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CASE REPORT

A case of respiratory akathisia in a cancer patient: A case report

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ABSTRACT

Objective: It has been reported that akathisia is a neurological side effect induced by antiemetic drugs and/or antipsychotics. Akathisia can occur in any area of the body, but respiratory akathisia is an unusual type of akathisia. Cases of respiratory akathisia in cancer patients taking antiemetic drugs have not previously been reported.

Methods: We report on a case of a cancer patient taking prochlorperazine as an antiemetic drug who experienced dyspnea accompanied by severe restlessness associated with respiration. By administration of biperiden, his restlessness in respiration and dyspnea promptly disappeared.

Results: This finding led us to conclude that this cancer patient was experiencing respiratory akathisia.

Significance of results: Respiratory akathisia is uncommon. It is important for cancer patients that dyspnea induced by disease progression be ruled out as a cause of the respiratory restlessness. It is necessary to consider the possibility of akathisia in patients that complain of vague anxiety, chest discomfort, or dyspnea following antipsychotic medication.

KEYWORDS: Respiratory akathisia, Cancer, Antiemetic drug

INTRODUCTION

Akathisia is a neurological side effect produced by antipsychotic or antiemetic drug therapy (Blaisdell, 1994). The clinical picture of akathisia is a feeling of inner restlessness in the limbs, especially in the legs (Gibb & Lee, 1986). However, reports have indicated that akathisia can occur in any area of the body,

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such as the arms or abdomen (Raskin, 1972; Ratey & Salzman, 1984; Walters et al., 1989). A rare manifestation of akathisia reported by patients receiving antipsychotic treatment is an inner restlessness in respiration as dyspnea.

Prochlorperazine is an antiemetic agent frequently used by cancer patients taking opioids (e.g., morphine, oxycodone) for cancer pain. In oncological settings, prochlorperazine is used as an antiemetic drug for nausea, a side effect of opioid. It is a phenothiazine antiemetic that has central dopamine antagonist properties and that has been reported to cause acute extrapyramidal side effects,

parkinsonism, dystonia, and akathisia (Bateman et al., 1989). It is well known that neuroleptic-induced akathisia may be difficult to recognize and can occur in the absence of other extrapyramidal signs. Furthermore, cases of akathisia due to antiemetic drugs used by cancer patients have been little reported.

CASE REPORT

The patient was an 66-year-old man with squamous cell carcinoma of the esophagus, stage II(T2N0M0). Due to his renal impairment and the presence of emphysema, surgical resection was not performed; furthermore, chemotherapy was not indicated. Therefore, he attempted radiation therapy and received a total dose of 70.2 Gy. He used opioid, 20 mg/day of morphine hydrochloride, for pain of esophagitis by irradiation, with taking prochlorperazine as an antiemetic drug. He complained of chest discomfort after receiving 5 mg/day of prochlorperazine p.o. for 3 weeks and was admitted to the hospital. When he arrived in the hospital, he acknowledged dyspnea with vague anxiety and a subjective restlessness in respiration, with a temperature of 36.8°C, blood pressure of 118/72 mm Hg, pulse 79 beats/min, respiratory rate 18 breaths/min. Resting room-air oxygen saturation was 98%. First, radiation pneumonitis was suspected, but chest X-ray was normal. He felt that he could not respire leisurely nor stop breathing at any time because of this restlessness in respiration. He denied restlessness in the limbs or other body areas except for the chest. He showed no signs or symptoms of parkinsonism. He was administered 5 mg of biperiden d.i.v.; his restlessness in respiration and dyspnea simultaneously disappeared approximately 1 h later (Hirose & Ashby, 2000). Subsequently, 6 mg of oral biperiden was added to the treatment regimen. The next day, the dyspnea with vague anxiety and other restless movements completely ceased. No signs or symptoms of akathisia have appeared in this patient since that time.

DISCUSSION

We reported respiratory akathisia in cancer patients taking prochlorperazine as antiemetics. This is the first report of respiratory akathisia recognized in cancer patients.

It was necessary that other medical problems known to produce dyspnea, such as panic attacks and dyskinesia and dystonia or pulmonary diseases, could be ruled out as a cause of the respiratory restlessness (Hirose, 2000). In this case, the patient did not have anxiety about dying or a history of panic disorder before. Respiratory dyskinesia presents

as involuntary movements of respiratory muscles, but not as a restless feeling in respiration, and is not improved on treatment with biperiden (Kruk et al., 1995; Esmail et al, 1999; Heard et al., 1999). Furthermore, in this case, dystonia was ruled out by the absence of tonic contractions of respiratory muscles (Dressler & Benecke, 2005).

Respiratory akathisia is uncommon, so one needs to ask specific questions about restlessness in breathing to recognize this type of akathisia. Therefore, if physicians is not aware of inner restlessness in respiration, it is possible that dyspnea in akathisia may be overlooked or misdiagnosed as a symptom of anxiety disorders, agitation, or respiratory symptoms of cancer itself (Hirose, 2000).

Antiemetics possessing a central antidopaminergic effect are suspected to have caused the akathisia (Seeman, 2002; Matsui-Sakata et al., 2005). Antiemetic-induced akathisia has been reported in cancer patients receiving metoclopramide or prochlorperazine to help control chemotherapy-related nausea and vomiting (Fleishman et al., 1994; Tsuji et al., 2006). In this case, prochlorperazine was used as an antiemetic drug for nausea and vomiting, a side effect of opioid.

Prochlorperazine is a phenothiazine antiemetic that has central dopamine antagonistic properties. It has been reported that the presumed community standard of prescribing prochlorperazine, dexamethasone, or a 5HT3 receptor antagonist after moderately high to highly emetogenic chemotherapy results in equivalent outcomes in terms of control of vomiting and measures of satisfaction and quality of life (Burris et al., 1996; Crucitt et al., 1996).

In Japan, many cancer patients taking opioids for cancer pain clinically use prochlorperazine as an antiemetic drug. Therefore, it should be noted that akathisia is considered a possible side effect during the management of cancer pain.

The clinicians' attitude toward akathisia is important to recognize. It is also important to consider the possibility of akathisia in patients that complain of vague anxiety, chest discomfort, or dyspnea following antipsychotic medication.

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RESEARCH PAPER

Assessment of degree of satisfaction of cancer patients and their families with rehabilitation and factors associated with it – results of a Japanese population

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Abstract
Purpose. To evaluate the effectiveness of rehabilitation from the standpoint of both cancer patients and their families and their degree of satisfaction with it and to assess factors associated with their degree of satisfaction.
Method. The subjects were 23 inpatients for whom rehabilitation had been prescribed during the period of the survey, and their families. Degree of satisfaction with rehabilitation and associated factors were assessed using questionnaires by both patients and their families twice: Before and 2 weeks after the start of rehabilitation.
Results. The mean scores for degree of patient satisfaction and degree of family satisfaction were 8.6 and 7.7 (0–10), respectively. Awareness of rehabilitation (after rehabilitation), willingness for rehabilitation (before and after rehabilitation), emotional state (before and after), effectiveness of rehabilitation, and communication with staff were significantly correlated with degree of patient satisfaction. Emotional state of the patient (before), change in emotional state of the patient, family awareness of rehabilitation (after), change in emotional state of the family, and communication with staff were significantly correlated with degree of family satisfaction.
Conclusions. The results indicated that both the cancer patients and their families were satisfied with rehabilitation. They also suggested a need to understand and provide care for the emotional state of patients and their families in order to increase their degree of satisfaction, and a need for adequate explanation and active involvement to increase awareness and willingness in regard to rehabilitation.

Keywords: *Cancer patient, family, satisfaction, rehabilitation*

Introduction

The survival rate of cancer patients has improved with advances in treatment, and the number of long-term survivors has been increasing. Nevertheless, the everyday life of a considerable number of patients has been impaired by adverse reactions associated with powerful therapy and by the sequelae of treatment, and because of this the importance of cancer patient rehabilitation, for example, therapeutic intervention designed to improve capacity for activities of daily living (ADL) and intervention to prevent secondary impairments, such as disuse syndrome associated with deterioration of general condition, is now being recognized [1].

Dietz [2] classified cancer rehabilitation into four categories according to cancer patients' physical and personal needs: (i) Preventive, (ii) Restorative, (iii) Supportive, and (iv) Palliative, and effectiveness of rehabilitation in each of these categories has been reported during each stage of cancer treatment, from physical rehabilitation in the acute stage, such as pre-operative and post-operative treatment [3–5], to physical and psychosocial rehabilitation in terminal stage [6–8].

However, it would be difficult to claim that cancer rehabilitation has generally been adequately recognized. Because of the trend toward improving outcome up until that time, Dietz [9] pointed out that in

the future the focus must be on the concept of care, saying: "What is the optimal assistance that can be provided to cancer patients to enable them to readjust to society?", while DeLisa [10] has declared: "Now that the cancer survival rate has increased, we should turn our attention to maintaining the quality of life (QOL) of cancer patients or to prolonging their current condition". In other words, it is now necessary to switch to an approach whose aim is to maintain the QOL of cancer patients at a high level, and not just improve their function or prognosis. Moreover, attention has been turning toward improving the QOL of the family at the same time as that of the cancer patient [11]. Thus, by assessing the effectiveness of cancer patient rehabilitation together with the needs of cancer patients and their families from the standpoint of both, and their degree of satisfaction, it would appear possible to carry out intervention that is even more strongly linked to improving the QOL of both patients and their families.

Several assessments of the needs of cancer patients in regard to rehabilitation have already been conducted. A survey of rehabilitation needs in the initial stage of treatment in the United States revealed that 87% of the patients as a whole had such needs, and the need for improvement of deconditioning, impaired mobility, ROM limitations, and impaired ADL and the need for recreation were specifically cited as their needs [12]. In The Netherlands, 26% of all participants desired specialized assistance consisting of intervention to strengthen their physical functions, to cope with their physical and social circumstances, and to find new goals in life [13], and broader needs related to everyday life, including needs related to property, housework, transportation methods, were mentioned for those dwelling in the community [14]. However, the results of interventions related to such needs have never been elucidated. Moreover, a questionnaire survey of surviving families of patients who had been on a palliative care unit revealed pain, impaired mobility, and impaired capacity for ADL as problems that troubled the patients during their hospital stay. The results indicated that even in the terminal period 85% of the patients had desired to be able to move about by walking or in a wheelchair, and the families said that the intervention in those regards had been effective and that the patients were satisfied [15]. However, that was a surrogate evaluation by the families and did not determine how the patients themselves felt about its effectiveness or whether they were satisfied; and there have been no reports of studies that have assessed the degree of the families' satisfaction or changes in the families' emotions. The purpose of the present study was to evaluate the effectiveness of rehabilitation from the standpoint of both cancer patients and their families and their degree of

satisfaction, and to assess factors associated with their degree of satisfaction.

Patients and methods

Subjects

The subjects were patients admitted to Chiba Cancer Center Hospital or Chiba Cancer Center's Palliative Care Center who had received a prescription for rehabilitation during the period of the survey and met the following criteria:

(1) Diagnosis of cancer and informed of the diagnosis;
(2) Rehabilitation prescribed for the first time;
(3) No severe cognitive impairments;
(4) Family member (key person) capable of participating in the study;
(5) General condition not very severe.

Subject participation

Patients for whom there were requests for rehabilitation between July and September 2004 at Chiba Cancer Center Hospital or Chiba Cancer Center's Palliative Care Center were recruited as subjects. The recruitment yielded a total of 43 subjects, 28 of whom met the eligibility criteria, and informed consent was obtained from all of them. Five of the 28 subjects dropped out after the initial evaluation, and 23 ultimately completed the entire survey (Figure 1).

Subjects' characteristics

The characteristics of the 23 subjects who completed the survey are shown in Table I. Their mean age was 56.7 years (15–87 years). The most common site of the primary tumors was bone or soft tissue (8 patients, 34.8%). Bone was the most common site of metastasis (7 patients, 13.0%), followed by the brain (5 patients, 21.7%). The subjects' treatment history showed that within one month prior to the survey 9 patients (39.1%) had undergone surgery, 8 (34.8%) had received chemotherapy, and 4 (17.4%) had received radiotherapy. In addition, 6 patients each (26.1%) were receiving chemotherapy and radiotherapy at the time of the survey, and there were only 3 patients (13.0%) who had received no treatment at all within 1 month prior to the survey. The general condition of 2 (52.2%) of the subjects was rated PS 3, and the general condition of 8 (34.8%) was rated PS 4; thus the general condition of approximately 87% of the patients was rated PS 3 or more. According to ADL status at the start of rehabilitation, 14 patients (60.1%) were using a

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┌─────────────────────────────┐
│ Total subjects (n = 43)     │
│                             │
│ Hospital (32)               │
│ Palliative Care Center (11) │
└─────────────────────────────┘
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┌──────────────────────────────┐
│ Ineligible (n = 15)   │
│ Poor condition   │
│ Presence of cognitive   │
│   impairments   │
│ Re-prescription   │
└──────────────────────────────┘

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┌─────────────────────────────┐
│ Eligible subjects (n = 28)  │
│                             │
│ Hospital (21)               │
│ Palliative Care Center (7)  │
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┌──────────────────────────────┐
│ Refusal to participation   │
│ (n = 0)   │
└──────────────────────────────┘

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┌─────────────────────────────┐
│ Baseline survey (n = 28)    │
│                             │
│ Hospital (21)               │
│ Palliative Care Center (7)  │
└─────────────────────────────┘
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┌──────────────────────────────┐
│ Dropped out (n = 5)   │
│ Discharge (2)   │
│ Poor physical   │
│ condition (3)   │
└──────────────────────────────┘

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┌─────────────────────────────┐
│ Second survey (n = 23)      │
│                             │
│ Hospital (20)               │
│ Palliative Care Center (3)  │
└─────────────────────────────┘
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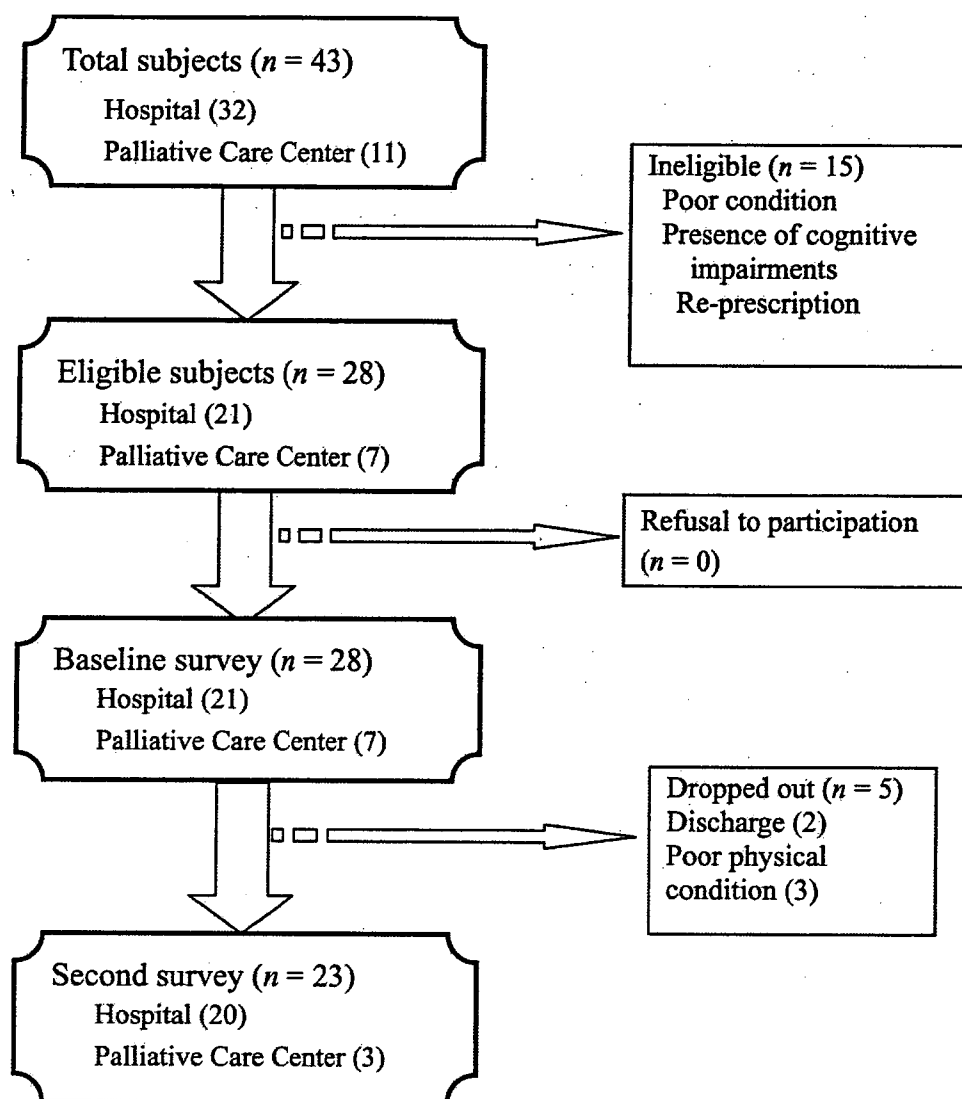
Figure 1. A summary of study participants sampled.

wheelchair for mobility and 6 (26.1%) were relying on stretchers, with almost all of the patients spending their daytime hours on a bed in their living room.

Measures

1. Sociodemographic information. Age and gender were obtained from the information on the patient's chart.

2. Medical information. The following information was obtained from the patient's chart or from the observation and interview survey: (i) site of the primary cancer, (ii) site of metastases, (iii) treatment history, (iv) performance status (PS), and (v) ADL status during the hospital stay.

3. Subjective evaluation of symptoms by the Japanese-language version of the M.D. Anderson Symptom

Inventory (MDASI-J). The symptom inventory used is the Japanese version of the M.D. Anderson Cancer Center Symptom Inventory (MDASI) created by Cleeland et al. [16] in 2000. It consists of a 13-item symptom scale and a 6-item interference scale. The reliability and validity of both the original version and the Japanese-language version have been demonstrated [17]. The symptom scale scores the severity of each symptom item within the past 24 h, from "0", for "Not at all", to "10", for "I can't imagine it being any worse". The interference scale evaluates the extent to which the symptom interfered with a variety of aspects of the patient's daily life, and it scores each symptom item within the same previous 24 h from "0", for "It didn't interfere at all", to "10", for "It completely interfered". Both scales contain 11 grades with 1-point intervals between them, and lower scores mean milder symptoms and less interference.

4. *Questionnaire on rehabilitation.* We prepared a questionnaire containing questions related to rehabilitation regarding expectations of rehabilitation (freely written descriptions), emotional state, communication with the rehabilitation staff, awareness of rehabilitation, willingness to participate in rehabilitation, effectiveness of rehabilitation, and degree of satisfaction with rehabilitation (0–10 numerical scale). The survey of the patients and their families was conducted in the form of interviews by the investigator conducting the survey or in the form of self reports.

Evaluation procedure

After confirming informed consent, the baseline evaluation was performed before the start of rehabilitation by measures 1–4 above. The outcome evaluation was performed by measures 2–4 above approximately 2 weeks after the start of rehabilitation.

Statistical analysis

Comparisons between scores on the evaluation scales before and after the start of rehabilitation. The patients' scores before and after rehabilitation with respect to PS and scores for symptom items and interference items on the MDASI-J, patients' and families' awareness of rehabilitation, willingness to participate, and emotional state were compared by means of the Wilcoxon signed-rank test.

Factors associated with degree of satisfaction of the patients and their families. Associations between the patients' satisfaction scores and other scores, and between the families' satisfaction scores and other scores were assessed by means of Spearman's rank correlation coefficients. The p-values for all of the tests are two-tailed, and p values <0.05 were considered significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) ver. 12.0J for Windows.

Results

Expectations of rehabilitation by the patients and their families

The expectations the patients and their families had of rehabilitation at the time of the initial evaluation are shown in Table II. The most common expectation was related to recovery or improvement of the ability to walk, and was mentioned by 17 patients (74%) and 10 families (43%). Other expectations mentioned by patients and their families were toilet independence or ADL independence and a return to living at home.

Table I. Subjects' characteristics.

	n	Mean	SD
Age		56.7	20.7
Gender			
Male	14		
Female	9		
Site of the primary cancer			
Head and neck	2		
Lung	1		
Digestive organ	3		
Breast	2		
Kidney	2		
Hematologic malignancy	3		
Bone or soft tissue	8		
Unknown	2		
Site of metastases			
Bone	7		
Brain	5		
Lung	3		
Lymph node	3		
Other	1		
Performance status (PS)			
1	1		
2	2		
3	12		
4	8		
Treatment history			
(within one month prior to survey)			
Surgery	9		
Chemotherapy	8		
Radiotherapy	4		
(at the time of survey)			
Chemotherapy	6		
Radiotherapy	6		

Table II. Expectations of rehabilitation by patients and their families.

Content	n	%
Patient		
Improvement of the ability to walk	17	74
Improvement of the superior limb function	3	13
Toilet independence	2	9
ADL independence	4	17
Return to living at home	4	17
Family		
Improvement of the ability to walk	10	43
Toilet independence	3	13
ADL independence	2	9
Recovery of physical condition	5	22
Palliation of pain	1	4
Psychological support	1	4
Return to living at home	5	22

The main difference between the expectations of patients and their families was that many of the patients themselves mentioned expectation of recovery of function, whereas families mentioned expecting overall recovery of physical condition and elimination of the patient's distress, such as by psychological support.

Comparison between scores on the evaluation scales before and after the start of rehabilitation (Table III)

The scores for 9 items before and after the start of rehabilitation were compared: PS, MDASI-J symptom items (S), MDASI-J interference items (I), patient's awareness of rehabilitation, willingness for rehabilitation, and emotional state, and family's awareness of rehabilitation, willingness to participate in rehabilitation, and emotional state. The results showed significant improvement in the scores for 6 items: PS ($p<0.01$), patient's awareness of rehabilitation ($p<0.01$), willingness for rehabilitation ($p=0.03$), and emotional state ($p<0.01$), and family's awareness of rehabilitation ($p<0.01$) and emotional state ($p<0.01$).

Degree of patient and family satisfaction with rehabilitation and factors associated with it

Degree of patient satisfaction, and factors associated with it. The mean score for degree of patient satisfaction was 8.6 (0−10), and the results showed significant correlations between degree of patient satisfaction and 7 factors: awareness of rehabilitation (after the start of rehabilitation), willingness for rehabilitation (before the start of rehabilitation), willingness for rehabilitation (after), emotional state (before), emotional state (after), effectiveness of rehabilitation, and communication with staff (Table IV).

Degree of family satisfaction, and factors associated with it. The mean score for degree of family satisfaction was 7.7 (0−10), and the results showed significant correlations between degree of family satisfaction and 5 factors: emotional state of the patient (before), change in emotional state of the patient, family awareness of rehabilitation (after),

Table III. Comparison between scores on the evaluation scales before and after the start of rehabilitation.

Variables	n	Rank Mean	Sum	Z	p[a]
Performance status				−3.051	0.002
Negative rank	12	7.00	84.00		
Positive rank	1	7.00	7.00		
Same rank	10				
MDASI-J: S[b]				−0.796	0.426
Negative rank	10	10.20	102.00		
Positive rank	12	12.58	151.00		
Same rank	1				
MDASI-J: I[c]				−0.335	0.738
Negative rank	10	12.70	127.00		
Positive rank	13	11.46	149.00		
Same rank	0				
Patient					
Awareness of rehabilitation				−3.326	0.001
Negative rank	1	6.50	6.50		
Positive rank	16	9.16	146.50		
Same rank	6				
Willingness for rehabilitation				−2.232	0.026
Negative rank	6	3.50	21.00		
Positive rank	0	0.00	0.00		
Same rank	17				
Emotional state				−3.115	0.002
Negative rank	12	6.50	78.00		
Positive rank	0	0.00	0.00		
Same rank	11				
Family					
Awareness of rehabilitation				−2.768	0.006
Negative rank	5	6.30	31.50		
Positive rank	15	11.90	178.50		
Same rank	3				
Willingness for rehabilitation				−0.222	0.824
Negative rank	6	8.17	49.00		
Positive rank	8	7.00	56.00		
Same rank	9				
Emotional state				−3.258	0.001
Negative rank	14	8.32	116.50		
Positive rank	1	3.50	3.50		
Same rank	8				

[a]Wilcoxon signed-rank test; [b]Japanese-language version of the M.D. Anderson Symptom Inventory: symptom scale; [c]Japanese-language version of the M.D. Anderson Symptom Inventory: interference scale.

Table IV. Factors associated with degree of patient satisfaction with rehabilitation.

Variables	r	p[a]
Age	0.250	0.250
Gender	0.072	0.746
Performance status (before the start of rehabilitation)	0.047	0.833
Performance status (after the start of rehabilitation)	−0.020	0.928
MDASI-J: S (before)	−0.321	0.136
MDASI-J: S (after)	−0.055	0.802
MDASI-J: I (before)	−0.279	0.197
MDASI-J: I (after)	−0.235	0.280
Number of times rehabilitation was performed	−0.273	0.207
Number of times the family participated	−0.446	0.033
Patient		
Change in awareness of rehabilitation	−0.105	0.633
Awareness of rehabilitation (before)	0.397	0.060
Awareness of rehabilitation (after)	0.547	0.007
Change in willingness for rehabilitation	0.346	0.106
Willingness for rehabilitation (before)	0.554	0.006
Willingness for rehabilitation (after)	0.600	0.002
Change in emotional state	0.122	0.580
Emotional state (before)	−0.504	0.014
Emotional state (after)	−0.795	<0.001
Effectiveness of rehabilitation	0.681	<0.001
Communication with staff	0.810	<0.001

[a]Spearman's rank correlation coefficients.

change in emotional state of the family, and communication with staff (Table V).

Discussion

Subjects' participation in the study

Data were collected continuously throughout the 3-month period from July to September 2004. Rehabilitation was prescribed for 43 patients during that period, but 15 of them were ineligible for the study. The main reasons for their ineligibility were re-prescription (having previously received rehabilitation at the same institution) and cognitive impairment. Since approx. 12% of all prescriptions were re-prescriptions, rehabilitation together with

Table V. Factors associated with degree of family satisfaction with rehabilitation.

Variables	r	p^a
Age	0.348	0.104
Gender	−0.178	0.416
Performance status (before the start of rehabilitation)	0.213	0.329
Performance status (after the start of rehabilitation)	0.277	0.200
MDASI-J: S (before)	−0.128	0.561
MDASI-J: S (after)	0.154	0.483
MDASI-J: I (before)	0.097	0.659
MDASI-J: I (after)	0.327	0.128
Number of times rehabilitation was performed	−0.255	0.241
Number of times the family participated	−0.086	0.695
Patient		
Change in awareness of rehabilitation	0.128	0.560
Awareness of rehabilitation (before)	−0.115	0.600
Awareness of rehabilitation (after)	−0.086	0.697
Change in willingness for rehabilitation	−0.187	0.393
Willingness for rehabilitation (before)	0.262	0.227
Willingness for rehabilitation (after)	0.116	0.599
Change in emotional state	−0.446	0.033
Emotional state (before)	−0.428	0.042
Emotional state (after)	−0.034	0.877
Effectiveness of rehabilitation	0.025	0.911
Communication with staff	0.209	0.339
Degree of patient satisfaction with rehabilitation	0.254	0.242
Family		
Change in awareness of rehabilitation	−0.109	0.619
Awareness of rehabilitation (before)	0.363	0.089
Awareness of rehabilitation (after)	0.535	0.008
Change in willingness for rehabilitation	−0.072	0.742
Willingness for rehabilitation (before)	0.304	0.158
Willingness for rehabilitation (after)	0.230	0.290
Change in emotional state	0.462	0.026
Emotional state (before)	0.301	0.163
Emotional state (after)	−0.210	0.335
Effectiveness of rehabilitation	0.155	0.481
Communication with staff	0.476	0.022

[a]Spearman's rank correlation coefficients.

treatment for their disease appeared to have been considered necessary for patients with cancer recurrence. Rehabilitation for patients with cognitive impairments was also shown to be considered necessary by families and medical personnel, including physicians. The prescriptions for two patients receiving palliative care at the Palliative Care Center were found to have been for consultation alone, showing that rehabilitation had been added as a link in the team approach even though direct rehabilitation was not performed.

There were 5 drop-outs immediately after completion of the initial survey, however, the reasons were discharge to home and deterioration of condition. Since all 3 patients whose condition deteriorated had been admitted to the Palliative Care Center, special consideration for palliative care subjects, such as shortening the survey period, appears to have been necessary.

Subjects' characteristics

The care of the largest number of the 23 subjects who completed the survey was managed by the orthopedics department. The sites of the primary cancers varied considerably, and the reason the greatest number of patients was managed by the orthopedics department appears to have been that the largest group of patients had bone metastases and were undergoing treatment in the orthopedics department even though their primary cancer was not a bone or soft tissue tumor as well as because the functional recovery training unit in the institutions was part of the orthopedics department.

PS at the time of the initial evaluation was 3 in 12 (52.2%) of the patients and 4 in 8 (34.8%). This shows that rehabilitation had been prescribed even for patients whose general condition was poor, suggesting that rehabilitation was considered necessary by the patient, family, and the medical personnel responsible for the patients' treatment, even when patients' general condition was poor.

Expectations of rehabilitation by the patients and their families at the start of rehabilitation

At the time of the initial evaluation, the most commonly mentioned expectation of patients and their families was related to walking, and the requests by the attending physicians were almost exactly what the patients were hoping for. The same content accounted for a high percentage of the requests in other studies, and the results of our study can be said to corroborate the findings of earlier research [12,15,18]. Toilet independence and ADL independence were other shared expectations and also seemed to imply lessening the burden of nursing

care on the family from the standpoint of living at home. Actually, 4 patients (17%) and 5 family members (22%) mentioned hope for a return home, and linking of the hospital, which is the treatment setting, to home life appeared to be one of the functions desired of rehabilitation.

The results also suggested that families expected rehabilitation to eliminate the patient's physical and mental distress by restoring their physical condition, relieving discomfort and pain, or providing psychological support.

Changes in patients after the rehabilitation intervention

The results of the MDASI-J showed significant changes in scores for both the symptom items (S) and the interference items (I), but because many patients were undergoing treatment, the changes appeared to be related to the occurrence of adverse reactions to treatment or to the fact that the general condition of the patients in the terminal stage tended to change.

Comparisons of the evaluation scale scores of patients and their families for 3 items, awareness of rehabilitation, willingness to participate in rehabilitation, and emotional state before and after the intervention, revealed significant changes in the patients in regard to awareness of rehabilitation, willingness to participate in rehabilitation, and emotional state. With respect to the changes in awareness and willingness, it seemed that patients' awareness of what rehabilitation is and its purpose may have deepened with their renewed awareness of their mental and physical condition during the actual process of the conduct of rehabilitation, and that their willingness may have increased in association with the deepening of their awareness. The changes in emotional state of the patients appeared to have been attributable to the influence of the surrounding environment in addition to rehabilitation. However, as stated by Matsushima [19], "Being able to maintain and improve activities of daily living while skillfully utilizing the physical strength that remains is a source of great pleasure, and is linked to the desire to live", and it was inferred that patients' starting to confront their own situation and trying to rebuild their own lives as a result of performing rehabilitation was linked to the changes in their emotional state.

Significant changes in the family were seen in regard to awareness of rehabilitation and emotional state. The reason for the change in awareness of rehabilitation seems to be the same as for the change in the patients' awareness. With respect to emotional state, there also appeared to be a sense of relief that something had been found that would be of use to the patient. No significant difference was found in

regard to willingness to participate in rehabilitation. This finding was suspected of being attributable to family circumstances having made it impossible to participate despite wanting to, or to the influence of the family's view that performing rehabilitation was something patients do themselves.

Factors associated with degree of satisfaction

Factors associated with degree of patient satisfaction. The finding that communication with the staff and the effectiveness of rehabilitation were correlated with the degree of patient satisfaction corroborated the results of previous questionnaire surveys of families by Yoshioka et al. [15]. In regard to willingness for rehabilitation, Yoshioka et al. [20] pointed to increasing motivation as a way of advancing rehabilitation in the terminal stage; however, they suggested that increasing patients' degree of satisfaction is necessary to inspire cancer patients to willingly work on rehabilitation, regardless of the time. Emotional state, both before and after the start of rehabilitation, was also correlated with degree of patient satisfaction. The psychological problems of cancer patients include many problems associated with their disease, and one in three of them has been shown to require special mental care. Based on this finding, it was concluded that it is necessary to pay attention to the emotional state of the patient and properly understand it from the standpoint of performing rehabilitation as well, and at the same time to provide care as needed in order to increase the degree of satisfaction of cancer patients with rehabilitation.

Factors associated with degree of family member satisfaction. The finding of correlations between the degree of family satisfaction and both the emotional state of the patient (before) and change in the emotional state of the patient suggested that understanding and providing care for the emotional state of the patient are necessary to increase the degree of satisfaction of the family. Mantani [21] has stated in regard to the need for providing information to the family that: "Information reduces the family's anxiety about the disease and treatment, and makes decision-making increasingly easy". The finding that both awareness of the family of rehabilitation (after) and communication with the staff were associated with the degree of family satisfaction in this study suggested a need to adequately explain the patient's rehabilitation to the family and increase the family's awareness of rehabilitation, and at the same time to become actively involved with the family. Moreover, since a correlation was also found between "changes in the emotional state of the family" and degree of family satisfaction, in the same way that the family is now seen as the subject of a therapeutic approach as

"a second patient", it was concluded that rehabilitation of the patient also requires understanding the emotional state of the family and appropriately addressing it.

Limitations of the study

The first limitation of this study was that, in principle, interviews by the investigator conducting the survey were adopted as the method of administering the questionnaire used in the survey, but because it sometimes became a self report based on the condition and desires of the subjects themselves, bias may have developed in the results. The second limitation was that the small number of subjects who completed the survey, only 23, made it impossible to perform analyses according to type of cancer and stage. We would therefore like to increase the number of subjects and conduct a reassessment. The third limitation was that the surveys of the subjects were scheduled for before the intervention and 2 weeks after the start of the intervention, but the patients' treatment and discharge schedules and families' scheduled visiting days made it difficult to time the surveys exactly 2 weeks apart. There were many instances in the Palliative Care Center, in particular, in which subjects' condition deteriorated and they dropped out of the second survey, and there were times when the second survey had to be performed before 2 weeks had passed. Thus, in the future it seemed desirable to establish survey methods and survey periods according to the patients' treatment situation and living conditions.

Acknowledgements

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ORIGINAL ARTICLE

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Factors related to posttraumatic stress in adolescent survivors of childhood cancer and their parents

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Abstract *Goals of work:* The purpose of this study was to investigate factors related to severe posttraumatic stress symptoms (PTSS) in adolescent survivors of childhood cancer and their parents. *Materials and methods:* Eighty-nine families (88 adolescent survivors of childhood cancer, 87 mothers, 72 fathers) completed a self-report questionnaire. Multivariate logistic regression analyses were performed using the following risk factors for severe PTSS: trait anxiety, family functioning, demographic and medical variables. *Main results:* Severe PTSS were reported by 10.9% ($n=9$) of the survivors, 20.7% ($n=18$) of the mothers, and 22.2% ($n=16$) of the fathers. Preliminary analyses found significant correlations of PTSS between mother–survivor (Spearman's $\gamma=0.377$, $p<0.01$) and mother–father (Spearman's $\gamma=0.483$, $p<0.01$). The results of multivariate analyses indicated that higher trait anxiety [odds ratio (OR):1.16; 95% confidence interval (CI): 1.03–1.31; $p<0.05$] and having medical sequelae (OR: 5.85; 95% CI:1.02–33.72; $p<0.05$) were significant factors

related to PTSS for survivors. For mothers, the significant PTSS-related factors were: higher trait anxiety (OR:1.13; 95% CI:1.04–1.23; $p<0.01$); 5- to 9-year interval from the first diagnosis to the present investigation, compared to more than a 10-year interval (OR: 6.45; 95% CI:1.67–24.89; $p<0.01$); and a relatively lower rating on "roles" of family functioning (OR: 12.34; 95% CI:1.11–136.97; $p<0.05$). For fathers, trait anxiety was a significant related factor (OR: 1.07; 95% CI:1.01–1.14; $p<0.05$). *Conclusions:* Survivors and their parents suffered from PTSS after long interval from completion of treatment, and PTSS-related factors varied for each family member. Appropriate allocation of responsibility for family functioning may promote the ability to decrease PTSS, especially for mothers.

Keywords Psychology ·
Posttraumatic stress · Long-term
survival · Quality of life · Parents

Introduction

During the last three decades, the treatment of childhood cancer has dramatically improved, and the number of long-term survivors is increasing. A number of researchers have reported observing physical and psychological delayed adverse effects of treatment among survivors of childhood

cancer [24]. Recent perspectives on the psychological outcomes for cases of childhood cancer have been based on the assumption that both cancer and its treatment are fundamentally traumatic events. In fact, "being diagnosed with a life-threatening illness" is mentioned as an example of a traumatic event that is included among the diagnostic criteria for posttraumatic stress disorder (PTSD) listed in

the American Psychiatric Association's diagnostic manual [1]. A cluster of symptoms (e.g., reexperiencing the traumatic event, hyperarousal, and avoidance of event reminders) is characteristic of PTSD.

Previous research has revealed that the prevalence of clinically significant levels of PTSD and/or posttraumatic stress symptoms (PTSS) in survivors ranged from 2 to 20%, and young adult survivors tended to show higher levels of posttraumatic stress [27]. Cancer affects not only patients but also entire families. In cases of childhood cancer, 10–30% of parents of survivors showed symptoms of posttraumatic stress [27]. Several factors may predict PTSS, including the individual's general level of anxiety [9, 13], medical factors, posttreatment factors, maternal psychological vulnerability [17], family functioning, and social support [12, 21]. Most studies have noted that predictors for PTSS were different for each family member.

In addition to the factors related to PTSS for each family member, oncology clinicians need to view the family as a system. The family system framework, as well as consideration of individual differences, is important for supporting families of childhood cancer survivors. Cancer might impact on multiple family members, and it might be reasonable to agree on the level of PTSS within family members. Kazak et al. [14] reported that one-third of two-parent families had both parents fulfill criteria for the arousal symptom cluster, and 84% of families had both parents endorse symptoms of reexperiencing, and suggested the importance of evaluating all family members for PTSS. As for family functioning, Pelcovitz et al. [21] found that PTSD symptoms are associated with chaotic family functioning among adolescent survivors. Brown et al. [4] found a significant correlation between PTSD symptoms and family supportiveness, and a negative correlation between PTSD symptoms and family conflict among the mothers of survivors of childhood cancer. In general, however, the relationship between PTSS and family functioning or framework is not well understood because few researchers have focused on this issue.

The purpose of this study was to investigate the prevalence of severe PTSS in a sample of 12- to 20-year-old childhood cancer survivors and their parents. We examined the contributions to severe PTSS of family functioning, trait anxiety, medical factors, and posttreatment factors. We also explored PTSS within the family members and assessed the impact of cancer for family. We predicted that medical factors, elevated trait anxiety, and impaired family function would account for a significant amount of the variance in PTSS. In addition, the relative influence of these factors was expected to differ among family members.

Materials and methods

Study sample and recruitment

Japanese pediatric cancer survivors and their parents were recruited from three large hospitals in urban areas located in western Japan. Survivors who met the following criteria were identified from the tumor registry of each hospital during the 15-month period from July 2003 to September 2004: (1) age of 12–20 years at the time of the investigation; (2) first diagnosis at least 5 years before the interview and off treatment for a minimum of 1 year; (3) the cancer was in remission; (4) receiving regular medical follow-up treatment as an outpatient; (5) physical health was good enough for the patient to complete several questionnaires; (6) Eastern Cooperative Oncology Group performance status (PS) of 0–2; and (7) absence of cognitive impairment. Survivors of brain tumors were excluded.

The registries of Research on the Treatment of Specific Chronic Childhood Diseases identified 144 eligible patients at three sites as follows: 65 at Hiroshima University hospital, 57 at Kurume University hospital, and 22 at Hiroshima Red Cross-Atomic Bomb hospital. When a patient and his/her parent(s) visited an outpatient clinic, a pediatric oncologist provided the family with an outline describing the purposes and protocol of the current study. The interviewer was allowed to meet with the participants, provided that the parent(s) agreed to participate in the investigation. Survivors who visited the outpatient clinic alone were handed letters for their parents that explained the study and invited them to participate. Written consent was obtained after the participants had been fully informed about the study. Then questionnaires were handed or mailed to the participants after a brief interview. A 1,000-yen book coupon was given to families upon agreement of study participation. The participants completed the questionnaires at home and returned them by mail. A reminder card was mailed to those participants who did not return the questionnaires 1 month after they had been delivered. To maintain anonymity, the questionnaires were returned without names or any type of identification code on the envelope. The protocol was approved by the Institutional Review Board of each institution.

Questionnaires completed by parents and children

The Impact of Event Scale-Revised (IES-R) is a 22-item self-report instrument that assesses three symptoms of PTSD: intrusion, avoidance, and hyperarousal [28]. Symptoms are rated on a five-point Likert scale for frequency of

occurrence during the previous week. High scores indicate a high frequency of symptoms of PTSD. Participants were asked to focus on the child's cancer experience as the stressful event. The Japanese version of the IES-R [2] has a high internal consistency (Cronbach α=0.92–0.95) and test–retest reliability (Pearson γ=0.86). According to the standardization study, IES-R scores of 25 or more are indicative of severe posttraumatic stress.

The State-Trait Anxiety Inventory (STAI) is a 40-item self-report instrument that measures anxiety symptoms that are either current (state) or related to personality (trait) [25]. A higher score indicates a higher level of anxiety. The STAI has high internal consistency as well as adequate construct and discriminative validity across diverse samples. The Japanese version of the STAI has yielded satisfactory internal consistency [20]. Only trait anxiety was evaluated in this study because prior studies reported that trait anxiety predicts PTSS/PTSD for childhood cancer survivors and their parents [9, 12, 13].

The Family Assessment Device (FAD) [7] is a 60-item self-report scale that assesses seven dimensions of family functioning based on the McMastar Model of Family Functioning (MMFF) [6]. Seven of the scales on the FAD reflect the following dimensions of family functioning: (1) Problem solving: the ability to resolve problems to maintain effective family functioning. (2) Communication: how the family members exchange information. (3) Roles: the repetitive patterns of behavior by which the individuals fulfill family functions; role allocation and role accountability are elemental components. (4) Affective responsiveness: the ability to respond to a range of stimuli. (5) Affective involvement: the degree to which the family shows interest in and values the activities and interests of family members. (6) Behavior control: the pattern the family adopts for handling behavior. (7) General functioning. Low scores indicate good functioning and high scores indicate poor functioning. The English and Japanese versions of the FAD have been shown to have adequate validity and reliability [23].

Life events data were obtained from the Japanese version of Holmes–Rahe measure of social adjustment [11, 18]. If a responder had had one or more life event(s) listed on the measure since the first diagnosis, the responder was classified as positive (+) for life events.

Variables obtained from medical records

An intensity of therapy rating was based on medical record review. Each child's medical information was obtained from the medical chart and rated by a pediatric oncologist (M.K.). The intensity of therapy was classified as follows: I (mild; 12%)=less than 6 months of chemotherapy only and/ or surgery; II (intermediate; 62%)=therapy for standard to high-risk cancers according to the protocol of children

cancer study groups in Japan; or III (severe; 25%)=stem cell transplantation, or extremely high-risk cancers. The medical sequelae were also assessed based on chart review by a pediatric oncologist (M.K.). Survivors were classified into two groups as follows: I (none; 64%)=survivors who needed no limitations of activity and no special medical attention; II (yes; 36%)=survivors who needed medical attention because of disease or the longer-term effects of treatment. Information about patients' diagnosis, age at first diagnosis, age at the investigation, interval from diagnosis to the investigation, treatment of cranial irradiation, and relapse were picked up from charts and assessed as medical factors.

Statistical analysis

All analyses were conducted with SPSS 11.5J for Windows (SPSS, Chicago, IL, USA), and two-tailed probabilities were reported. Analyses were separately undertaken on data sets from survivors, mothers, and fathers. First, Spearman's correlation coefficiencies were calculated to examine intercorrelations among family members using the IES-R total score as continuous variables. Second, the IES-R was used to categorize subjects as having severe PTSS (25 or greater), or a mild-to-no PTSS (24 or less) [2]. Preliminary statistical comparisons between the two groups used the Pearson chi-square (for categorical variables) and the non-parametric Mann–Whitney U test (for continuous variables). To identify the final association factors, variables with a p value of less than 0.05 in the bivariate analysis were entered into a multivariate logistic regression model as independent variables. The independent explanatory values of the characteristics were expressed in odds ratios (OR), with 95% confidence intervals (CI). Before the study initiation, the necessary sample size was determined to detect differences in bivariate groups. Response rates were expected to be about 70%. Based on the review by Taïeb et al. [27], a prevalence of severe PTSS (P) of 0.20 and an OR of 2.5 were assumed. It was estimated that a minimum of 77 of each category of participants would be needed to detect a minimum difference with a power of 0.80 and an α level of 0.05 calculated by Whittemore's formula [29]. A p value of less than 0.05 was set as the level of significance for all the statistical analyses.

We adopted a stepwise forward selection for the logistic regression model because the purpose of this analysis was to identify which variables were the most relevant risk factors associated with severe PTSS. For the stepwise selection, a "provisional model" was first applied, including all potential explanatory variables, and then the non-significant variables were removed, or significant variables were added one at a time, until those remaining in the model were found to contribute significantly.

Results

Characteristics of the study sample

Among the 144 eligible families, 125 families visited the outpatient clinic during the study's entry period, and 103 families agreed to participate in the study. Finally, a total of 89 families (61.8%) returned the questionnaires. Characteristics of the study population and the reasons for non-participation are shown in Fig. 1. All participants were Japanese.

A comparison of participants and non-participants revealed no significant differences among survivors in terms of current age, age at diagnosis, gender, type of cancer, interval since the first diagnosis, interval since the end of treatment, treatment intensity, cranial irradiation, medical sequelae, and relapse.

There were also no significant differences in terms of survivor's age, gender, medical sequelae, family size, socioeconomic status, parents' age, and history of psychological care between each institution. However, several differences were found among the three samples. The site 1 and site 2 samples contained a higher number of infant neuroblastoma and other solid tumor survivors than the site 3 sample [$\chi^2(8, n=89)=23.478, p<0.01$]. The site 3 sample contained a higher number of survivors who received more intensive treatment [$\chi^2(4, n=89)=29.185, p<0.01$] and cranial radiation [$\chi^2(2, n=89)=10.938, p<0.01$]. The demographic and medical factors of survivors, which were combined, are shown in Table 1.

Table 1 Demographic and medical characteristics of survivors ($n=89$)

	No. of survivors (%)	
Male gender	40	(45)
Age at investigation (mean±SD)	16.2±2.3	
Age at diagnosis (<6 years)	57	(64)
Time since diagnosis (<10 years)	39	(44)
Relapse ≥1	12	(14)
Diagnosis		
Acute lymphoblastic leukemia	46	(52)
Other leukemia	14	(16)
Malignant lymphoma	9	(10)
Infant neuroblastoma	11	(12)
Other solid tumor	9	(10)
Treatment intensity		
I (mild)	11	(12)
II (intermediate)	55	(62)
III (severe)	23	(25)
Medical sequelae		
I (None)	57	(64)
II (Yes)	32	(36)
Socioeconomic status		
I	2	(2)
II	17	(19)
III	57	(64)
IV	11	(13)
V	2	(2)

Socioeconomic status was calculated using Hollingshead and Redlich two-factor index of social position [10].

Fig. 1 Flow chart showing the study population

Fig. 1 Flow chart showing the study population
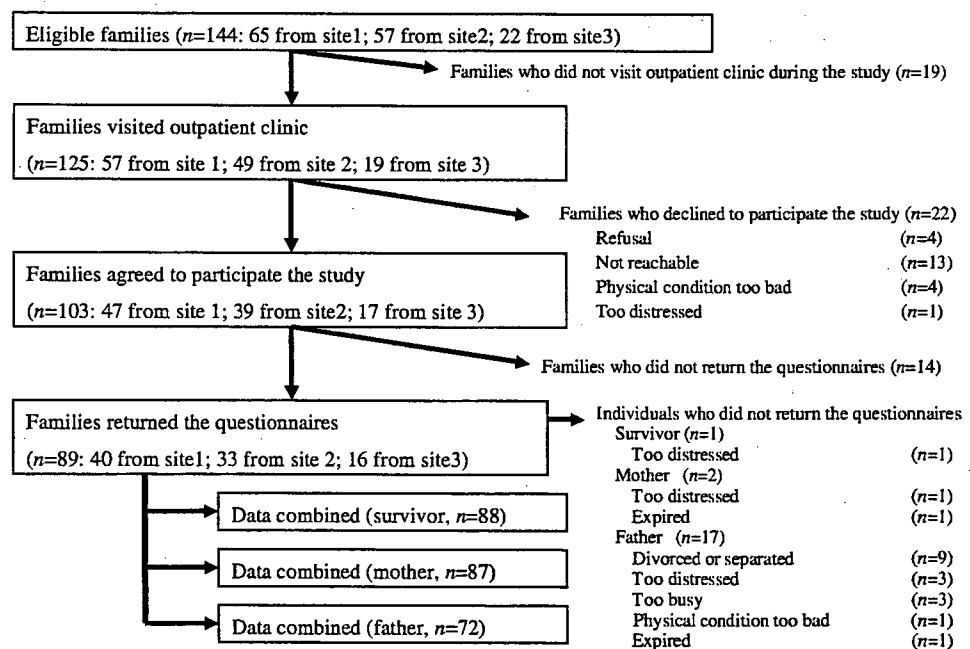
IES-R dimensional scores and intercorrelations of PTSS for each family member

The means and SDs for the IES-R dimensional scores are shown in Table 2. Compared to survivors, mothers and fathers showed relatively higher ratings on intrusion and avoidance, and mothers and fathers showed comparable scores on each dimension. Using 24/25 as the cutoff for the IES-R, severe PTSS were present in 9 of the 88 survivors (10.9%), 18 of the 87 mothers (20.7%), and 16 of the 72 fathers (22.2%). Spearman's intercorrelation coefficiencies for the total IES-R scores were significant for survivor–mother and father–mother pairs. The survivor–father correlations were not significant.

Severe PTSS and related factors for survivors

Results of bivariate comparisons of demographic characteristics, medical variables, trait anxiety, and family functioning between those with either severe PTSS or not severe PTSS are shown in Table 3. The results indicated that subjects with severe PTSS had higher trait anxiety and exhibited a lower level of family functioning with respect to factors such as roles and affective responsiveness. Also, these subjects were more likely to have medical sequelae. As predicted, no significant differences were found with respect to the ratings for treatment intensity, time lapse from diagnosis to the study, history of relapse, and cranial radiation.

Table 4 shows the results from the multivariate logistic regression model in which severe PTSS was used as the bivariate outcome. Higher rating on trait anxiety and having medical sequelae were found to be significant factors related to severe PTSS, whereas family functioning was not found to be a significant PTSS-related factor.

Severe PTSS and related factors for mothers of survivors

The results of the bivariate comparisons of variables between those with severe or not severe PTSS are shown in Table 3. The results indicate that subjects with severe PTSS had higher trait anxiety and lower levels of family functioning, as determined by the dimension of roles and general functioning. For mothers with severe PTSS, the child was diagnosed as having cancer at an older age, and the time interval since the first diagnosis to the present study was shorter. However, no other significant differences were found in terms of age of the mother and life events [$\chi^2(1, n=87)$ 0.5, $p=0.47$].

The results of the multivariate logistic regression model yielded three significant factors for severe PTSS: higher trait anxiety, a 5- to 9-year period since the first diagnosis to the present investigation as compared to an interval of more than 10 years, and a relatively lower rating on "roles" of family functioning (Table 4).

Severe PTSS and related factors for fathers of survivors

The results of the bivariate comparisons of variables between those with severe or not severe PTSS are shown in Table 3. The results indicate that subjects with severe PTSS had higher trait anxiety scores. However, no other significant differences were found in terms of any family functioning, medical variables, child's age at diagnosis [$\chi^2(1, n=72)$ 2.6, $p=0.11$], time since disease onset ($\chi^2(1, n=72)$ 1.4, $p=0.24$], life events [$\chi^2(1, n=72)$ 0.8, $p=0.37$], and demographic factors. Higher rating on trait anxiety was found to be a significant factor related to severe PTSS in logistic regression model (Table 4).

Discussion

The current study examined the prevalence of severe PTSS among long-term childhood cancer survivors and their parents. This study also investigated other factors, including family functioning, for each family member. The results indicate that some survivors and their parents suffered from symptoms of posttraumatic stress after a long interval from the completion of treatment. The prevalence of severe PTSS obtained for the survivors (10.9%) was comparable to that reported by Stuber et al. [26] (severe PTSS 12.5%), Erickson and Steiner [8] (current PTSD 10%), and Langeveld et al. [16] (severe PTSS 12.5%), although a higher prevalence of PTSD was reported by Hobbie et al. [9] (20.5%) and Meeske et al. [19] (22%).

The prevalence of severe PTSS in the present study for mothers (20.7%) and fathers (22.2%) were somewhat higher than those reported by Barakat et al. [3] (10.1% of

Table 2 Means(SD) of IES-R dimensional score and correlations of IES-R between family members

	Survivors (n=88) Mean (SD)	Mothers (n=87) Mean (SD)	Fathers (n=72) Mean (SD)
IES-R total	9.0 (10.4)	15.0 (12.4)	16.0 (14.3)
Intrusion	2.9 (3.9)	5.7 (4.7)	6.0 (5.3)
Avoidance	3.1 (4.8)	6.0 (5.4)	6.8 (6.0)
Hyperarousal	3.0 (3.3)	3.3 (3.8)	3.2 (4.1)
Correlations (IES-R total)			
1. IES-R survivors			
2. IES-R mothers	0.377**		
3. IES-R fathers	0.179	0.483**	

IES-R Impact of Event Scale-Revised; **$p<0.01$

Table 3 Comparison of medical factors and psychological variables between survivors and their parents with severe PTSS and those with not severe PTSS

	No. with severity of PTSS (%)		Analysis	
	Severe PTSS	Not severe PTSS	Statistic	P
Survivors (n=88)	n=9	n=79		
Age; mean (SD)	16.1 (1.9)	16.2 (2.3)	T(df=86) 0.16	0.87
Male gender	5 (56)	34 (43)	χ^2(1, n=88) 0.5	0.47
Medical sequelae: I (none)	3 (33)	55 (70)	χ^2(2, n=88) 8.3	<0.01
Medical sequelae: II (yes)	6 (66)	24 (30)		
Trait anxiety; mean (SD)	56.2 (8.6)	43.2 (9.9)	112.5[a]	<0.01
FAD-Roles; mean (SD)	2.3 (0.3)	2.1 (0.4)	193.0[a]	0.03
FAD-Affective responsiveness; mean (SD)	2.5 (0.6)	2.1 (0.5)	208.5[a]	0.04
Mothers (n=87)	n=18	n=69		
Age; mean (SD)	43.4 (5.0)	43.9 (4.8)	t(df=85) 0.44	0.69
Child's age at diagnosis (<6 years)	11 (61)	21 (30)	χ^2(1, n=87) 5.8	0.02
Time since disease onset (<10 years)	13 (72)	23 (33)	χ^2(1, n=87) 8.9	<0.01
Trait anxiety; mean (SD)	52.2 (10.2)	41.5 (9.9)	280.5[a]	<0.01
FAD-Roles; mean (SD)	2.2 (0.3)	2.0 (0.4)	383.0[a]	0.01
FAD-General functioning; mean (SD)	2.1 (0.4)	1.9 (0.5)	425.0[a]	0.04
Fathers (n=72)	n=16	n=56		
Age; mean (SD)	47.1 (7.8)	47.4 (5.5)	t(df=70) 0.19	0.85
Trait anxiety; mean (SD)	46.5 (10.5)	39.4 (9.7)	266.5[a]	0.01

PTSS Posttraumatic stress symptoms, *SD* standard deviation, *FAD* family assessment
[a]Mann–Whitney *U* test

mothers and 7.1% of fathers had severe PTSS) and Kazak et al. [12] (10.2% of mothers and 7.1% of fathers had severe PTSS), although they were lower than those reported by Stuber et al. [26] (39.7% of mothers and 33.3% of fathers had severe PTSS). Differences in the prevalence of PTSS among these samples may be affected by differences in sample size, sample age, psychological

Table 4 Factors related to severe PTSS in survivors (n=88), mothers (n=87), and fathers (n=72): logistic regression analysis of medical and psychological variables

	B	exp(B)
Survivors		
Step 1: trait anxiety	0.15*	1.16 (1.03–1.31)
Step 2: medical sequelae (Yes)	1.77*	5.85 (1.02–33.72)
Step 3: FAD-Affective responsiveness	1.00	5.20 (0.73–37.06)
FAD-roles	1.19	1.15 (0.11–11.76)
Mothers		
Step 1: trait anxiety	0.12**	1.13 (1.04–1.23)
Step 2: time since disease onset (<10 years)	1.86**	6.45 (1.67–24.89)
Step 3 FAD-Roles	2.51*	12.34 (1.11–136.97)
FAD-General functioning	−1.42	0.24 (0.03–1.78)
Fathers		
Step 1: trait anxiety	0.07*	1.07 (1.01–1.14)

FAD Family Assessment Device; *p<0.05; **p<0.01

instruments used, cultural background, and the state of disease among survivors. Generally, the results of the present study are consistent with previous studies, which found that the prevalence of severe PTSS/PTSD among parents was higher than that among patients.

The association of impaired "roles" of family functioning with posttraumatic stress in mothers suggests two important issues. First, when the assignment of responsibilities for family functions is not appropriately distributed, an excessive burden may fall on a specific family member. Second, as a result of impairment of the accountability for the responsibilities that are allocated to each family member, the effectiveness of the job being done would be diminished. This situation may place a specific member of a family at greater risk for poor adaptation to a traumatic stressor and, subsequently, to possible psychiatric disorder, including PTSD.

These findings are in accord with the findings of Brown et al. [4], who found that mothers' greater self-reported level of support within their families was predictive of fewer or less intense maternal PTSS, although no such association was found among survivors. Kazak et al. [13] reported similar findings that family functioning was associated with anxiety and posttraumatic stress in both mothers and fathers. One possible reason for this discrepancy is that the study of Kazak et al. [13] used the Family Adaptability and Cohesion Evaluation Scales—Version III A, which has only three dimensions as family system variables. A path analysis was then used, which might be

more sensitive to identify an association of PTSS with family functioning.

Preliminary analyses found the moderate correlation of PTSS between mother and father. While speculative, this indicates that mothers and fathers share a similar perception about their child's state of disease. Interestingly, these findings contradict those reported in another paper by Kazak et al. [14] in which they report very low levels of concordance of PTSD within a family. Cultural difference might contribute to these contradictions. Our finding of a correlation between mothers and survivors indicates that survivors' PTSS are resonant with mothers but not fathers. It is not clear why a correlation was not found between survivors and fathers. One possible speculation is that most of the adolescent survivors spend much time attending school, participating in extracurricular activities, or in peer relationships. They may not spend much time with their fathers, who, in Japan, come home late in the evening because of work. These situations decrease communication with fathers more than with mothers.

The time elapsed after the first diagnosis of cancer was found to be a significant factor for mothers' PTSS. It is commonly reported that trauma-induced psychological symptoms decrease with time. Kessler et al. [15] reported in a general population study that about two-thirds of people with an episode of PTSD recovered over time, even without treatment. The results of our study are consistent with the finding of Phipps et al. [22] that parents of recently diagnosed patients showed higher levels of PTSS than parents of long-term survivors. Kazak et al. [13] reported similar findings that a mother's posttraumatic stress was indirectly related to the interval since the final treatment, as determined by the mother's appraisal of the degree of threat to the life of the child.

As regards the fathers of survivors, Kazak et al. [12] reported that the number of months off treatment was negatively related to variables of posttraumatic stress. However, it is not necessarily the case that a time lapse reduces PTSS. The present study did not establish the associations of time lapse with severe PTSS in survivors and their fathers. One possible reason for this discrepancy is that because our sample was families of long-term survivors with a mean follow up period 10.8 years (range 5–19), they might be affected by medical sequelae or other concurrent stressors rather than the past intensive cancer treatment. This pattern may be more appropriate for a diagnosis of adjustment disorder than PTSD, although several participants showed a clinical level of PTSD.

Our study also revealed that trait anxiety was an associated factor for PTSS for survivors and parents. It must be noted that caution is warranted in interpreting anxiety as a predictor for PTSS, as trait anxiety is well-known to coexist with PTSD-like symptoms. Moreover, it is important to distinguish symptoms of anxiety from PTSS because they are conceptually overlapping but not identical. PTSS is attributed to reexperiencing and avoidant behavior based on the traumatic memories and is closely related to the general level of anxiety. Thus, clinicians should carefully rule out a primary anxiety disorder from the anxiety related to PTSS.

The existence of medical sequelae was a significant factor related to severe PTSS in survivors. Some of these survivors may have experienced physical symptoms at the time of the study and continued limitations of activities in daily life. Thus, it would not be surprising if they reported experiencing increased anxiety or if they perceived their life as currently threatened. This pattern is consistent with the findings from Langeveld et al. [16] that severe sequelae or health problems were associated with posttraumatic stress. However, these findings are not in accord with reports by Hobbie et al. [9], who did not find any association between medical sequelae and PTSS. Specifically, Hobbie et al. [9] reported that subjective factors related to cancer and its treatment (e.g., beliefs regarding a life threat and/or perceived treatment intensity) are more important than the objective medical data about cancer. While speculative, the reason for this discrepancy may be that the study of Hobbie et al. [9] contains a relatively larger proportion of survivors (about 65%) who had moderate to severe medical sequelae, while only 36% of the survivors in our study had medical sequelae, so it was more difficult to identify the relationship between PTSD and medical sequelae.

Limitations

The current study has several limitations. First, only 62% (89 of 144 families) of the subjects could be included in the analysis, and the prevalence of severe PTSS in survivors was relatively lower than that of parents, so the current study may not have had optimal statistical power. As the present results suggest that only 10.9% of survivors showed severe PTSS, researchers would have to investigate twice as many families to get more valid results.

Second, the result relies on self-reported questionnaires only, which do not allow a proper diagnosis of clinically relevant disorder. Further study is needed to determine the true prevalence of current PTSD compared to "severe PTSS".

Third, the design of the study was cross-sectional, and this investigation lacked a matched control group, so no conclusions regarding causality can be drawn. It needs further consideration that family functioning from the mother's viewpoint is affected by the phase of adolescence, with ensuring conflicts, role changes, and developmental tasks. Comparison to families with healthy adolescents probably would yield further information.

Fourth, as this study was conducted at three sites, and the disease distribution differed among these sites, an institutional bias may have influenced the results.

Finally, the assessments of the treatment intensity and medical sequelae were conducted by an ad hoc method, and the validity and reliability of these measures was not well established, and they may have resulted in classification errors. Replication of the present study with a large, longitudinally followed sample and more optimal assessment tools is needed to provide a better description of factors related to PTSS in childhood cancer survivors and their families.

Clinical implications

The present data give rise to several important clinical implications for families with childhood cancer survivors. Even when the treatment was successful, some survivors cannot avoid suffering from medical sequelae, so long-term follow up of physical and psychological functioning after treatment is clearly desirable. The Children's Oncology Group website [5] provides detailed guidelines and information about specific later-onset effects for long-term survivors. Moreover, as the risk factors for severe PTSS vary for each family member, health care professionals in pediatric oncology units should assess each member of families and provide suitable treatment. The regular use of "family conferencing" would enable clinicians to bring the dynamics of the family system into relief and focus on the specific individual issues as well. It is important to specify the family functions, to ascertain whether the family has allocated the responsibilities for these functions appropriately, and whether there are suitable mechanisms built in for accountability.

Parents also may benefit from education about their child's and their own symptoms and how to manage them effectively. At the same time, clinicians should assess and treat the general level of anxiety of each family member. Cognitive-behavioral approach and educational information may provide structure and support when anxiety and avoidance discourage exploration. If the situation becomes complicated, referral to a social worker, psychologist, or consultation-liaison psychiatrist would be a good option. Further research is needed to develop intervention programs that are effective in improving family functioning, and that may reduce PTSS in families with childhood cancer survivors.

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