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主論文

The elevation of natural killer cell activity induced by laughter in a crossover designed study

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Abstract. The elevation of natural killer cell activity (NKCA) by laughter was not confirmed due to incomplete methodology of previous studies although positive emotion is believed to be favorable for health. To verify NKCA elevation by laughter in a crossover design, we measured NKCA before and after watching films, presenting 75-min comic film and non-emotional control film at different days to the same 21 healthy male subjects. Electromyogram of left major zygomatic muscle was obtained during the films to quantify the magnitude of laughter as an index of emotional expression. As indices of emotional experience, the self-rated pleasantness of the comic film and mood state before and after film were measured using visual analogue scale and Profiles of Mood State (POMS), respectively. The comic film significantly elevated NKCA (26.5-29.4%, $p<0.05$), whereas the control film did not (27.1-24.8%, not significant). This is the first study to demonstrate NKCA elevation by laughter in a crossover designed study. To examine the contribution of experiential and expressive aspects of laughter to NKCA elevation, correlation of NKCA elevation with the self-rated pleasantness, mood scores before and after comic film and the magnitude of laughter was statistically tested. We found that NKCA elevation was negatively correlated with the scores of negative mood scales of POMS while NKCA elevation had no significant correlation with self-rated pleasantness and the magnitude of laughter. Further group analysis revealed that high scores of depression and anger-hostility suppressed NKCA elevation by laughter. We also found that NKCA before and after comic film had tendency of correlation with self-rated pleasantness of the comic film while NKCA had no correlation with the magnitude of laughter. These findings suggest that NKCA elevation and NKCA before and after comic film seem to be related with the experiential aspects of laughter rather than with the expressive aspects.

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Key words: laughter, natural killer cell activity, crossover design, electromyogram, pleasantness

Introduction

Cheerful heart is a good medicine. As shown in the Old Testament, it has been believed from the ancient times that positive emotion has favorable effect on health, whereas there were few studies to corroborate this idea. In the research field of psychoneuroimmunology, the effects of negative psychological stress on immune function were investigated in detail (1,2), in contrast, little was known about the effects of positive psychological events on immune function. Laughter is an innate emotional expression of joy, happiness and high spirit (3). Since the first report of Norman Cousins (4), scientific studies have started to clarify immunological effect of laughter. There are a few reports that laughter elevated natural killer cell activity (NKCA) (5,6), but the sample size of these studies was small, indicating the limited reliability of these results. Laughter is an emotion with experiential and expressive aspects. These studies also omitted the measurement of the two aspects of laughter like pleasant experience, changes of mood states during experiments and the magnitude of facial expression, so that these studies could not uncover the relation between NKCA elevation and the experiential and expressive aspects of laughter. In the present study, we measured the elevation of NKCA induced by laughter and non-emotional control experiments in a crossover design and examined the relation between NKCA elevation and experiential and expressive aspects of laughter.

Materials and methods

Subjects. Twenty-one young healthy male subjects (age 18-26 years) participated in the present study. All the subjects gave written informed consent. The experimental procedure was conducted conforming to the policies and principles contained in the Declaration of Helsinki. The subjects did not take any medication during the experimental period. We

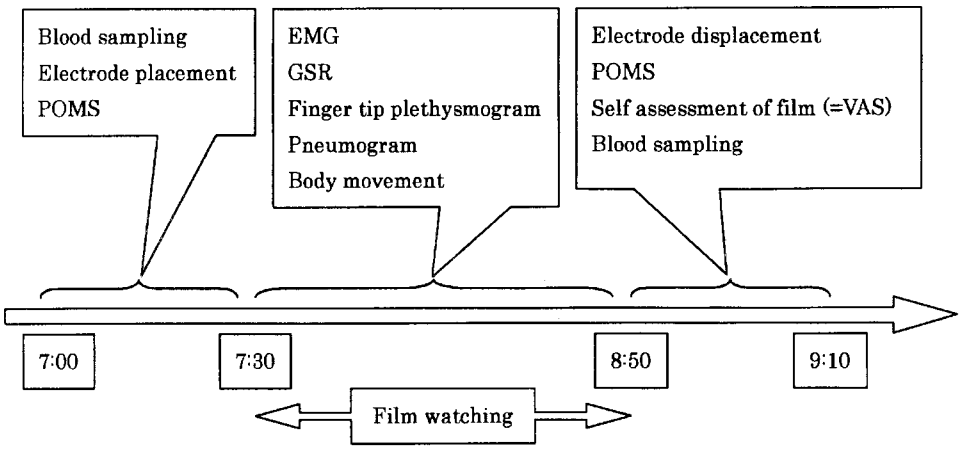

Figure 1. Protocol of the experiment. From 7:00 a.m. to 7:30 a.m., mood assessment with Profiles of Mood States (POMS), blood sampling and placement of electrode were undertaken in the given order. At 7:30 a.m., film presentation started and electromyogram of left major zygomatic muscle, skin conductance response, finger tip plethysmogram, pneumogram, body movement were polygraphically recorded during film watching. Facial expression of the subjects was also recorded using a video camera. At the end of the film (approximately 8:50 a.m.), displacement of electrodes, mood assessment with POMS, self-rating of pleasantness of the comic film and blood sampling were performed.

limited our study to male subjects due to the unknown effect of female menstrual cycle on NKCA. All the participants were paid ten thousand yens (corresponding to approximately US$80) after the completion of the experimental protocol.

Experimental procedure. The protocol of the experiment is displayed in Fig. 1. Subjects were instructed to avoid intensive exercise, to sleep well, not to take alcohol, tobacco and caffeine from the day before the experiment and not to have breakfast in the morning of the experimental day. Blood samplings were undertaken at 7:20 a.m. and 9:00 a.m. because of the circadian rhythm of NKCA (7). The experiment started at 7:00 a.m. At first, mood states of the subject were assessed by Profiles of Mood States (POMS), then blood sampling and placement of electrodes and probes to the subject were undertaken. The subject watched a comic film or a non-emotional control film presented in the 14-inch TV monitor approximately 2 m apart, alone in a shielded room. The duration of the films was 75 min. The content of the comic film used in the study was part of comedy series produced by popular Japanese comedians, and that of non-emotional control film was a documentary TV program that did not contain any emotional elements. The subject watched the other film within 4 weeks in the same experimental protocol. The order of both films was randomized to address potential order effect. During watching a film, electromyogram of left major zygomatic muscle, skin conductance response in the left palm, finger tip plethysmogram of left forefinger, pneumogram, body movement and vocalization were measured using digital electroencephalograph (Synafit 2514, GE Marquette Medical Systems, Tokyo, Japan). According to the guideline of Fridlund and Cacioppo (8), Ag-AgCl surface electrodes with 5 mm diameter were placed on the left major zygomatic muscle, which was mainly involved in the facial expression of laughter (9). These polygraphical data were recorded in magneto-optical discs. Simultaneously, the facial expression of the subject was recorded with a digital video camera. After watching a film (approximately 9:00 a.m.), the assessment of mood states with POMS, blood sampling, self-rating of the pleasantness of the comic film with visual analogue scale were undertaken. All these measurements were undertaken in the shielded room to minimize environmental noise.

Immunological measurements. We measured NKCA, the percent of NK cell marker (CD16, CD56, CD57), red blood cells, white blood cells and platelets. The measurements were performed at BML, INC (Tokyo, Japan). We assumed $CD16^+$ $CD56^+$ cells as NK cells in the present study (10). To obtain the number of NK cell, the percent of $CD16^+$ $CD56^+$ cell subtype was multiplied by total lymphocytes. NKCA was determined by standard chromium release assay as described by Kay and Horwitz (11) at two effector-to-target ratios (20:1, 10:1). Target cells were ^{51}Cr-labeled human myeloid K562 cells. The assays of NKCA were finished within the day of blood sampling. NKCA elevation was defined as the difference of NKCA before and after the film (NKCA before film minus NKCA after film). To determine the NKCA per unit cell count, NKCA was divided by the percent of $CD16^+$ $CD56^+$ cell subtype.

Quantification of laughter. At first, we removed artifactual activities of major zygomatic muscle from electromyographic data by simultaneous and follow-up observation of subjects' faces monitored and recorded with a video camera. In the off-line analysis, mean muscle discharge (μV) of zygomatic muscle was calculated from integrated electromyogram, using data analysing software DaDisp Pro ver 4.0. The details of the analysis were described in our previous study (12).

Psychological measurements. The pleasantness of the comic film was evaluated with visual analogue scale (VAS) of 10 cm bar (full mark is 10 point). We instructed the subjects that the left end of the bar corresponds to no pleasantness and the right end, the most pleasant state ever experienced. Mood before and after watching comic or control film were evaluated with

Table I. NKCA and the number of NK cells before and after watching the comic and control film.[a]

	NKCA (%)		NK cell (cells/mm^3)	
	Laughter	Control	Laughter	Control
Before	26.5	27.1	240	249
After	29.4	24.8	219	167
p-value (paired T-test)	p<0.05	NS	NS	p<0.01

[a]Laughter significantly elevated NKCA at the effector-to-target ratio (20:1), whereas control did not. Significant decrease in the number of NK cell was found in control condition. NKCA, natural killer cell activity.

Profiles of Mood State (POMS). POMS is a questionnaire for mood assessment consisting of six scales of tension-anxiety (T-A), depression (D), anger-hostility (A-H), vigor (V), fatigue (F), confusion (C). To evaluate psychological background of the subjects, the 16 personality factor (16-PF) questionnaire and Daily Life Stress Scale (Holmes & Rahe) were performed.

Results

Before and after watching the comic film, significant elevation of NKCA was found at the effector-to-target ratio (20:1), (before 26.5%; after 29.4%, df=20, t=1.85, p<0.05, paired T-test, one-tailed), whereas no significant changes were observed before and after the control film (before 27.1%; after 24.8%, not significant). There was no significant changes in the number of NK cells before and after the comic film (before 236 cells/mm^3; after 217 cells/mm^3, not significant), though the number of NK cells in the control condition indicated significant decrease (before 249 cells/mm^3; after 173 cells/mm^3, df=20, t=3.27, p<0.01, paired T-test, one-tailed), (Table I). NKCA per unit cell count did not show significant changes during either the comic or the control conditions. The averaged EMG discharge during the comic was significantly larger than that during the control film (comic 42.4 μV; control 7.5 μV, df=18, t=4.43, p<0.001, paired T-test, one-tailed). We performed this comparison among 19 subjects since EMG data of two subjects during control film were incomplete. The average score of self-rated pleasantness of the comic film was 6.2 points. On the other hand, control film did not elicit any pleasantness since all the subjects reported that they did not feel any pleasantness or funniness at all.

The scores of mood scales measured with POMS are shown in Table II. Significant decrease of scores by the comic film was found in tension-anxiety (df=20, t=2.42, p<0.01, paired T-test, one-tailed), depression (df=20, t=4.06, p<0.001, paired T-test, one-tailed), anger-hostility (df=20, t=1.92, p<0.05, paired T-test, one-tailed), confusion (df=20, t=2.59, p<0.01, paired T-test, one-tailed). Significant changes

Table II. a, The scores of mood scale of POMS before and after watching the comic film.[a]

	T-A	D	A-H	V	F	C
Before	50.4	51.0	48.4	54.3	49.3	50.7
After	47.0	47.9	46.8	55.4	46.8	48.4
p-value (one-tailed)	p<0.01	p<0.001	p<0.05	NS	NS	p<0.01

[a]There were significant changes in the scales of tension-anxiety (p<0.01), depression (p<0.001), anger-hostility (p<0.05), confusion (p<0.01). T-A, tension-anxiety; D, depression; A-H, anger-hostility; V, vigor; F, fatigue; C, confusion.

b, The scores of mood scale of POMS before and after watching the control film.[a]

	T-A	D	A-H	V	F	C
Before	50.5	52.3	52.0	55.5	50.4	51.3
After	48.4	51.0	49.2	50.4	53.2	52.0
p-value (one-tailed)	NS	NS	p<0.05	p<0.01	p<0.05	NS

[a]There were significant changes in the scales of anger-hostility (p<0.05), vigor (p<0.01), fatigue (p<0.05).

of scores by the control film were found in anger-hostility (df=20, t=1.90, p<0.05, paired T-test, one-tailed), vigor (df=20, t=3.75, p<0.001, paired T-test, one-tailed) and fatigue (df=20, t=1.96, p<0.05, paired T-test, one-tailed).

To examine the contribution of experiential and expressive aspects of laughter to NKCA elevation, the correlation of NKCA elevation with the self-rated pleasantness, the scores of mood scales in POMS and the magnitude of laughter was tested in the laughter experiment. NKCA elevation by laughter had significant negative correlation with the scores of depression (r=-0.56, p<0.01) and anger-hostility (r=-0.56, p<0.01) before comic film and those of tension-anxiety (r=-0.58, p<0.01), depression (r=-0.60, p<0.01), anger-hostility (r=-0.52, p<0.05) and fatigue (r=-0.48, p<0.05) after the comic film (Table III), though there was no significant correlation of NKCA elevation with self-rated pleasantness and the magnitude of laughter (Table IV). The scores of depression and anger-hostility had significant negative correlation with NKCA before and after the comic film. In further analysis, the subjects were divided into three groups, namely a group with high depression and high anger-hostility which exhibited higher scores of both mood scales than each mean, a group with low depression and low anger-hostility which exhibited lower scores of both mood scales than each mean and a group of the rest. The numbers of the subjects belonging to each group were ten, eight and three before the comic, and nine, seven and five after the comic film,

Table III. Correlation between NKCA elevation and the scores of mood scales of POMS before and after the comic film.[a]

	T-A	D	A-H	V	F	C
Before	NS	-0.56[b]	-0.56[b]	NS	NS	NS
After	-0.58[b]	-0.6[b]	-0.52[c]	NS	-0.48[c]	NS

[a]NKCA elevation was negatively correlated with the scores of depression and anger-hostility before watching the comic film and those of tension-anxiety, depression, anger-hostility and fatigue after the comic film. T-A, tension-anxiety; D, depression; A-H, anger-hostility; V, vigor; F, fatigue; C, confusion. [b]$p<0.01$; [c]$p<0.05$; one-tailed.

Table IV. Correlation of NKCA before and after the comic film and NKCA elevation with the magnitude of laughter evaluated with electromyogram and self-rated pleasantness of the comic film.[a]

	NKCA		
	Before	After	Elevation
EMG	NS	NS	NS
VAS	0.395[b]	0.428[b]	NS

[a]Self-rated pleasantness of the comic film had tendency of correlation with NKCA before and after the film. EMG, the maginitude of laughter evaluated with electromyogram; VAS, self-rated pleasantness of the comic film using visual analogue scale; before, NKCA before the comic film; after, NKCA after the comic film; elevation, NKCA elevation. [b]$p<0.1$.

respectively. The comparison of NKCA elevation in the former two groups revealed significantly lower NKCA elevation in the group with high depression and high anger-hostility before and after the comic film [before 7.1% (low group) and -2.5% (high group), df=16, t=3.25, $p<0.005$, Student's t-test, one-tailed; after 6.0% (low group) and -2.3% (high group), df=14, t=2.30, $p<0.05$, Student's t-test, one-tailed] (Fig. 2).

To examine the relation of experiential and expressive aspects of laughter with NKCA before and after the comic film, the correlation of NKCA with self-rated pleasantness of the comic film and the magnitude of laughter was statistically tested. Self-rated pleasantness had tendency of correlation with NKCA before and after the comic film (NKCA before comic r=0.395, $p<0.1$; NKCA after comic r=0.428, $p<0.1$), though there was no significant correlation of NKCA with the magnitude of laughter (Table IV).

There was no relation between the results of 16-PF questionnaire and NKCA elevation and NKCA before and after the comic film.

Discussion

Although the elevation of NKCA by laughter was suggested by previous studies (5,6), the results were uncertain due to the small sample size in these studies. Another study, which lacked the comparison to control group, failed to indicate NKCA elevation by humorous video (13). The present study conquered methodological issues of the previous studies using large sample size and a crossover designed experiment and demonstrated significant NKCA elevation by laughter and no NKCA changes by the control film. In regard to the number of NK cells, significant decrease during control was found. It is known that NKCA has circadian rhythm of the highest activity in the early morning and the lowest activity in

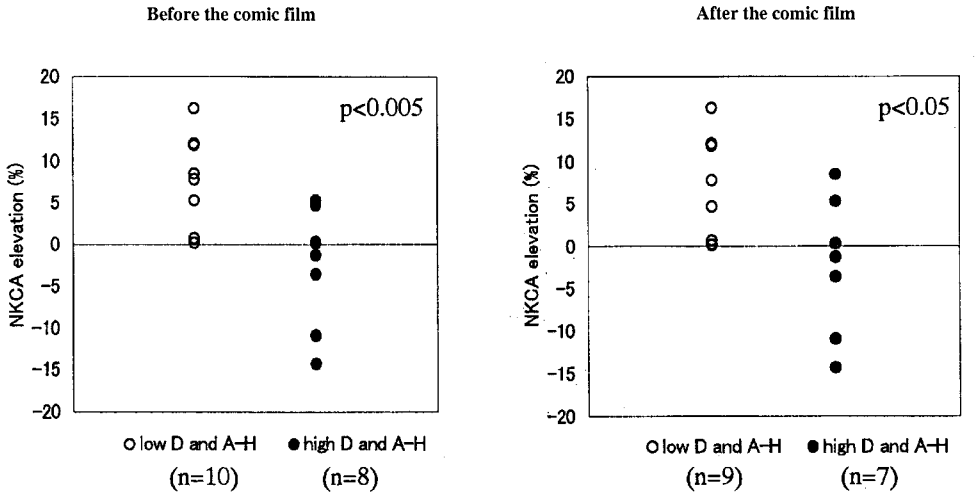

Figure 2. NKCA elevation of the low depression and low anger-hostility (low D and A-H) group and high depression and high anger-hostility (high D and A-H) group. The subjects were divided into three groups according to the scores of D and A-H before and after the comic film, namely a group with high D and A-H which exhibited higher scores of both mood scales than each mean, a group with low D and A-H which exhibited lower scores of both mood scales than each mean and a group of the rest. High D and A-H group exhibited significantly lower NKCA elevation than low D and A-H group before (left) and after (right) the comic film.

the evening (7). Thus, decrease in the number of NK cells during the control film could be explained by circadian rhythm. On the contrary, no significant change of NK cells was observed during the comic film. These findings suggest the increase in the number of NK cells during laughter compared with the control. NKCA per unit cell count indicated no significant changes in either experiment. In summary, NKCA elevation by laughter could be related with the number of NK cells rather than NKCA per unit cell count.

As indicated in Table IIa, the comic film significantly improved the scores of negative mood like tension-anxiety, depression, anger-hostility and confusion. The average of self-rated pleasantness of the comic was 6.2 point. These findings suggested sufficient pleasantness induced by the comic film. Non-emotional control film significantly aggravated the scores of vigor and fatigue. It is possible that the scores of vigor and fatigue in the control experiment might be affected by experimental environment where subjects watched a film with electrodes and probes on their face and body, though control film should have no effect on mood essentially. In summary, the data of mood scores assessed by POMS clearly indicated that the comic film improved the mood of the subjects compared with the control film and that both films were appropriate as visual stimuli.

The relation between NKCA elevation and experiential and expressive aspects of laughter is of importance. The present study indicated that the scores of negative mood in POMS were negatively correlated with the elevation of NKCA by laughter. Further comparison between the group with high depression high anger-hostility and the group with low depression low anger-hostility group revealed that high scores of depression and anger-hostility suppressed NKCA elevation by laughter. The present study also indicated that higher scores of pleasantness to the comic film tended to be related with higher NKCA, implying that high sensitivity to pleasant stimuli predicts high NKCA before and after the comic film. On the other hand, the magnitude of laughter evaluated with EMG did not show significant correlation with NKCA elevation or NKCA before and after the comic film. These findings suggest that the immunological effect of laughter could be attributable not to expressive aspects like the magnitude of facial expression of laughter but to subjective experiential aspects like mood states and pleasant emotional experience to the comic film.

It is known that physical exercise elevates NKCA via marked increase in circulating NK cell number (14). It is reported that NKCA elevation during exercise is mediated by epinephrine (15). Laughter is an emotional expression with facial expression as well as somatic motion like vocalization and body movement, while epinephrine, norepinephrine and cortisol were lowered during mirthful laughter (16). The present study did not indicate marked increase in NK cell number by laughter. These findings suggest distinct mechanism of NKCA elevation by laughter from that during physical exercise. Recent studies in neuroscience indicate that experiential aspects of emotion are related with medial prefrontal and orbitofrontal cortices (17) which have dense connection to hypothalamus. The present study suggests the relation between experiential aspects of laughter and NKCA and NKCA elevation. It might be postulated that the activities of brain regions related with pleasantness should affect hypothalamic activities, which could regulate systemic immune function via autonomic nervous system and/or hypothalamus-pituitary-adrenal axis.

Although our results demonstrated NKCA elevation by laughter in the short-term experimental environment, it is still unclear whether the immunological effect of laughter persists for a long period and whether laughter has actual preventive and curative effects on viral infection, cancer and chronic fatigue syndrome (CFS) in which NK cell is believed to play an important role. Reportedly, psychological intervention to the patients with breast cancer significantly improved the survival period (18). Another study reported that psychotherapy to the patients with malignant melanoma significantly elevated NKCA after 6 months (19). These lines of evidence support the idea that psychological intervention to cancer by laughter could be effective. CFS is currently an operational concept to clarify the unknown etiology of the syndrome characterized primarily by chronic fatigue. The characteristic symptoms of CFS are: prolonged generalized fatigue, muscle weakness, myalgia and postexerertional malaise. It is well known that most patients with CFS have a deterioration of NKCA (20), and so CFS has been referred to as low NK syndrome (LNKS) (21). Since LNKS seems to be related to the pathophysiology of CFS, much attention has been paid to how to treat LNKS. Chinese herbal medicine is frequently used to elevate NKCA in Japan. The improvement of NKCA was found in some of patients with CFS after this administration, but it is not enough. If laughter is effective in elevating NKCA in these patients, it will be a novel intervention for CFS available in daily life. Our preliminary examination in the same protocol revealed NKCA elevation in 4 of the 8 patients with CFS. We expect that laughter is effective for activating NKCA not only in normal human volunteers but also in some patients with CFS.

In the future, well-designed prospective studies are needed to verify the hypothesis that laughter has preferable effects on various diseases like cancer, viral infection and CFS via NKCA elevation.

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参考論文

Diminished Facial Expression Despite the Existence of Pleasant Emotional Experience in Schizophrenia

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SUMMARY

In order to investigate the relationship between pleasant emotional experience and facial expression (i.e., laughter), mood before and after watching comic film clips, self-rated pleasant emotional experience for each film clip and electromyographic activities of facial muscles involved in laughter while watching film clips were measured for 25 patients with schizophrenia and 20 normal controls. Patients with schizophrenia who showed a significant correlation between self-rated emotional experience and major zygomatic activity were equivalent to normal controls in self-rated emotional experience and in mood after film clips; they had a significant increase in mood scores related with pleasure. Although these patients were thought to have sufficient pleasant emotional experience, they showed significantly low major zygomatic activity as compared to normal controls. It is suggested that these patients have a disturbance in the process of emotional expression rather than emotional experience.

Key words: Schizophrenia - Emotion - Subjective experience - Facial expression - Laughter - Electromyogram

INTRODUCTION

Schizophrenia is one of the major psychiatric disorders, which exhibits hallucination and delusion as well as various disturbances in emotion. Classically, emotional disturbances in schizophrenia include diminished facial expression, curious facial expression such as grimace, a silly smile, inappropriate affect, ambivalence, anhedonia, poor rapport, *etc.*

Emotion comprises the processes of cognition, experience and expression (1), and it is unclear which process of emotion is disturbed in schizophrenia. Emotional disturbance in schizophrenia is usually evaluated with behavioral symptoms which are observed objectively. While aspects of emotional experience have been neglected due to the uncertainty of its measurement, they should not be avoided in order to clarify emotional disturbance in schizophrenia. Recent reports focusing on emotional experience in schizophrenia were in agreement with the result that patients with schizophrenia showed diminished facial expression although their self-reported emotional experience was equivalent to that of normal controls (2-5).

On the other hand, abnormal self-monitoring is supposed to be one of the major cognitive disturbances which underlies positive symptoms (6). This suggests that self-rated emotional experience in schizophrenia might be unreliable.

In order to reduce the problems encountered in previous studies, the following strategies were undertaken to investigate the relationship between emotional experience and facial expression. First, we chose pleasant laughter as the target emotion. The expression pattern of laughter is robust compared to other emotions therefore making it a favorable emotion for quantitative measurement and major zygomatic activity can be used as an indicator of laughter. Moreover, laughter is easily induced by watching comic film clips and the condition of presenting emotional stimuli can be set constant through use of the film clip method. Second, facial muscle electromyograms were used in order to measure facial expression quantitatively. Thirdly, mood before and after emotional stimuli was measured with a standardized mood scale. If the mood scales related with pleasure was elevated, the existence of a pleasant emotional experience would be suggested. Fourthly, multiple stimuli were used in order to vary the intensities of induced emotional experience. Correlation coefficient between self-rated emotional experience and facial

expression was calculated. If subjects had sufficient emotional experience and accuracy in self rating, there should be significant correlation between the self-rated experience and the expression measured objectively.

There are few studies on laughter in schizophrenia. Tanaka (7) and Kawasaki (8) reported diminished expression of laughter in schizophrenics while watching comic film clips. Yamashita *et al.* reported the similarity between the laughter of schizophrenia with inappropriate affect and compulsive laughter in patients with organic brain damage (9). In the Azuma's study on silly smile in schizophrenia, he interviewed patients immediately after the silly smile was observed and reported that inner experience during silly smile was usually incomprehensible (10).

The reports of Yamashita *et al.* and Azuma indicate that expression of laughter could occur without pleasant emotional experience. Their reports suggest disjunction between emotional experience and emotional expression in schizophrenia. The purpose of the present study was to clarify the relationship between emotional experience and expression in schizophrenia, emphasizing both the emotional experience and emotional expression with improvement in the measurement of experience and expression

MATERIALS AND METHODS

Subjects

Twenty-five patients (11 males, 14 females), meeting the DSM-IV criteria (11) for schizophrenia, were recruited from the outpatients attending Osaka University Hospital Department of Neuropsychiatry or inpatients in the neuropsychiatric ward of the hospital. All patients were clinically stable and mild in symptoms. Demographic and clinical data of the patients were as follows (mean ± SD): age = 27.4 ± 5.3 years old; education = 13.6 ± 1.5 years; medication = 577 ± 523 mg/day chlorpromazine equivalent dose; age of onset = 21.8 ± 3.8 years old; duration of illness = 5.6 ± 4.1 years; and number of hospitalizations = 1.3 ± 1.5 times. Twenty individuals (10 males, 10 females) without any psychiatric episodes were recruited as normal controls. Demographic data of normal controls were as follows (mean ± SD): age = 26.1 ± 3.7 years old; education = 14.7 ± 2.0 years. All subjects gave informed consent.

Procedures

The subject was comfortably seated alone in a silent, electrically shielded room. A 14-inch TV monitor was installed in front of the subject at a distance of approximately 2 m. Twenty comic film clips were edited on a video tape and presented on the TV monitor with each film clip lasting 63 to 103 seconds. The total time of film clip stimuli was 1553 sec. The video tape was stopped at the end of each film clip and the subject was asked to rate the pleasant emotional experience for each of the former 10 film clips using a visual analogue scale with 10-point anchors (emotional experience monitoring task). For each of the latter 10 film clips, the subject was asked to rate the amount of facial expression (laughter), using the same visual analogue scale (expression monitoring task). The subject was instructed that zero point signified no pleasant experience or laughter and 10 points indicated the maximum level of pleasant experience or laughter in life. The subject was instructed that rating for a film clip should be done after the video tape was stopped and that the same rating score should not be used in the same task. Both tasks were undertaken in the reverse order not to produce an order effect.

Laughter occurring while watching the comic film clips was measured with a facial muscle electromyogram. Silver/silver-chloride surface electrodes were placed on the major zygomatic muscle, outer portion of orbicular muscle and corrugator muscle in a bipolar configuration in the left side of the face using the placement suggested by Cacioppo and Fridlund (12). Electromyograms were recorded with multipurpose electroencephalograph (1A64, San-ei) and digitized at 200 Hz with data recorder (DR-M3a, TEAC). The time constant was 30 msec.

Mood was measured with the Profiles of Mood State (POMS), Japanese edition (13), before and after watching the comic film clips. POMS have 6 scales which represent tension-anxiety, depression, anger-hostility, vigor, fatigue and confusion. Change of mood was defined as the difference of score before and after the film clips.

Symptom evaluation

Clinical symptoms in patients with schizophrenia were evaluated with the Positive and Negative Syndrome Scale (PANSS) (14) and the Scale for the Assessment of Negative Symptoms (SANS) (15). Neuroleptic-induced extrapyramidal symptoms were assessed with the Drug-Induced Extrapyramidal Symptom Scale (DIEPSS) (16). Semi-structured interviews for approximately 1 h were undertaken by 2 psychiatrists to evaluate clinical symptoms. Factor analysis was performed for PANSS subscales using a 5-factor model (17). The PANSS subscale scores were transformed to the 5 factor scores and PANSS factor scores were used in further statistical analysis.

Data analysis

Facial muscle activities were quantified as follows. Electromyogram during a film clip were digitally recorded and analyzed on a PC-AT compatible computer using DaDisp ver 4.0. Two envelope curves were drawn over and under the waveform of electromyogram. The area bound by two envelope curves was computed. This area divided by the duration of the film clip corresponded to

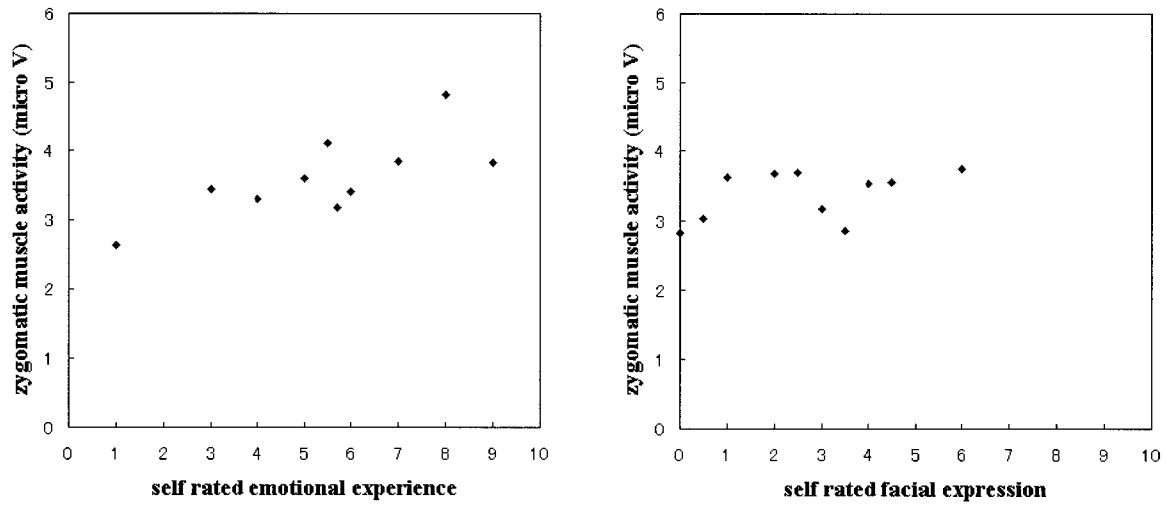

FIG 1. Task performance of a patient with schizophrenia. One dot corresponds to a comic film clip. The patient showed significant correlation in the emotional experience task (A) and was classified into the significant group in this task although significant correlation was lost in the expression monitoring task (B).

the average muscle discharge during the film clip (mcV). The average values of muscle discharges in three facial muscles were calculated for each of the 20 film clips. Zygomatic muscle activity was considered the amount of laughter since it a major component of laughter (18).

In the emotional experience monitoring task, the correlation coefficient between self ratings of pleasant emotional experience and zygomatic muscle activities (amount of laughter) was calculated. In expression monitoring task, the correlation coefficient between self ratings of facial expression and zygomatic muscle activities was calculated. In each of the 2 tasks, subjects were divided into 2 groups according to whether a significant correlation was found or not. The subjects with significant correlation were classified as the "significant" subgroup while subjects without significant correlation were classified as the "nonsignificant" subgroup. Figure 1 shows an example of a patient with schizophrenia. This patient was classified in the significant subgroup in emotional experience task and in the nonsignificant subgroup in expression monitoring task. Self-rated pleasant emotional experience, mood before and after experiments, average muscle activity of 3 facial muscles, age and education were compared in the normal controls and 2 subgroups of schizophrenia patients. Clinical symptoms, medication, age of onset, duration of illness and number of hospitalizations were compared in the 2 subgroups in schizophrenia.

Statistical analysis

The results were analyzed using Student's *t*-test when comparing 2 groups and by parametric one-way analysis of variance (ANOVA) when comparing 3 groups. Further statistical analysis for *post hoc* comparison was performed using Bonferroni's multiple comparison test (two-tailed). Peason's correlation coefficient was estimated in both monitoring tasks using the significance level of 0.05 (two-tailed).

RESULTS

Self-rated emotional experience, mood, and facial expression

Self-rated pleasant emotional experience, mood before and after watching the comic film clips and facial muscle activities of normal controls and patients with schizophrenia are described in Table 1. Self-rated emotional experience was a mean of ratings for the 20 film clips. There was no significant difference in self-rated emotional experience between normal controls and patients with schizophrenia. Before watching film clips, patients with schizophrenia were in a significantly unpleasant mood state in the 5 scales of POMS, that is, tension-anxiety ($t[43] = 3.06$, $p < 0.01$), depression ($t[43] = 3.68$, $p < 0.01$), anger-hostility ($t[38] = 3.25$, $p < 0.01$], vigor ($t[43] = 2.26$, $p < 0.05$) and fatigue scale ($t[43] = 3.50$, $p < 0.01$), compared to normal controls. After the film clips, patients with schizophrenia showed significantly unpleasant mood states in the scales of tension-anxiety ($t[43] = 2.70$, $p < 0.01$), depression ($t[43] = 2.38$, $p < 0.05$) and anger-hostility ($t[29] = 3.15$, $p < 0.01$). Significant mood changes were observed in the scales of tension-anxiety ($t[19] = 2.55$, $p < 0.05$), anger-hostility ($t[19] = 3.12$, $p < 0.01$) and confusion in normal controls. In patients with schizophrenia, significant mood changes were observed in all the scales (tension-anxiety: $t[24] = 2.07$; depression: $t[24] = 3.87$, $p < 0.001$; anger-hostility: $t[24] = 2.92$, $p < 0.01$; vigor: $t[24] = 2.52$, $p < 0.05$; fatigue: $t[24] = 2.44$, $p < 0.05$; confusion:

TABLE 1. Self-rated pleasant emotional experience, mood scores by POMS and electromyogram activities while watching comic film clips.

	Control	Schizophrenia	*p*
Self-rated experience	4.4 ± 1.2	4.7 ± 1.9	NS
POMS before film			
tension-anxiety	46.6 ± 7.1	54.1 ± 8.8	< 0.01
depression	48.7 ± 8.0	59.1 ± 10.0	< 0.001
anger-hostility	43.1 ± 4.9	50.2 ± 9.1	< 0.01
vigor	50.6 ± 8.3	44.0 ± 10.2	< 0.05
fatigue	41.7 ± 7.8	50.8 ± 9.0	< 0.01
confusion	51.3 ± 11.7	56.7 ± 9.7	NS
POMS after film			
tension-anxiety	42.7 ± 8.9	51.0 ± 11.1	< 0.01
depression	46.7 ± 7.9	53.8 ± 11.1	< 0.05
anger-hostility	40.2 ± 2.8	46.7 ± 9.6	< 0.01
vigor	51.9 ± 9.0	47.0 ± 10.9	NS
fatigue	42.5 ± 9.0	47.3 ± 10.4	NS
confusion	47.3 ±10.2	53.6 ± 11.8	NS
Mood change			
tension-anxiety	-3.9 ± 6.7*	-3.1 ± 7.3*	NS
depression	-2.1 ± 6.7	-5.2 ± 6.6***	NS
anger-hostility	-3.0 ± 4.1**	-3.5 ± 5.8**	NS
vigor	1.3 ± 9.0	2.9 ± 5.7*	NS
fatigue	0.8 ± 9.2	-3.5 ± 7.1*	NS
confusion	-4.0 ± 6.6*	-3.0 ± 7.0*	NS
EMG(μV)			
zygomatic	16.6 ± 13.4	7.6 ± 5.1	0.005
orbicular	12.9 ± 10.0	11.0 ± 5.9	NS
corrugator	7.3 ± 6.4	6.3 ± 4.9	NS

Mean ± SD. EMG: electromyogram; NS: not significant; asterisks: significant mood change between before and after film clips, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, paired *t*-test

t[24] = 2.14, $p < 0.05$). All significant mood changes were in the direction of mood improvement into pleasant state.

In facial muscle activities, zygomatic activities of patients with schizophrenia were significantly lower than those of normal controls (t[24] = 2.80, $p < 0.01$). Neither orbicular nor corrugator activities had significant differences in both groups.

Clinical symptoms and drug-induced extrapyramidal symptoms

PANSS scores in patients with schizophrenia were as follows (mean ± SD): positive scale (11.2 ± 4.6), negative scale (15.8 ± 5.3), composite scale (-4.7 ± 6.8), general psychopathology scale (29.2 ± 6.3). SANS scores were as follows (mean ± SD): affective flattening or blunting (10.0 ± 6.1), alogia (4.5 ± 2.9), avolition-apathy (9.7 ± 3.3), anhedonia-asociality (10.4 ± 4.1), attention impairment (5.8 ± 3.5), summary score (9.6 ± 2.3), composite score (40.4 ± 13.6).

Factor analysis of PANSS items extracted 5 factors which were named negative, positive, excitement, cognitive and depression, respectively. This result was almost consistent with the 5-factor model of PANSS reported by Lindenmayer *et al.* (17).

Drug-induced extrapyramidal symptoms in patients with schizophrenia were minimal (overall severity of DIEPPS: 1.0 ± 0.6, mean ± SD).

Differences between two subgroups in schizophrenia divided by task performance

Figure 2 indicates the correlation coefficients of both tasks in normal controls (A) and in patients with schizophrenia (B). The numbers of subjects classified in the significant subgroup in both tasks, in the emotional experience monitoring task and in the expression monitoring task or in the nonsignificant subgroup in both tasks were 14, 3, 2 and 1 in normal controls, and 8, 5, 6 and 5 in patients with schizophrenia, respectively.

Table 2 indicates the items with significant difference between normal controls and the two subgroups in schizophrenia. Only items with significant difference were displayed.

In the emotional experience monitoring task, the significant subgroup in schizophrenia and normal controls had greater scores of vigor after the film clips as compared to the nonsignificant subgroup in schizophrenia (F[2,42] = 5.76, $p < 0.01$). The significant subgroup showed an elevated mood score in vigor scale

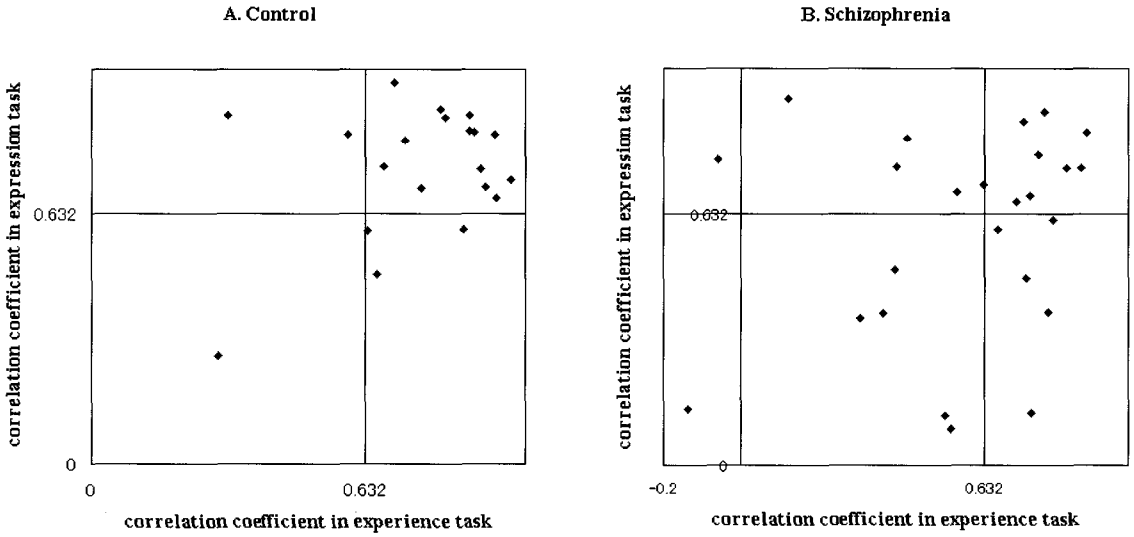

FIG 2. Correlation coefficients in two monitoring tasks in normal controls (A) and patients with schizophrenia (B). Each dot corresponds to a subject. In normal controls, most subjects were distributed in the right upper area where two correlation coefficients reach a level of significance. Patients with schizophrenia were widely distributed throughout the graph.

Table 2. Items which show significant differences between controls and the two schizophrenic groups divided by task performance.

		Emotional experience monitoring task		
	Control	Significant*	Nonsignificant**	*p*
POMS after film vigor	51.9 ± 9.0	52.4 ± 10.5	41.2 ± 8.0	< 0.01
		Expression monitoring task		
		Significant*	Nonsignificant**	*p*
Hospitalization		0.71 ± 0.80	2.00 ± 1.81	< 0.05

Mean ± SD. *significant subgroup in schizophrenia; **nonsignificant subgroup in schizophrenia.

(t[12] = 2.31, p <0.05]. No significant differences were observed in other mood scales, self-rated emotional experience, electromyogram activities and clinical symptoms.

In the expression monitoring task, the nonsignificant subgroup showed a significantly greater number of hospitalizations as compared to the significant subgroup (t[13] = 2.24, $p < 0.05$). No significant differences were noted in other items.

DISCUSSION

In the present study, patients with comparably mild symptoms and capable of understanding and performing tasks were enrolled due to complexities of the required tasks. Clinical symptoms evaluated with PANSS and SANS showed that subjects in the present study were mild in symptoms. Silly smile was not observed in the present study, which shows that the results obtained are not affected by inappropriate affect. Mood in both normal controls and patients with schizophrenia was improved by watching the comic film clips and the mood-improving effect was equivalent in both groups demonstrating that the stimuli used in the present study were appropriate.

Although attention deficit and disorder of working memory, known to be major cognitive impairments in schizophrenia, may be confounding factors in the present study, these dysfunctions probably disturbed the performance of both tasks. In the present study, only a small number of subjects were classified in the nonsignificant subgroup in both tasks. These impairments therefore would not explain the subjects classified as the significant subgroup in only one task. The results of the present study could be considered as not due to cognitive impairments but instead, reflecting emotional disturbance in patients with schizophrenia.

The important feature of the present study was to indicate the existence of emotional experience with higher reliability as compared to previous studies by assessing the inner experience in the point of view of self-rated

emotional experience, correlation between self-rated emotional experience and facial expression and mood changes by watching comic film clips. In the emotional experience monitoring task, self-rated emotional experience of the significant subgroup in schizophrenia was equivalent to that of normal controls. This subgroup showed a significant correlation between emotional experience and the amount of laughter suggesting the existence of sufficient emotional experience and accuracy in self rating; significantly elevated vigor scales in POMS supports the existence of emotional experience in this subgroup. These results suggest that the significant subgroup in emotional experience monitoring task was equivalent to normal subjects in pleasant emotional experience, whereas this subgroup showed a significantly lower amount of laughter as compared to normal controls. Thus, low facial expressivity in this subgroup in schizophrenia was interpreted as emotional expression disturbance despite the existence of emotional experience.

The relationship between emotional experience and facial expression in the nonsignificant subgroup in the emotional experience monitoring task cannot be easily explained. One possibility is that self-rated emotional experience was not accurate in this subgroup. Another possibility is that no sufficient emotional experience occurred or that emotional experience and facial expression act independently even if self rating is accurate. No vigor change was observed in this subgroup suggesting that emotional experience was not sufficient. However, this subgroup included subjects classified into the nonsignificant subgroup in both tasks who might have cognitive impairments other than emotional disturbances. These possibilities are not exclusive of each other. The reasons this subgroup had no correlation between experience and expression were probably multiple and complex and thus cannot be easily discussed.

In the expression monitoring task, the nonsignificant subgroup showed a significantly greater number of hospitalizations as compared to the significant group. As a feature of the expression monitoring task, subjects monitor their own facial expressions without visual feedback. No significant correlation between self-monitored facial expression and objectively observed facial expression indicates impaired self-monitoring to self-generated behavior. A relationship between the tendency to relapse and impaired self-monitoring may be evident.

It is known that neuroleptics exhibit extrapyramidal symptoms including diminished facial expression. In the present study, patients with schizophrenia exhibited only minimal extrapyramidal symptoms assessed with DIEPSS. There was no significant correlation between electromyogram activities and chlorpromazine equivalent dose. Kring *et al.* reported diminished facial expression in medication-free patients with schizophrenia (3). In addition, diminished facial expression had already been observed in the era of Kraepelin and Breuler, long before neuroleptics were recognized in the treatment of psychiatric disorders. Thus, taking into account these previous observations, the results from the present study can be considered as not due to the side effects of neuroleptics.

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参考論文

乳児期よりほぼ毎夜エピソードが出現する sleep related head-banging の1例

A case report of sleep related head-banging with almost every night episode since early infancy

岩瀬 真生 *IWASE Masao*
山下 仰 *YAMASHITA Ko*
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永 井 書 店

＜症　　例＞

乳児期よりほぼ毎夜エピソードが出現する sleep related head-banging の1例

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はじめに

sleep related head-banging とは睡眠中あるいは睡眠前にみられる律動的な頭打ち運動のことを指すが，睡眠に関連した律動的な運動はこのほかに，head-rolling（頭左右回転型），body-rocking（軀幹前後振り型），body-rolling（軀幹左右回転型）があり，睡眠障害国際分類（1990）ではこれらは律動性運動障害（rhythmic movement disorder：RMD）として一括されている[1]．RMD は乳幼児期にはよくみられるが，小児期にはほとんどが自然消失する．思春期まで残存することはまれであり，終夜脳波まで施行しえた報告例は稀少である．今回われわれは乳児期よりほぼ毎夜エピソードが出現する11歳の女性患者において，エピソード出現時の終夜脳波記録およびビデオ記録を施行し得たので，若干の考察とともに報告する．

I. 症　　例

11歳，女性

出生・発育・発達　正常

知　　能　正常，学業成績は中程度，兄弟より良いくらい

既 往 歴　誘因となる疾患（脳炎，頭部外傷，中耳炎など）の既往はない．てんかんの既往もない．

現 病 歴　生後3ヵ月に頸定．頸定直後から寝入りばなに頭を横に振ることが始まった．それから前後に振るようになった．午睡中にもあった．head-banging，head-rolling はそれからずっと，ほぼ毎晩続いている．現在は入眠して3，4時間後が多い．よく寝ている状態から始まり，放っておくと2，3分は続く．トントンと軽く叩くと止まる．主に頭部を横に振る．右手を左側頭部の下に回してから始まることが多い．前後に振るときは，うつ伏せになってからする．終了後はそのまま眠り続ける．直後に覚醒させたときにも本人にはその自覚はない．前額部にタコ，あごにアザができたことがあるが，大きなけがはない．林間学校を前に両親が心配して近医神経科受診し，終夜脳波施行目的で大阪大学医学部附属病院神経科精神科を紹介され受診した．

1．検査所見

ルーチン脳波・頭部 MRI　正常．

ビデオ所見・終夜脳波所見・睡眠指標　終夜脳波

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施行前に両親にエピソードのビデオ撮影を依頼し，2回のエピソードが記録された．1回は左側臥位で軀幹と頭部の回転を繰り返す body-rolling と head-rolling の複合した運動で，他の1回は腹臥位で頭部を前後に振る head-banging であった．運動の周期は1Hz前後であった．終夜脳波第1夜にはエピソードは観察されなかった．終夜脳波第2夜にエピソードが4回出現した．はじめの3回は30秒ほどの休止期間をはさんで連続して出現した．1回のエピソードの持続は90秒ほどで，左側臥位で右手を頭部の下にまわしてから軀幹と頭部の回転を始め，徐々に回転は激しくなっていくが周期には大きな変化はなかった．エピソードは激しい運動状態から唐突に終了した．3回目のエピソードの際には頭部の回転の方向が逆向きになり，後頭部を床に打ちつけだしたのでシールドルーム内に入室してエピソードを制止した．覚醒直後に本人に問いただすと，首振りなどの運動を行っていたという自覚はなく，また打ちつけた後頭部の痛みも訴えなかった．4回目のエピソードは左側臥位より開始し20秒ほど持続してすぐに終焉した．1回目のエピソードが起こる直前の睡眠ポリグラフを図1に示す．オトガイ筋筋電図は一晩中で最も低下した状態であり，この図には載っていないが直前まで急速眼球運動もみられており，エピソードの直前の睡眠段階は stage REM であると考えられた．残りの3回は stage I であった．第4回目エピソードの直前の睡眠ポリグラフを図2に示す．いずれの律動性運動も周期は家で記録されたものと同様に1Hz前後であった．

エピソードがみられた終夜脳波第2夜の睡眠経過図を図3に，睡眠指標を表1に示す．睡眠構築に問題はなく，睡眠指標も正常と考えられた．

2．治療経過

Clonazepam 1mg の就眠前投与を行ったが，夜尿，昼間のふらつきのため0.5mg に減量した．しかし朝に眠気が残り登校に支障をきたすため imipramine 20mg の就眠前投与に切り替えたが効果がなかった．Clonazepam 1mg の就眠前投与に再び戻したが2，3週で効果が薄れ，眠気などの副作用の問題もあり服薬を中断し，修学旅行のときなどの機会投与のみにしている．非服薬時には現在も継続してエピソードが出現している．

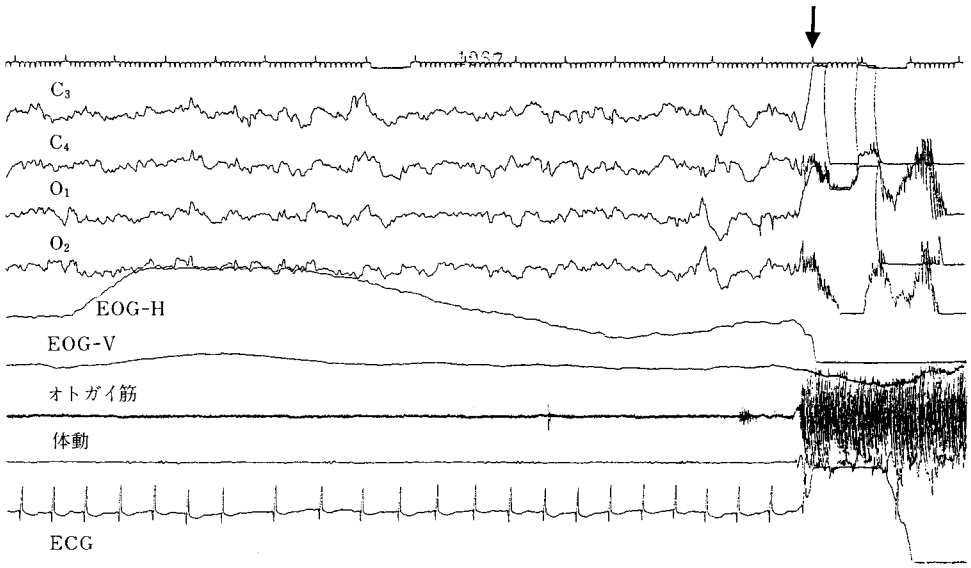

図1　1回目のエピソード直前の睡眠ポリグラフ

図の矢印の時点からエピソードが開始しており，脳波の基線が大きく揺れている．急速眼球運動はエピソード開始数十秒前にあり，急速眼球運動の出現した時点からオトガイ筋筋電図はエピソード開始直前まで同レベルであり，エピソード開始直前の睡眠段階は stage REM と考えられた．

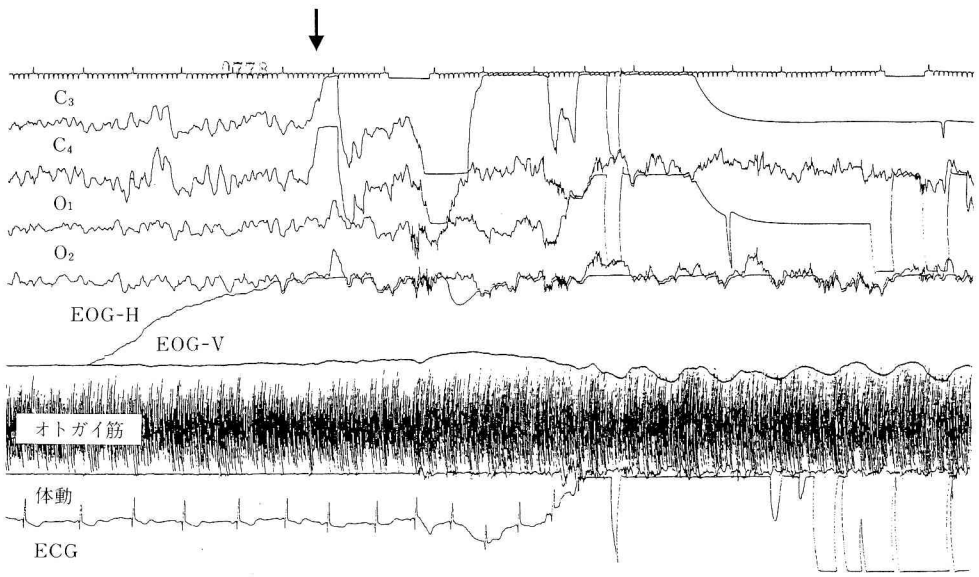

図2　4回目のエピソード直前の睡眠ポリグラフ
図の矢印の時点からエピソードが開始している．エピソード直前の睡眠段階は stage I と考えられた．

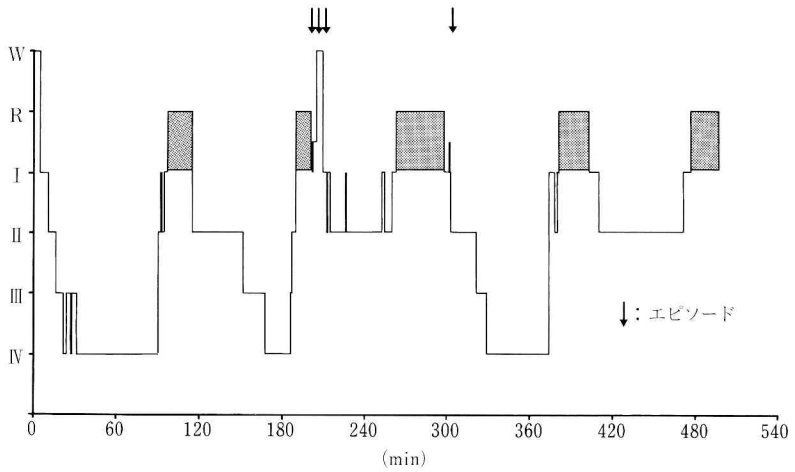

図3　終夜脳波第2夜の睡眠経過図
W：stage W，R：stage REM，Ⅰ：stage Ⅰ，Ⅱ：stage Ⅱ，Ⅲ：stage Ⅲ，Ⅳ：stage Ⅳ

表1　睡眠指標

睡眠指標（終夜脳波第2夜）	
就床時間（分）	496.7
全睡眠時間（分）	486.7
睡眠効率（%）	97.9
入眠潜時（分）	5.0
REM 潜時（分）	92.0
stage W（%）	2.0
stage Ⅰ（%）	8.3
stage Ⅱ（%）	34.8
stage Ⅲ（%）	7.4
stage Ⅳ（%）	25.4
stage REM（%）	21.3
movement time（%）	0.7

II. 考　　察

RMD の異常運動では head-banging が最もよくみられる[1]．本症例では head-banging，head-rolling，body-rolling の3つの type の異常運動がみられたが，主な異常運動の型は head-rolling もしくは body-rolling であると考えられた．異常運動のエピソードは乳児期よりほぼ毎夜出現していることから，RMD の重症度基準，持続基準では重度，慢性に相当した．

病因，病態には諸説あるが詳細は不明である．心理的ストレスや母子関係の問題によるものとする説[1]があるが，本症例ではエピソードがほぼ毎夜に

表2　律動性運動障害の終夜脳波実施例

報告例	性別	年齢	発症年齢	誘因	異常運動の type	睡眠段階
Regestein[4] (1977)	女	25y	1.5y		head-banging？	REM
Freidin[5] (1979)	男	27m	17m		head-banging	Ⅰ&Ⅱ
Walsh[6] (1981)	女	8y	7m		body-rocking？	Ⅰ&Ⅱ
Thorpy[7] (1984)		7～36y (3例)				REM, all stage, Ⅰ&Ⅱ
Gagnon[8] (1985)	男	24y	？		head-banging？	REM
Drake[2] (1986)	女	16y	16y	頭部外傷	head-banging？	Ⅱ
Tuxhorn[9] (1993)	女	2y	2y		body-rocking	Ⅲ
Kempenaers[10] (1994)	女	34y	early infancy		body-rolling	REM
Chisholm[11] (1996)	男	24y	since birth	ストレス	head-banging	主にⅠ&Ⅱ
本間[12] (1998)	男	21y	6m		head-banging	REM
本症例	女	11y	3m	なし	head-rolling	Ⅰ&REM

わたることから，心理的要素の関与は低いと考えられた．精神遅滞，自閉症に伴うことが多く発達障害によるものとする説[1]もあるが，本症例では発達は正常であり，発達障害という観点でも説明できない．頭部外傷[2]，中耳炎[3]などが誘因となって発症する例が知られているが本症例では誘因となる疾患の既往もない．さまざまな仮説はあるがいずれも RMD のすべてを説明しきれるものでなく，おそらく病因的には heterogeneous であり，最終的には共通の律動的な運動パターンが発現されるものと思われるが，現時点では推測の域を出ない．

エピソードが出現する睡眠段階に関しては，いくつかの報告がされており，表2にまとめて示した．これまでの報告では軽睡眠期にエピソードが出現するものと，REM 睡眠時に出現するものとに分かれているが，本症例ではエピソード開始直前の睡眠段階は stage REM と stage Ⅰ の両方であった．これまでの報告例からは主に小児例では軽睡眠期に，成人例では REM 睡眠時にエピソードが出現する傾向にあるようである．本症例では興味深いことに両方の睡眠段階でエピソードが出現しており，小児例と成人例の間に移行がある可能性を示唆している．今後この症例のエピソードが出現する睡眠段階が変化していくものかどうか経時的な観察が必要と思われる．

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