoassay was employed for the measurement of IL-6 levels, radioimmunoassay for the cortisol levels, flow cytometry for the CD4/CD8 ratio and 51-Cr release assay for the NK cell activity. The IL-6 levels, CD4/CD8 ratio and NK cell activity were measured to assess changes in the immune system. In particular, levels of serum IL-6 and cortisol showed a statistically significant circadian rhythm in both the healthy subjects and RA patients, their values peaking in the morning and falling towards the evening (11, 12). All assays were done by an SRL (Special Research Laboratory, Tokyo, Japan) in a blind manner. Prior to the study, written informed consent was obtained from all patients and healthy subjects, and the study was

approved by our hospital ethics committee.

There were no significant differences in age, gender, duration of the disease, stage of the disease and drugs prescribed between the 12 patients with easily controlled RA and difficult-to-control RA. It was observed that the CRP levels were maintained at less than 1.0 within one recent year in the former group of patients, and in the difficult-to-control RA patients the CRP levels were more than 1.0 within one recent year.

We carried out a questionnaire survey after the experiment; in the survey, the patients with RA could be divided into two groups: those who were moved to tears (deep emotion with tears) by the sentimental story, and those who were affected by the sentimental story but not moved to tears (deep emotion without tears). We investigated the correlation between the number of subjects who were moved to tears and their RA activity level, and the correlation between their sensitivity to psychological stress (the degree of ease in being moved to tears, and the progression of RA). We measured the period from the onset of RA to the time when good control of RA was achieved (the time when CRP < 1.0 mg/dl) and compared the results between patients expressing deep emotion with tears and those expressing deep emotion without tears.

#### Statistical analysis

The Wilcoxon signed-rank test was used to compare the level of each parameter before and after listening to the sentimental story. A *p* value less than 0.05 was considered to indicate a significant difference.

#### Results

##### Comparative study of the parameters measured in the peripheral blood

Significant differences in the levels of plasma cortisol and IL-6, and CD4/CD8 ratio in the peripheral blood before listening to the sentimental story (psychological stress) were observed between the healthy subjects and the patients with RA, and also between the patients with easily controlled and those with difficult-to-control RA. Immedi-

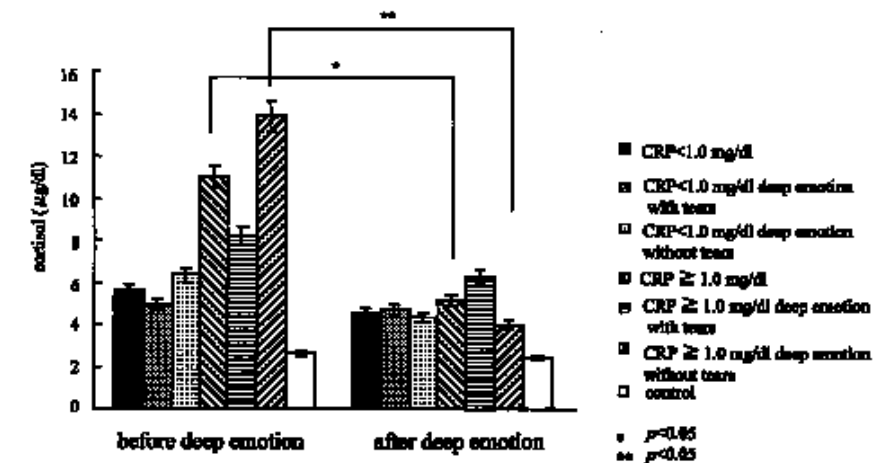


Fig. 1. Two RA groups and healthy subjects were compared based on the levels of cortisol in the peripheral blood.

\* and \*\*: Significant group difference at *p* < 0.05.

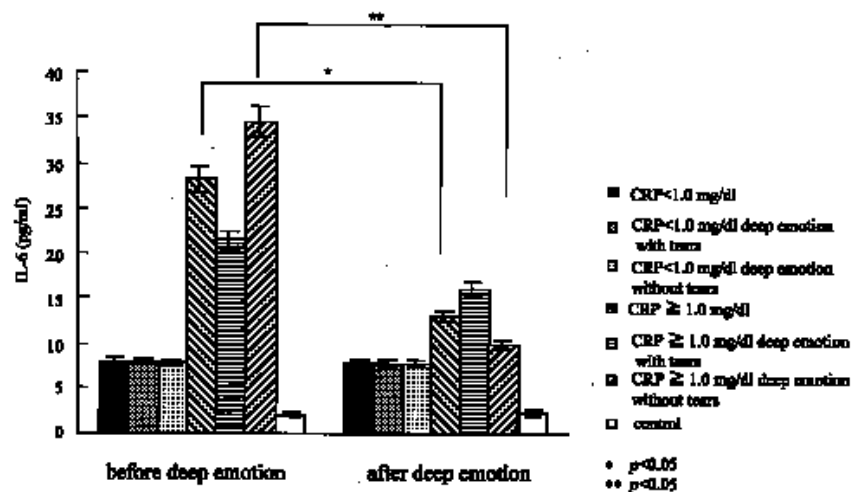


Fig. 2. Two RA groups and healthy subjects were compared based on the levels of interleukin-6 (IL-6) in the peripheral blood.

\* and \*\*: Significant group difference at *p* < 0.05.

ately after listening to the sentimental story, the levels of plasma cortisol and IL-6, and the CD4/CD8 ratio in the peripheral blood in the patients with RA decreased significantly. When the patients with easily controlled RA and those with difficult-to-control RA were compared, it was found that in the latter group, the levels of plasma cortisol (Fig. 1) and IL-6 (Fig. 2), and the CD4/CD8 ratio (Fig. 3) decreased significantly (*p* < 0.05), while NK cell activity increased significantly (*p* < 0.05) compared to levels before listening to the story (Fig. 4).

Particularly, in the patients with difficult-to-control RA (CRP 1.0 mg/dl),

the levels of plasma cortisol (Fig. 1) and IL-6 (Fig. 2), and the CD4/CD8 ratio (Fig. 3) were significantly lower (*p* < 0.05) and the NK-cell activity (Fig. 4) was significantly higher (*p* < 0.05) in those who were not moved to tears than in those who were moved to tears.

##### Comparative study by questionnaire survey

In patients with easily controlled RA (CRP < 1.0 mg/dl), the percentage of patients who were moved to tears was significantly higher than patients who were not moved to tears, while in the patients with difficult-to-control RA (CRP 1.0 mg/dl), the percentage of

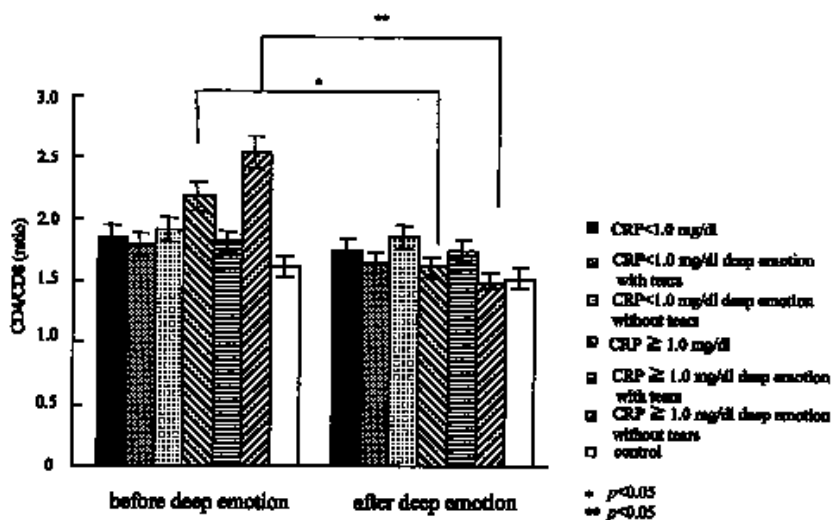


Fig. 3. Two RA groups and healthy subjects were compared based on the CD4/CD8 ratio in the peripheral blood. \* and \*\*: Significant group difference at  $p < 0.05$ .

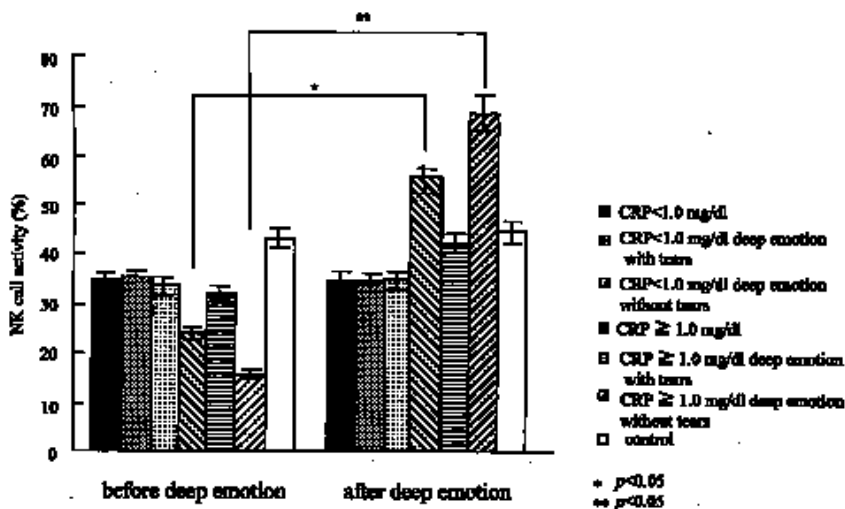


Fig. 4. Two RA groups and healthy controls were compared based on the levels of NK cell activity in the peripheral blood. \* and \*\*: Significant group difference at  $p < 0.05$ .

those who were not moved to tears was significantly higher than patients who were moved to tears (Fig. 5).

In the patients with easily controlled RA (CRP < 1.0 mg/dl) who were moved to tears, the percentage of those who achieved good control of RA within one year of its onset was significantly higher than for patients who obtained good control after one or more years of its onset (patients whose CRP levels did not decrease to < 1.0 mg/dl within one year of its onset). In the patients with easily controlled RA who were affected but not moved to tears, the percentage of those whose RA was under good control one or more years from its

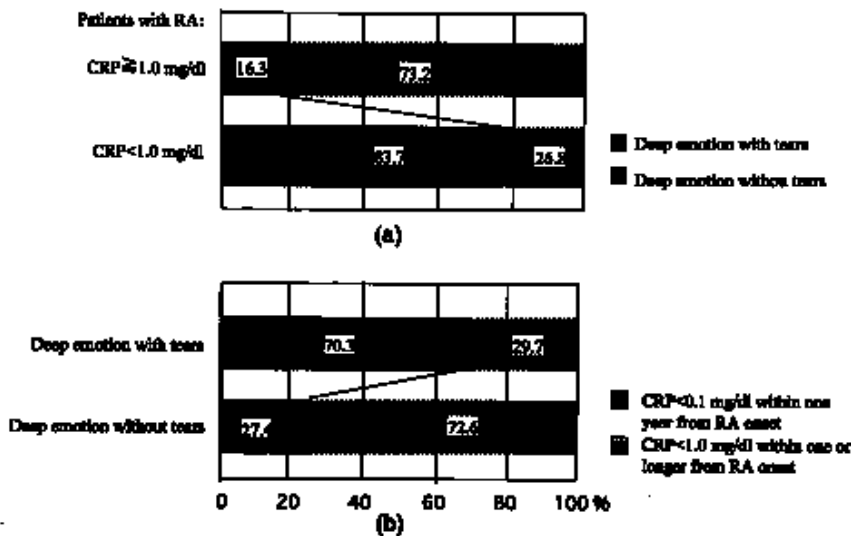
onset was significantly higher than those whose RA was under good control within one year of its onset (Fig. 5). These results suggest that patients with easily controlled RA are easily moved to tears as an emotional expression. Shedding tears is considered to suppress the influence of stress on the NEIRs, thus preventing the buildup of stress.

#### Discussion

The first half of our study suggests that the NEIRs of patients with difficult-to-control RA is easily activated by psychological stress (13); in this group of patients, those who were not moved to

tears showed the highest level of activation of NEIRs probably due to psychological stress (14). An individual who is easily moved to tears seems to be emotionally unstable and tends to build up stress (10). However, the above results suggest that those who are easily moved to tears have more stable NEIRs. In the patients with RA, those who were affected but not moved to tears tended to have an unstable and variable NEIRs and their RA was difficult to control.

Among the measured parameters of the immune system, the levels of IL-6, cortisol, and the CD4/CD8 ratio were significantly higher, whereas the NK cell activity was significantly lower in patients with difficult-to-control RA than in patients with easily controlled RA. From these results, we consider that the NEIRs are in a state of disequilibrium in patients with difficult-to-control RA compared with either healthy subjects or patients with easily controlled RA. Also the interacting pathways between stress and immune system are activated, thereby increasing the sensitivity of the subjects to psychological stress, subjecting the immune system, including its response of producing high levels of IL-6 under the strong influence of stress (15). The significant decrease in the levels of IL-6 and cortisol was caused only by the relief from psychological stress. NEIRs and the immune systems of patients with difficult-to-control RA are always in a state of activation, and after the relief from psychological stress, for example, by listening to a sentimental story or mirthful laughter, these systems are activated as in healthy subjects and in patients with easily controlled RA. In relation to stresses, changes are easily observed in the immune system like the levels of IL-6 and NK cell activity. Yoshino *et al.* (6) have reported that by relief from stress in RA patients, including listening to a traditional Japanese comic story (raku-go), the level of IL-6 decreases. Walker *et al.* reported that the type of stressor and individual differences in stress appraisal and reactivity may prove to be important prognostic factors in the onset or progression of RA (16).



**Fig. 5.** Correlation between the percentage of subjects who were moved to tears and their RA activity level (a). A comparison of the percentage of patients in whom RA was under good control (CRP < 1.0 mg/dl) within or after one or more years of onset between patients expressing deep emotion with tears and those expressing deep emotion without tears (b).

These results should be useful for developing a pharmacotherapeutic strategy for early RA (16), to determine if the knowledge of a patient with early RA and who is easily moved to tears can be used to predict that the disease will progress rapidly or gradually. The administration of multiple drugs at an early stage is currently the main pharmacotherapy for RA. Some patients suffer from side effects due to high doses and chronic uses of drugs intended to control RA; while in other patients, the progression of RA can not be suppressed due to taking inadequate doses or non-selectivity of drugs. We believe that it is possible to predict (to some extent) whether or not a patient is predisposed to build up of stress, by inquiring if the patient is easily moved to tears or not. If the patient has a predisposition to easily build up stress, then administration of multiple drugs at an early stage will be recommended (17). If not, a patient with RA can be well controlled without administration of multiple doses of drugs at an early stage. As one of the means to determine the predisposition of a patient, the usefulness of our examination of whether or not a patient is easily moved to tears was scientifically verified in this experiment.

The emotional reaction of weeping is a phenomenon observed only in humans

(18). We present the following hypothesis regarding the relationship between tears in response to emotion and stress. When an individual is under psychological stress, the cerebral frontal lobe of the cerebrum, which is responsible for the personality of the individual, is activated and its neurons fire (19). This may block the circuit connected to the upper central nervous system (20, 21); subsequently, the personality tentatively collapses (22). After shedding tears, the activated frontal lobe returns to its normal state, and the stress is alleviated. Therefore, in individuals who are affected but not moved to tears, the blockade in the circuit connected to the upper central nervous system continues and the activated frontal lobe can not return to its normal state quickly, resulting in the continuous instability of the NEIRs (19, 20); this causes the buildup of stress in the body.

The patients who were moved to tears had more easily controlled RA because they had more stable NEIRs than those who were affected but not moved to tears. We suggested that therapies that focus on stress management and enhancement of social support to control RA symptoms may prove to be important.

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