died of bleeding from a tracheostomy. The autopsy was limited to the brain.

Neuropathological findings

The fixed brain weighed 460 g. Macroscopic examination revealed generalized gyral atrophy in both cerebral hemispheres, especially in the frontal and temporal lobes (Fig. 2a). Serial coronal sections of the brain showed severe cortical atrophy involving the orbital and cingulate gyri (Fig. 2b) as well as the medial temporal lobe, including the amygdala and hippocampus (Fig. 2c). The caudate nuclei were severely atrophied, and there was marked dilatation of the lateral ventricles. Additionally, the globus pallidus was light brown and atrophied (Fig. 2c). Serial axial sections of the brain stem showed brown discoloration of the substantia nigra and locus coeruleus. Serial sagittal sections of the cerebellum revealed severe cortical atrophy as well as brown discoloration and atrophy of the dentate nuclei. Meninges and blood vessels were normal.

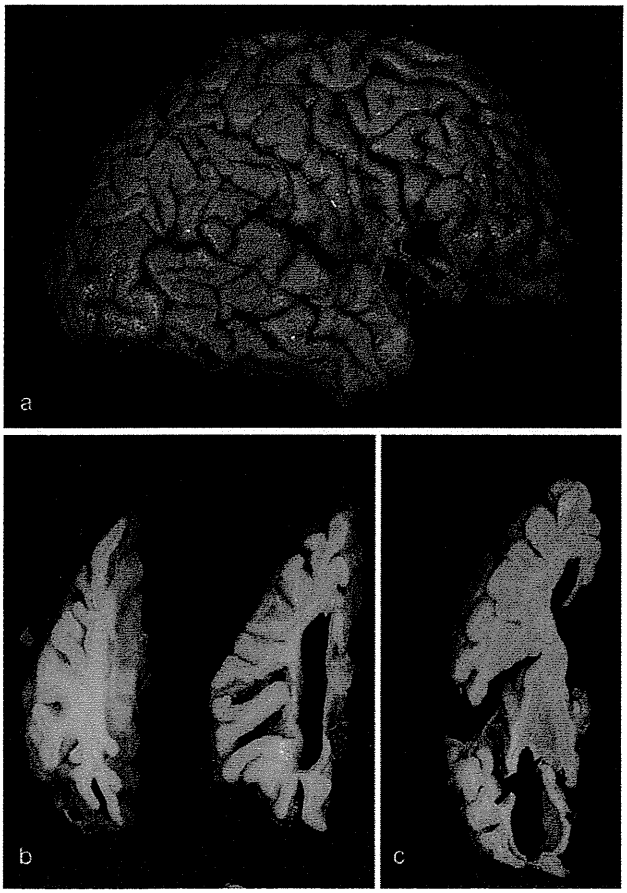

Fig. 2 External lateral view, coronal sections of the right hemisphere. (a) Cerebrum after stripping of the leptomeninges showing "knife-edge" atrophy of the frontal and temporal lobes. (b) Prominent atrophy of orbital surface of the frontal lobe and cingulate gyri. (c) Severe atrophy of the cingulate gyri, insula, amygdala, and temporal lobe. Mild pigmentation of the inner segment of the globus pallidus (arrow).

The brain was fixed in 10% buffered formalin. Multiple paraffin-embedded tissue blocks were prepared, and 6-μm-thick sections were cut. These sections were stained with HE, KB, Bodian, Berlin blue, and Gallyas-Braak methods.

The following primary antibodies and dilutions were used for immunology studies: anti-phosphorylated tau (AT8; mouse monoclonal; 1:1000; Innogenetics, Ghent, Belgium), anti-phosphorylated α-synuclein (pSyn#64; mouse monoclonal; 1:5000; Wako, Osaka, Japan), anti-phosphorylated TDP-43 (pS409/410–2; rabbit polyclonal; 1:5000; Cosmo Bio, Tokyo, Japan).

Microscopic examination showed brown-pigmented, iron-positive granules around the blood vessels and throughout the neuropil in the globus pallidus (Fig. 3a) and the pars reticulata of the substantia nigra. In addition, numerous axonal spheroids were observed predominantly in the subthalamic (Fig. 3b) and dentate nuclei, globus pallidus, substantia nigra pars reticulate, and cerebellar cortex. Marked neuronal loss and gliosis were most pronounced in the frontal (Fig. 3c) and temporal cortices. In the most affected regions microvacuolar changes were seen within the outer cortical laminae. Marked gliosis was found in the frontal (Fig. 3d) and temporal white matter. Severe loss of neurons with gliosis was also found in the globus pallidus and neostriatum. The substantia nigra pars compacta was characterized by marked neuronal depletion, and the remaining cells had a low melanin content (Fig. 3e). In the medulla oblongata the cuneate and gracile nuclei were severely affected, showing neuronal loss and gliosis. A moderate depletion of Purkinje cells and proliferation of Bergmann astrocytes was noted in the cerebellum (Fig. 3f). In the dentate nucleus there was moderate neuronal cell loss, as well as several axonal spheroids. In addition to these changes, many NFTs and neuropil threads were found in the cerebral neocortex (Fig. 3g), hippocampus, basal ganglia, thalamus, substantia nigra and reticular formation of the brain stem. These NFTs and threads reacted strongly with anti-phosphorylation-dependent tau protein (Fig. 3h). Immunohistochemistry for α-synuclein enabled the detection of numerous foamy spheroids in the substantia nigra (Fig. 3i). Approximately 90% of foamy spheroids were positive for α-synuclein. However, no LBs or Lewy neurites were observed. The axonal spheroids in the subthalamic nuclei and globus pallidus were consistently negative for α-synuclein and tau. TDP-43-positive neuronal cytoplasmic inclusions (NCI) were found with moderate frequency in the dentate gyrus granular

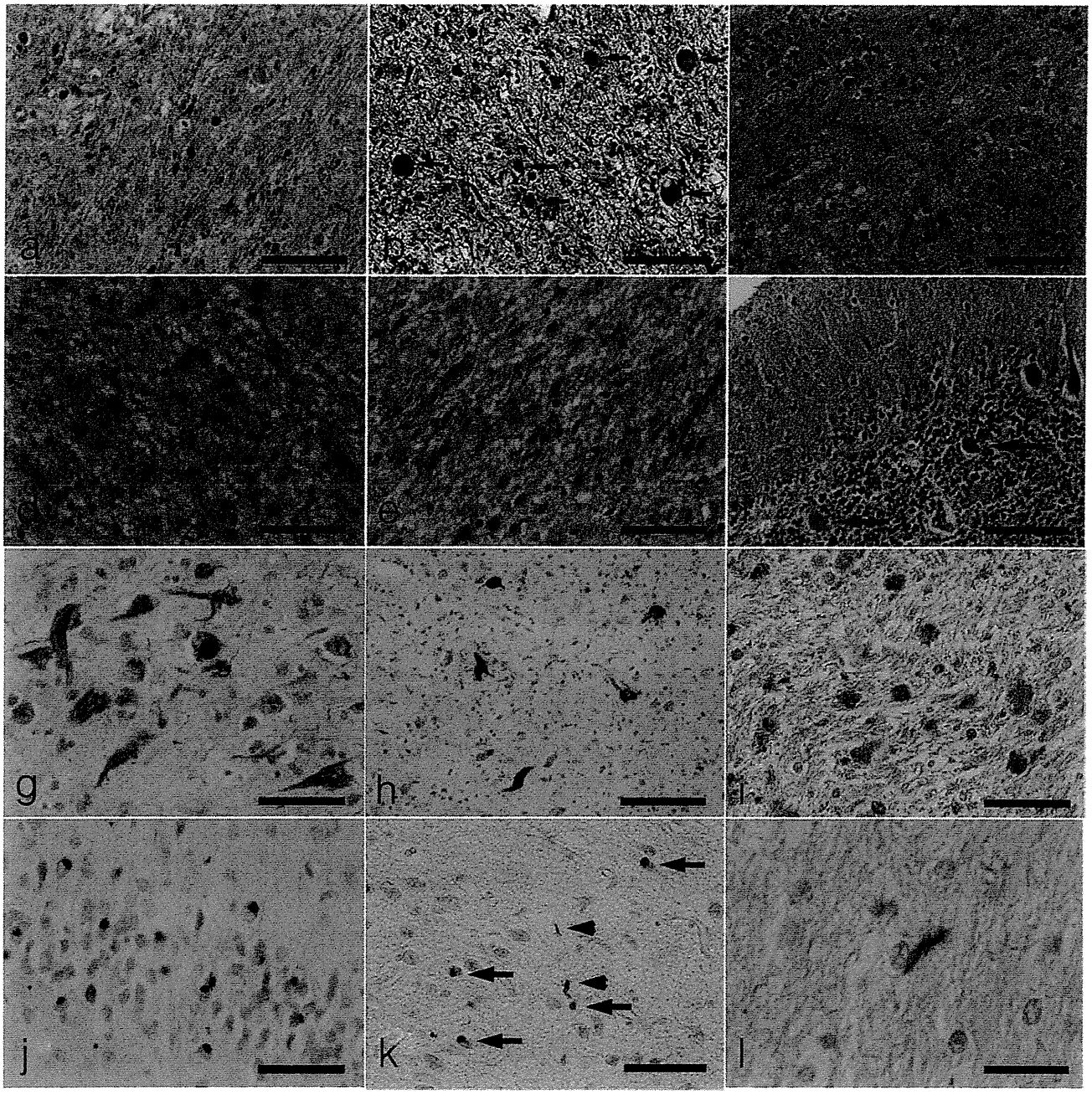

Fig. 3 Microscopic appearance of representative lesions. (a) Perivascular and parenchymal deposits of iron-containing pigments in the globus pallidus; Berlin blue stain. (b) Numerous spheroids (arrows) in the subthalamic nuclei; Bodian stain. (c) Marked neuronal loss and gliosis in the frontal cortex; HE. (d) Marked gliosis in the frontal white matter; HE. (e) Marked neuronal loss and gliosis in the substantia nigra; HE. (f) Moderate loss of Purkinje cells with several axonal torpedoes (arrows) in the granular layer of the cerebellum; HE. (g) Many NFTs and neuropil threads in the temporal cortex; Gallyas-Braak stain. (h) Many NFTs and neuropil threads in the temporal cortex; AT-8 immunostaining. (i) Foamy spheroids in the substantia nigra; α-synuclein immunostaining. (j) TDP-43-positive neuronal cytoplasmic inclusions in the dentate gyrus granular cells; TDP-43 immunostaining. (k) TDP-43-positive neuronal cytoplasmic inclusions (arrows) and neuronal dystrophic neurites (arrowheads) in the temporal cortex; TDP-43 immunostaining. (l) TDP-43-positive glial cytoplasmic inclusion in the temporal white matter; TDP-43 immunostaining. Scale bars = (a) 100 μm, (b) 50 μm, (c) 100 μm, (d) 50 μm, (e) 40 μm, (f) 100 μm, (g) 50 μm, (h) 100 μm, (i) 50 μm, (j) 50 μm, (k) 50 μm, (l) 15 μm.

Table 1 Previous cases of autopsied NBIA-1 with NFTs

Author	Sex	Age at death (years)	Age at onset (years)	Disease duration (years)	Brain weight (g)	NFT	LB
Wisniewski *et al.*[17]	F	25	8	17	ND	+	–
	M	13	2	11	ND	+	–
Hartmann *et al.*[18]	F	45	18	27	910	+	–
Eidelberg *et al.*[19]	F	48	42	6	1060	+	+
	F	42	32	10	920	+	–
	F	33	31	2	1135	+	–
Fuse *et al.*[9]	M	38	8	30	600	+	+
Gaytan-Garcia *et al.*[24]	M	26	18	8	960	+	+
Yamamoto *et al.*[20]	M	64	57	7	1050	+	–
Hayashi *et al.*[25]	M	26	10	16	850	+	+
Halliday[22]	F	31	1	30	810	+	–
Wakabayashi *et al.*[13]	M	39	9	30	510	+	+
Saito *et al.*[14]	F	44	9	35	775	+	+
	M	38	8	30	600	+	+
Neumann *et al.*[12]	F	27	21	6	1240	+	+
Grimes *et al.*[23]	F	85	76	9	ND	+	–
Zarranz *et al.*[15]	M	61	55	6	ND	+	+
Present patient	F	49	22	27	460	+	–

–, absent; +, present; LB, Lewy body, ND, not determined; NFT, neurofibrillary tangle.

cells (Fig. 3j). These NCI were found with low frequency in the middle and upper cortical layers of the frontal and temporal cortices (Fig. 3k), with moderate frequency in the striatum and the globus pallidus, and were absent in the thalamus, substantia nigra, and amygdala. Relatively few neuronal dystrophic neurites (DN) were found (Fig. 3k) in the sites where NCI were observed. Moreover, TDP-43-positive glial cytoplasmic inclusions (GCI) were found with moderate frequency in the striatum and globus pallidus, and found with low frequency in the frontal and temporal lobes (Fig. 3l) and the thalamus. No neuronal intranuclear inclusions (NII) were observed. The distribution of this TDP-43 pathology overlapped with that of tau pathology. However, tau pathology was much more abundant than TDP-43 pathology. Neither tufted astrocytes nor astrocytic plaques were found. No amyloid plaques, globoid cells, or Pick bodies were observed.

Genetic analysis

These studies were approved by the Institutional Review Boards of Osaka University Hospital and the Minami-Okayama Medical Center, and performed after obtaining written informed consent from the patient's family. Genomic DNA was isolated from the subject's frozen brain tissue using Dr GenTLE (Takara Bio, Otsu, Shiga, Japan) according to the manufacturer's instructions. The entire coding region, exon1C to 7 and surrounding exon-intron boundaries of the pantothenate kinase 2 (*PANK2*) gene were amplified and analyzed by PCR.[4] The amplified products were purified and directly sequenced in both the forward and the reverse directions by Dye Terminator Cycle Sequencing Ready Reaction (ABI 310 Genetic Analyzer, Perkin-Elmer Biosystems, Foster City, CA, USA) and compared with control DNA. Information concerning the sequence of the PKAN genome was obtained from the website of GenBank accession number BK000010.[4]

No mutations were demonstrated in the *PANK2* gene. However, we found a homozygous polymorphism in the gene: the homozygous c.47G->C substitution resulted in p.G16A in exon 1C.

Survey of the literature

Eighteen NBIA-1 patients with NFT were included in this analysis: one was our original case, 17 were obtained by reviewing the literature[9,12–15,17–20,22–25] and confirming the detailed clinical and pathological findings. We first evaluated the age at onset, age at death and disease duration (Table 1). The ages at onset were 1 to 76 years, the ages at death were 13 to 85 years, and the durations were 2 to 35 years. These NBIA-1 patients appeared to comprise two different groups: one had NFT expression but no LB (NFT-type) and the other had both NFT and LB expressions (NFT/LB-type). The Mann-Whitney *U*-test was used for statistical comparison of the age at onset, age at death, and disease duration between the NFT type and the NFT/LB type. Fisher's exact probability test was used for comparison of the male-to-female ratio. P-values under 5% were accepted as statistically significant. These statistical analyses were performed using SPSS software version 13.0 for Windows (SPSS Inc., Chicago, IL, US).

There were no differences between the two groups in sex ratio (NFT-type; M/F 2/7, NFT/LB-type; M/F 6/3,

$P = 0.153$), age at onset (NFT-type; 27.4 ± 23.8 years, NFT/LB-type; 20.0 ± 16.1 years, $P = 0.658$), age at death (NFT-type; 43.0 ± 20.3 years, NFT/LB-type; 38.6 ± 10.9 years, $P = 0.691$), disease duration (NFT-type; 15.6 ± 9.6 years, NFT/LB-type; 18.6 ± 11.8 years, $P = 0.722$), and brain weight (NFT-type; 880.8 ± 215.1 g, NFT/LB-type; 824.4 ± 237.0 g, $P = 0.698$).

DISCUSSION

In most cases, the onset of NBIA-1 occurs in the first or second decade and death usually occurs before the age of 30 years. Recent studies suggest that NBIA-1 can develop at any age, and that the phenotype should be extended to include late onset parkinsonism.[32] In the present patient, the initial neurological manifestations were akinesia, resting tremor, and rigidospastic gait at the age of 22. These were later accompanied by progressive dementia, spastic tetraparesis, and myoclonic movements.

The pathological findings in the present case included numerous axonal spheroids and abundant iron deposition with severe neuronal loss and gliosis in the globus pallidus and substantia nigra pars reticulata. We therefore classified our patient as having adult-onset NBIA-1 without known *PANK2* mutations. We confirmed that the substitution in our case was unrelated to the onset of PKAN, and concluded this homozygous polymorphism to be of no significance. The other major pathological characteristics of our patient were the presence of innumerable NFTs and diffuse TDP-43-positive inclusions.

To our knowledge, this is the first report to demonstrate TDP-43 pathology in a NBIA-1 case. The neuronal subcellular localization of TDP-43-positive inclusions is diverse, and TDP-43-positive inclusions consist of neuronal cytoplasmic inclusions (NCI), neuronal dystrophic neurites (DN), and neuronal intranuclear inclusions (NII). Based on the morphology of ubiquitin- or TDP-43-positive inclusions, at least four subtypes were proposed for FTLD-U:[26,33–35] subtype 1 with DNs but few NCIs and no NIIs, subtype 2 with NCIs but few or no DNs and no NIIs, subtype 3 with NCIs and DNs with NIIs, and subtype 4 with NIIs and DNs but few NCIs.[36] Subtype 3 includes cases with *progranulin (PGRN)* mutations and others, and subtype 4 consists of cases with *valosin-containing protein (VCP)* mutations. The morphology of TDP-43-positive inclusions in our NBIA-1 case appears to correspond to that in FTLD-U subtype 2.

Recent reports have revealed various degrees of coexistence of TDP-43 immunoreactivity in a variety of neurodegenerative disorders, including AD, DLB, CBD, Guamanian ALS/PDC, and Huntington's disease.[27–30,37–39] In 2007, Higashi *et al.* investigated TDP-43 pathology in seven FTLD-U cases, 15 AD cases, and 11 DLB cases, and they found that the amygdalas and hippocampi that were vulnerable to tau or α-synuclein pathology demonstrated more severe TDP-43 pathology in AD and DLB cases than in FTLD-U cases. In contrast, while the frontal cortex and basal ganglia were vulnerable to TDP-43 pathology in FTLD-U, TDP-43 pathology was not observed there in AD and DLB cases. Thus, they suggested that FTLD-U may have a pathogenic mechanism leading to TDP-43 aggregation that is different from AD or DLB.[38] In our NBIA-1 case, severe TDP-43 pathology was widespread in not only the hippocampus but also the frontal and temporal lobes and basal ganglia, and almost absent in the amygdala. This neuroanatomical distribution of TDP-43-positive NCIs was obviously more similar to that in FTLD-U rather than in AD and DLB. In addition, Nakashima-Yasuda *et al.* reported that TDP-43 pathology was detected in the hippocampus and entorhinal cortex from a subset of DLB + AD (31.3%) but not pure DLB cases. These findings might suggest that AD rather than LB pathology is the more dominant risk factor for TDP-43 proteinopathy, as they speculated.[27] The pathological findings of our case, in which tau and TDP-43 pathology were exceedingly more abundant than α-synuclein pathology, are consistent with their speculation.

Clinical and pathological findings for previously described NBIA-1 patients with neurofibrillary pathology are summarized in Table 1. These patients ranged in age from 13 to 85 years (mean 40.8 years) at the time of death, with an average duration of illness of 17.1 years. Clinically, they revealed a slowly progressive or relatively abrupt cognitive decline. Pathologically, NFTs of several cases were widely distributed throughout the cerebral cortex and subcortical nuclei,[9,13–15,18,19,22,24,25] whereas others were relatively confined to the brainstem or hippocampus.[12,20,23] Thus, the distribution patterns of NFTs are diverse. Furthermore, they appear to comprise two different groups, that is, a NFT type and a NFT/LB type. However, the statistical analyses in our study showed no significant differences between the two groups in sex ratio, age at onset, age at death, disease duration, and brain weight. These findings could suggest that this pathological phenotypic difference is not due to an acquired factor. The coexistence of NFTs and LBs (NFT/LB-type) has been reported in only nine patients with NBIA-1.[9,12–15,19,24,25] In one of these nine cases, axonal spheroids were restricted to the globus pallidus, substantia nigra, and gracile and cuneate nuclei.[19] In the other eight patients, numerous spheroids were widely distributed throughout the central nervous system. Based on the above findings, it is likely that the wider the distribution of spheroids, the more extensive the occurrence of LBs in patients with NBIA-1 with LBs.[13] In our case, the abundant axonal spheroids in the subthalamic nucleus and dentate nucleus were also consistently

negative for α-synuclein. Similar negative findings were also reported by Wakabayashi *et al.*,[13] Saito *et al.*,[14] and Zarranz *et al.*[15] This negative finding is inconsistent with the observations made by several authors who have found that the axonal spheroids in NBIA-1 are strongly positive for α-synuclein antibodies.[10,12] Thus, NBIA-1 has various pathological phenotypes according to tau or α-synuclein pathology.

On the other hand, previously reported postmortem examinations consistently present the coexistence of two main histological hallmarks, namely, axonal spheroids and excessive brain iron accumulation. Some authors have favored the view that axonal spheroids are the primary pathological process,[7,40] leading to the classification of NBIA-1 within the spectrum of the diffuse axonal degenerations (Seilterberger disease). Other authors have emphasized that brain iron accumulation is not merely a histological hallmark of NBIA-1 but the first pathogenic abnormality.[8,41,42] In 2001, Koeppen *et al.* reported that double-labeling of ferritin, as an indirect marker of intracellular iron, and phosphorylated neurofilament protein, revealed the close proximity of ferritin-reactive microglial and oligodendroglial processes to tightly packed axons. It was proposed that a primary axonal disorder allows the seepage of iron into the axoplasm, although iron may also contribute to axonal damage.[43] Futhermore, in 2003, Hayflick *et al.* revealed 54 *PANK2* mutations among 123 patients from 98 families with NBIA-1.[41] Pantothenase kinase is a rate-determining enzyme in coenzyme A biosynthesis. It can also lead to a concentration of cysteine in the basal ganglia, and then to an accumulation of iron in these areas.[5]

Based on the above neuropathological perspective, the evidence favors the view that iron accumulation is the first step in the pathological process of NBIA-1. In our review, NBIA-1 has various pathological phenotypes according to tau or α-synuclein pathology. These findings support the possibility that they are a nonspecific cytoskeletal abnormality in NBIA-1, and should not be taken as the basis for its nosological classification. However, further clinicopathological and genetic studies of similar cases will be necessary to characterize this disease entity fully and determine its etiopathology.

ACKNOWLEDGEMENTS

We would like to thank Ms. M. Onbe (Department of Neuropsychiatry, Okayama University Graduate School of Medicine and Dentistry) for her excellent technical assistance. Brain tissues were obtained from the Research Resource Network, which was supported by a Research Grant for Neurological and Mental Disorders from the Ministry of Health, Labour and Welfare, Japan.

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Psycho-Oncology
Psycho-Oncology **20**: 647–654 (2011)
Published online 7 March 2011 in Wiley Online Library (wileyonlinelibrary.com). **DOI**: 10.1002/pon.1945

Usefulness of pharmacist-assisted screening and psychiatric referral program for outpatients with cancer undergoing chemotherapy

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Received: 27 January 2010
Revised: 11 January 2011
Accepted: 25 January 2011

Abstract

***Objective*: Major depressive disorder (MDD) and adjustment disorder (AD) are common psychiatric disorders in cancer patients but are often overlooked in clinical oncology settings. We introduced a clinical screening program utilizing the Distress and Impact Thermometer (DIT) to identify MDD and AD in cancer outpatients receiving chemotherapy. This study assessed the usefulness of the screening program.**

***Methods*: Pharmacists administered the DIT to consecutive patients undergoing chemotherapy at an outpatient clinic. Psychiatric treatment was recommended to all the patients with positive screening results. The proportion of patients referred to the Psychiatric Service during the program period was then compared with that during a usual care period.**

***Results*: Of the 520 patients who started chemotherapy during the 6-month program period, 5.0% (26/520) were referred to the Psychiatric Service and 2.7% (15/520) were diagnosed as having MDD or AD. No statistically significant difference in the referral rates was observed between the two periods (2.7 vs 1.0%, $p = 0.46$). However, the period from the first chemotherapy treatment until the visit to the Psychiatric Service was significantly shorter during the program period than during the period of usual care (12.9±13.2 days vs 55.6±17.6 days, $p < 0.001$).**

***Conclusions*: The proportion of patients referred to the Psychiatric Service for the treatment of MDD or AD during the program period was not different from that during the usual care period. However, the program was useful for introducing psychiatric treatment at an earlier stage. Further modifications to the program to improve the referral rate are necessary.**

Keywords: cancer; oncology; major depressive disorder; adjustment disorder; chemotherapy; outpatients

Introduction

Major depressive disorder (MDD) and adjustment disorder (AD) are the most distressing and prevalent psychiatric disorders in patients with cancer [1]. The prevalence of MDD in patients with cancer has been reported to be 3–7%, while that of AD has been reported to be 4–35% [2–7]. Several studies have indicated that MDD and AD have a serious negative impact on the quality of life of patients [8] and are related to severe suffering, poor adherence to treatment recommendations [9], requests for early death or euthanasia [10–13], suicidal ideation [14], suicide [15] and the psychological distress of family members [16,17].

Evaluating the psychological distress of cancer patients is extremely difficult for oncology medical staff, and psychological distress is often underrecognized in clinical oncology settings [18–20]. Once recognized, it is often too late to introduce pharmacotherapy to improve the depressive symptoms of advanced cancer patients [21]. As psychotherapy [22] and pharmacotherapy [23] are known to be effective means of treating these disorders, a screening strategy to enable early detection and treatment for depression in cancer patients

seems like a reasonable step in treating this condition.

Previous studies have confirmed the efficacy of psychological screening strategies for depression in primary-care settings, with programs combining psychological screening with referrals to mental health specialists appearing to be the most powerful intervention [24,25]. In oncology settings, although less empirical evidence is available than for primary-care settings, cancer patients are known to have a high risk of depressive disorders (mainly MDD and ADs according to the Diagnosis and Statistical Manual IV (DSM-IV) criteria) [2–7]. Psychological screening can detect depressive disorders in cancer patients [26], and psychological interventions can alleviate the depressive disorders that are detected by psychological screening [27–29]. Together, this evidence suggests the efficacy of psychological screening for cancer patients, and guidelines such as those published by the National Comprehensive Cancer Network [30] and the National Institute for Health and Clinical Excellence have been recommended as clinically feasible practices for combining screening with interventions from mental health specialists for the treatment of psychological distress in cancer patients.

We previously examined the usefulness of psychological screening for cancer patients using the Distress and Impact Thermometer (DIT) [31]. Furthermore, we have developed and introduced a Nurse-Assisted Screening and Psychiatric Referral Program (NASPRP) for inpatients [26].

With the recent introduction of chemotherapy being performed in outpatient clinics, the amount of time that physicians and medical staffs spend with their outpatients has been drastically reduced compared with inpatients [32]. Thus, we must modify the NASPRP for use in outpatient clinics.

We have planned two types of screening program for ambulatory patients. One program, reported in the present study, targets patients undergoing chemotherapy by cooperating with pharmacists. The other program, which was reported in a previous article [33], is a general outpatient model involving a collaboration among nurses, primary oncologists, and Psychiatric Services.

The primary aim of the current study was to examine preliminarily the usefulness of our screening program modified for outpatients with cancer who are undergoing chemotherapy. We hypothesized that the use of this screening program in outpatient clinics would result in a higher rate of the referral of cancer patients to the Psychiatric Service and earlier psychiatric referral for the treatment of major depressive and ADs. The secondary aim was to evaluate the feasibility of administering the DIT in an outpatient clinic setting.

Materials and methods

Modification of the screening program for use in an outpatient clinic setting

First, we modified the NASPRP to suit an outpatient clinic setting. As the utility of the NASPRP was limited by the amount of time required for nurses to administer the DIT, the NASPRP was adjusted as explained below. First, pharmacists were asked to administer the screening program. Pharmacists routinely explain the effects and adverse effects of first or new chemotherapy regimens to cancer patients undergoing chemotherapy in an outpatient setting. Therefore, pharmacists are in close communication with cancer patients. Second, to shorten the explanation time, we prepared a brief pamphlet introducing the Psychiatric Service and screening program; a detailed pamphlet describing the self-management of mental health was also prepared.

Before implementing the screening program, all the pharmacists attended a 2-hour lecture given by a trained psychiatrist regarding the epidemiology, impact, risk factors, under-recognition, and appropriate management of psychiatric disorders in cancer patients. Additionally, the pharmacists underwent role-play training to learn how to implement the DIT and to give recommendations for psychiatric referral.

Distress and impact thermometer

The DIT uses a two-item, self-administered rating scale. Our group developed the DIT by adding the Impact Thermometer to the Distress Thermometer [31,34,35]. Each 'distress' and 'impact' question is scored using an 11-point Likert scale, with scores ranging from 0 to 10 and a high score indicating an unfavorable status.

Screening program procedure

The screening program was implemented between April and September 2007, at the outpatient treatment center of the National Cancer Center Hospital East (NCCH-E). Consecutive cancer patients beginning chemotherapy at the outpatient treatment center of the NCCH-E during this period were enrolled. Pharmacists routinely provide instructions regarding new chemotherapy regimens to patients beginning chemotherapy; on such occasions, the pharmacists also provided information regarding the Psychiatric Service using a brief pamphlet and invited the patients to complete the DIT. The pharmacist then completed the screening program sheet, which is a record of the patient's DIT scores, age, sex, cancer site, cancer stage, and Eastern Cooperative Oncology Group (ECOG) performance status. The screening questionnaires

DOI: 10.1002/pon

were administered again during the second visit of each patient beginning a new chemotherapy regimen. If a patient scored equal to or more than each cut-off point (≧4 for distress and ≧3 for impact) the screening result was regarded as positive.

The pharmacist in charge recommended a consultation with the Psychiatric Service to all the patients with a positive screening result. If a patient accepted the recommendation, the patient visited the Psychiatric Service and was examined by trained psychiatrists using a clinical diagnostic interview based on the DSM-IV (published by the American Psychological Association) criteria. If a DIT-positive patient refused a consultation, the pharmacist gave them a detailed pamphlet regarding the self-management of mental health. However, if the patient was suspected of having severe psychological distress, the pharmacist discussed the case with the psychiatrists and monitored the patient carefully under their supervision. In addition, the pharmacist provided a brief feedback on the patient's medical chart regarding the screening results.

During the screening program, the pharmacists and psychiatrists held monthly meetings to discuss any issue that emerged.

Data collection

Clinical data were extracted from the patients' medical charts and the computerized database of the electronic medical record at NCCH-E.

Measures

The usefulness of the screening program was evaluated by calculating the proportion of patients referred to the Psychiatric Service and treated for major depressive or AD among all the outpatients who had begun a new chemotherapy regimen within 3 months of their visit to the outpatient clinic. The number of days from the first chemotherapy treatment to the first visit to the Psychiatric Service was examined as an indicator of early detection and the early introduction of treatment. The number of patients referred to psychiatrists and the number of days from the first chemotherapy treatment to the first visit to the Psychiatric Service were confirmed using the computerized database of the electronic medical record at NCCH-E, which provides a definitive record of the dates of chemotherapy and psychiatry consultation. The feasibility of the DIT in a clinical oncology outpatient setting was evaluated by calculating the proportion of patients that underwent screening, which was the portion of patients who completed the DIT on their first or second visit to the outpatient clinic among all the outpatients who began a new chemotherapy regimen.

Sample size estimation

We estimated that the psychiatric referral rate (%) for the treatment of major depressive and ADs in patients with cancer was 1% during a usual care period (January 2005–December 2005) and that a 5% improvement after the implementation of the screening program would be reasonable. At a 5% significance level (two-sided Student t-test) and a 80% power, a sample size of 332 patients was needed for each period. In our hospital, approximately 70 patients began receiving chemotherapy at the outpatient treatment center every month. Thus, we concluded that a 6-month study period would be adequate for both the screening program and the period of usual care.

Patients treated during the screening program

All consecutive cancer patients who began chemotherapy at the outpatient treatment center of NCCH-E in Japan between April 1 and September 30, 2007 (program-period) were included in the screening program.

Patients during the usual care

All consecutive cancer patients who began chemotherapy at the outpatient treatment center of NCCH-E between April 1 and September 30, 2006 (usual care-period) received usual care.

Analysis

The current study was conducted using a retrospective cohort analysis comparing patients treated during the program-period with historical control data gathered during the usual care-period. The characteristics (age, sex, and cancer site) of the patients treated during the program-period and those treated during the usual care-period were compared using a chi-square test. The usefulness of the screening program was evaluated by comparing the proportion of patients referred to the Psychiatric Service for major depressive or AD during the program-period and the usual care-period using a chi-square test. As an index for early treatment introduction, we compared the number of days from the first chemotherapy treatment until the first visit to the Psychiatric Service for the treatment of major depressive or AD during the program-period and the usual care-period using a Student t-test. All tests were two-tailed. All analyses were performed using SPSS 14.0 J for Windows statistical software (SPSS Japan Institute, Tokyo, Japan).

The administration of the DIT and the recommendations for psychiatric referral were performed based on clinical need, and all other data were obtained as part of routine clinical assessments.

DOI: 10.1002/pon

Therefore, the present study required very little deviation from standard clinical practice. As this study was a retrospective review of the program-period and the usual care-period for the purpose of comparing two types of clinical practices, the written consent of the patients was not obtained.

The medical record data used in this study were collected and analyzed after approval from the Institutional Review Board of the National Cancer Center, Japan. All data were de-identified and analyzed in aggregate form.

Results

Patient characteristics

During the program-period, 520 patients began receiving chemotherapy in an outpatient setting at the NCCH-E; 478 patients started receiving chemotherapy in an outpatient setting during the usual care-period. As shown in Table 1, the age, sex, and cancer sites of the patients treated during each period were comparable.

Usefulness of the screening program

Of the 478 patients who started chemotherapy during the usual care-period, 9 patients were referred to the Psychiatric Service; the referral rate was 1.9% (9/478). Of the nine patients that were referred, five patients were diagnosed as having MDD ($n = 3$) or ADs ($n = 2$) and began receiving treatment for these conditions. Two of the other four patients did not fulfill the DSM-IV diagnostic criteria for any psychiatric disorder, and the other two patients were diagnosed as having akathisia and sleep disorder, respectively. Thus, the proportion of patients referred for major depressive or ADs was 1.0% (5/478). The number of days from the first chemotherapy treatment to the first visit to the Psychiatric Service for the treatment of major depressive or AD was 55.6 days (SD = 17.6 days).

Figure 1 shows the process of the screening program. Of the 520 patients who started chemotherapy during the program-period, 26 patients were referred to the Psychiatric Service and were examined by psychiatrists; the referral rate was 5.0% (26/520). Of the 26 patients that were referred, 15 patients were diagnosed as having MDD ($n = 2$) or ADs ($n = 13$) and began receiving treatment for these conditions. Nine of the other eleven patients did not fulfill the DSM-IV diagnostic criteria for any psychiatric disorder, and the other two patients were diagnosed with delirium and sleep disorder, respectively. Thus, the proportion of patients referred for major depressive or ADs was 2.7% (15/520). The number of days from the first chemotherapy treatment to the first visit to the Psychiatric Service for the treatment of major depressive or AD was 12.9 days (SD = 13.2 days).

The proportion of patients referred to the Psychiatric Service and treated for a major

Table I. Characteristics of outpatients who received chemotherapy between April 1, 2007 and September 30, 2007 (program-period: $n = 520$) or April 1, 2006 and September 30, 2006 (usual care-period; $n = 478$) at NCCH-E

	No. of patients (%)		
	During program-period	**During usual care-period**	***p*-Value**
Total patients	520 (100)	478 (100)	
Age (mean ± SD)	61.4 ± 10.8	62.8 ± 10.9	0.66
Male (%)	281 (54.0)	271 (56.7)	0.40
Primary cancer site			0.18
Lung	114 (21.9)	86 (18.0)	
Colon, rectum	111 (21.4)	71 (14.9)	
Breast	82 (15.8)	56 (11.7)	
Hematopoietic and lymphatic tissue	56 (10.8)	72 (15.1)	
Stomach	39 (7.5)	40 (8.4)	
Pancreas	39 (7.5)	63 (13.2)	
Esophagus	24 (4.6)	31 (6.1)	
Liver, bile duct, gall bladder	16 (3.0)	30 (6.3)	
Head and neck	15 (2.9)	13 (2.7)	
Other	24 (4.6)	16 (3.3)	
Stage			
IV or recurrent	349 (67.1)		
III	108 (20.8)		
II	50 (9.6)		
I	13 (2.5)		
Performance status (ECOG)			
0	370 (71.1)		
1	136 (26.2)		
2	13 (2.5)		
3	1 (0.2)		
4	0 (0)		

DOI: 10.1002/pon

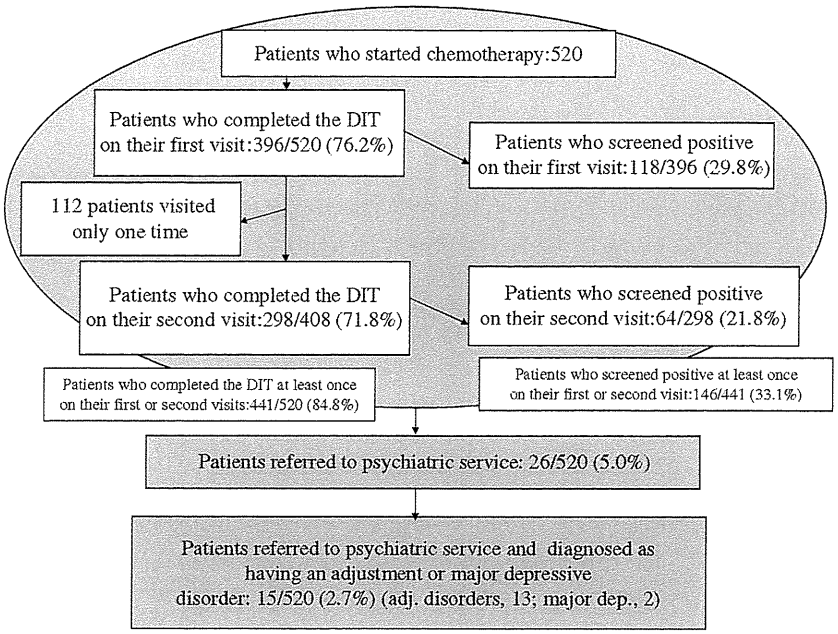

Figure 1. Number of patients screened and referred

depressive or AD was not significantly different between the two periods (2.7% during the program-period vs 1.0% during the usual care-period, $p = 0.46$). However, the number of days from the first chemotherapy treatment until the first visit to the Psychiatric Service was significantly shorter during the program-period than during the usual care-period (12.9 ± 13.2 days vs 55.6 ± 17.6 days, respectively; $p < 0.001$). In addition, the proportion of patients referred to the Psychiatric Service that did not fulfill the DSM-IV diagnostic criteria for any psychiatric disorder was not significantly different between the two periods (1.7% during the program-period vs 0.6% during the usual care-period, $p = 0.12$).

Feasibility of the screening program

During the program-period, 396 patients completed the DIT during their first visit to the outpatient clinic; thus, 76.2% of the patients participated in the screening. Of the 396 patients who were screened during their first visit to the outpatient clinic, the screening results were positive in 118 patients, yielding a positive screening rate of 29.8%. The mean levels of the distress and impact scores on the DIT were 3.5 (SD = 2.8) and 2.2 (SD = 2.5), respectively. Of the 520 patients treated during the program-period, 408 patients made a second visit to the outpatient clinic for chemotherapy. Of these 408 patients, 298 patients completed the DIT; thus, 71.8% of the patients participated in the screening. Of the 298 patients who were screened during their second visit to the outpatient clinic, the screening results were positive in 64 patients, yielding a positive screening rate of 21.8%. The mean levels of the distress and impact scores on the DIT were 2.4 (SD = 2.4) and 1.9 (SD = 2.3), respectively. Five to ten minutes were required for the pharmacists to provide information about the Psychiatric Service, invite the patient to complete the DIT, and recommend a consultation with the Psychiatric Service.

Discussion

This preliminary study examined the usefulness and feasibility of a modified psychological screening and intervention program administered by pharmacists to cancer patients receiving chemotherapy in an outpatient clinic. Unexpectedly, the proportion of patients referred to the Psychiatric Service and treated for major depressive or ADs was not significantly different between the program-period and the usual care-period. However, the number of days between the first chemotherapy treatment and the first visit to the Psychiatric Service for the treatment of a major depressive or AD was significantly shorter during the program-period than during the usual care-period.

A potential harm of the screening intervention is false-positive patients reaching the Psychiatric Service. However, the proportion of patients referred to the Psychiatric Service that did not fulfill the DSM-IV diagnostic criteria for any psychiatric disorder was not significantly different between the two periods.

We previously reported that our original program for screening cancer inpatients (NASPRP) achieved a higher referral rate than that obtained during usual care [26], but the presently reported

modified screening program for outpatients did not. One reason for this difference might be the study setting. Inpatients must remain in the hospital all day long, and if they accept a psychiatric referral, the psychiatric consultation occurs at their bedside. The presently reported screening program was intended for use in an outpatient clinic setting for patients who do not spend lengthy periods of time within a hospital. To receive psychiatric treatment in an outpatient clinic setting, the patient must quickly move to another room after completing their chemotherapy, and this burden might be a barrier to the acceptance of psychiatric referral. Second, adverse effects of chemotherapy such as fatigue and nausea on the day of treatment might make it difficult for patients to accept a psychiatric referral. Finally, the actual incidence of psychiatric disorders was relatively low, as the positive screening rate in this outpatient program was lower than that obtained using the NASPRP (29.8, 21.8 vs 49.6%).

The 'Distress Screening Program in Ambulatory Care' (DICPAC program) is a general outpatient screening model that has achieved a relatively high referral rate [33]. One difference between the DICPAC program and the presently reported screening program is the target population. The DISPAC program was used almost exclusively for female patients with breast or gynecological cancer. Female patients might be more likely to accept a referral to the Psychiatric Service than male patients [26]. Second, the attending oncologist provided the referrals to the Psychiatric service in the DISPAC program. The recommendations of physicians might have a larger impact on patients than the recommendations of pharmacists, regardless of the index disease [36]. Lastly, similar to the difference between the present screening program and the NASPRP, the positive screening rate obtained using this program was lower than that obtained using the DISPAC program (29.8, 21.8 vs 37.0%).

The positive screening rate was 29.8% at the time of the first visit and 21.8% at the time of the second visit, yet most of the positively screened patients did not accept the referral to the Psychiatric Service. Although we did not assess the prevalence of MDD and ADs in the targeted population, it is very likely that most of the patients with MDD and ADs would remain untreated, even if the screening program was introduced. In addition, patients who refused screening may contain the larger fraction of those in need of the Psychiatric Service. Thus, the presently reported screening program requires further improvement, and further study is needed to optimize the applicability of psychiatric consultations by addressing factors that promote the acceptance of psychiatric referral. Specifically, the communication skills of the pharmacists might need to be further strengthened. The changes in staff involving mental health screening may have significant effect. And we may need flag for clinicians those who refused screening for further assessment using other tools. In addition, mental health specialists might need to attend the bedsides of patients during their treatment in the outpatient clinic to reduce distance barriers to psychiatric treatment.

An additional but important finding was the feasibility of administering the DIT to outpatients with cancer. The percentages of patients who completed the DIT during their first and second visits to the outpatient clinic were 76.2 and 71.8%, respectively. In our previous report, 86% of the inpatients completed the DIT in a clinical oncology setting. Another study has reported that the Hospital Anxiety and Depression Scale was administered to 70% of oncology patients [37]; thus, the completion rate in the present study was marginally higher. Compared with these previous reports, the current results suggest that the DIT might be useful as a brief screening tool for detecting psychological distress in cancer patients undergo chemotherapy in busy outpatient settings. The reasons why some patients did not complete the DIT in this study are unknown.

This study has several limitations. First, this study was a retrospective analysis that compared available historical data and our experience with clinical intervention. The comparison group was not systematically controlled to ensure comparability, and some bias in patient selection might have occurred. Second, the results of this study must be considered provisional, as this study was performed at a single cancer center hospital. Our group must be careful in generalizing these results to other oncology settings. Third, although we made the clinical diagnoses according to the DSM-IV criteria, this method is less robust than a structured diagnostic interview. Some possibility of assessment bias also exists, since the four psychiatrists who diagnosed the referred patients were associated with this study. Furthermore, we were unable to assess the interrater reliability of the DSM-IV diagnosis. Fourth, although the screening program resulted in the earlier introduction of treatment for major depressive and ADs in outpatients with cancer, this result is a surrogate endpoint, and its clinical significance remains unclear. Further demonstration that these processes result in a better patient outcome, such as an improvement in the patients' quality of life or the successful treatment of major depressive and ADs, is needed.

In conclusion, a clinical screening program administered by pharmacists that uses the DIT to identify major depressive and ADs in cancer outpatients receiving chemotherapy and introduces them to psychiatric treatment was feasible and

DOI: 10.1002/pon

useful for the early introduction of treatment, but the proportion of patients referred for the treatment of major depressive or ADs was not different from that obtained during usual care. Thus, further modification of the present program to overcome barriers to introducing patients with positive screening results to the Psychiatric Service, resulting in the alleviation of psychological distress and a better quality of life, is needed.

Acknowledgements

We express our special gratitude to all the pharmacists and nurses in the outpatient clinics who cooperated with this study. This work was supported in part by a Grant-in-aid for Cancer Research, Clinical Cancer Research, and Third Term Comprehensive 10-year Strategy for Cancer Control, from the Japanese Ministry of Health, Labor and Welfare.

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DOI: 10.1002/pon

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2011;41(3)380–385
doi:10.1093/jjco/hyq213
Advance Access Publication 24 November 2010

Psychiatric Disorders in Patients Who Lost Family Members to Cancer and Asked for Medical Help: Descriptive Analysis of Outpatient Services for Bereaved Families at Japanese Cancer Center Hospital

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Received August 2, 2010; accepted October 22, 2010

Objective: There have been no previous studies about consultation of the bereaved who have lost a loved one to cancer and ask for medical help. The aim of this study was to investigate their basic characteristics and their psychiatric disorders.
Methods: A retrospective study using clinical and background data obtained over 30 months (from April 2007 to September 2009) was conducted at outpatient services for bereaved families at the Department of Psycho-Oncology at Saitama Medical University International Medical Center, Japan.
Results: During the period of investigation, 51 patients underwent consultation. The patients were frequently female ($P < 0.0001$) and the spouse of the deceased. Regarding the psychiatric diagnoses, major depression was the most common (39%), followed by adjustment disorders (28%).
Conclusions: This study revealed basic characteristics and psychiatric disorders of the bereaved who asked for medical help. Most of the patients were women (86.3%) and 86.3% of them received a psychiatric diagnosis. This information is important for both physicians and psychologists since the bereaved who have lost a loved one to cancer often ask for medical help in clinical settings.

Key words: cancer – bereaved family – consultation – psychiatric diagnosis – retrospective study

INTRODUCTION

Cancer is a disease that is increasing the awareness of mortality among the Japanese. This is due to the fact that one out of three Japanese dies of cancer, which has been the most common cause of death since 1981, and that there has been an increase in the number of fatalities (1). Not only patients but also their family members are affected by cancer. There have been several studies about the psychiatric consultation of cancer patients (2–5) and relatives of cancer patients (6,7) from the view of psycho-oncology. These studies suggest that cancer patients and their families suffer from physical and psychiatric disorders.

If a patient dies, the 'family of the patient' becomes a 'bereaved family'. The death of a person (spouse or close relative, in particular) is a stressful event in life (8). Bereavement, defined as 'other conditions that may be a focus of clinical attention' by the Diagnostic and Statistical Manual of Mental Disorders, 4th edn (DSM-IV-TR), of the American Psychiatric Association (9), from a medical viewpoint, is known to cause a variety of physical and mental disorders as well as increased mortality.

A study reported a 40% increase in mortality, of which 75% was due to heart disease, among males aged 54 years or older within 6 months of a wife's death (10). There has also been a report of increased mortality in females within 3 months of them losing their husbands (11). Other studies have also demonstrated high mortality rates in those who experience the death of a spouse (12,13).

As for physical disorders, there have been reports of heart trouble and high blood pressure, which can increase the risk of many different physical illnesses (14,15).

As for behaviors, around one-third of widows reported drinking alcohol for relief of grief (16), whereas changes in smoking habits and eating habits have also been reported (14).

As for psychiatric and psychological effects, an increased risk of suicide within 1 year of losing a loved one has also been reported (17–19). In a survey of the prevalence of depression after bereavement reported by Clayton et al., 42 and 16% of patients 1 month and 1 year after bereavement met the criteria for depression, respectively. Forty-seven percent of recently bereaved families experienced symptoms meeting the criteria for depression, while this was only 8% at 1 year and 11% overall in a control group, showing that the incidence in bereaved families was very high (20,21). It was also reported that the prevalence of depression in bereaved families was high: 24, 23, 16 and 15% at 2, 7, 13 and 25 months after bereavement, respectively (22). Furthermore, bereavement is one of the most important risk factors for depression among the elderly (23).

As already mentioned, if someone dies, people who were close to the deceased will become vulnerable to a variety of physical and psychological illnesses. Even if they undergo consultations, most patients do not name their distress over the death as a chief complaint to physicians and the relationship between their experience and the illness is often overlooked (24); therefore, appropriate help would not be provided for the bereaved when they need it.

However, the background and clinical status of bereaved families of cancer patients who ask for medical help have not previously been reported. It is necessary to describe the profiles of the bereaved who attend outpatient services for the bereaved.

The purpose of the present study was to investigate the characteristics, reasons for consultation and psychiatric disorders in patients who asked for medical help after the death of a loved one with cancer.

PATIENTS AND METHODS

Psychiatric Interventions at Outpatient Services for the Bereaved at Comprehensive Cancer Center, Saitama Medical University International Medical Center

Saitama Medical University (SMU) established a Comprehensive Cancer Center attached to the International Medical Center (IMC) and organized a cancer board. This is the first cancer center affiliated to a university hospital in Japan. The Department of Psycho-Oncology is associated with the cancer board and provides two main services, one for outpatients and one for inpatients. In addition, the Department of Psycho-Oncology provides services for psychologically distressed family members.

As mentioned above, the bereaved are vulnerable to a variety of physical and psychological disorders. Therefore, the International Medical Center, Saitama Medical University (SMUIMC), started an 'outpatient service for bereaved families' at the time of its establishment in April 2007, with the aim of alleviating these distresses in the bereaved. This service is designed to 'help those who have lost a loved one to cancer live a better life', which is in line with the concept of 'postvention' proposed by Schneidman (25), and 'palliative care' as defined by the World Health Organization (WHO). WHO has included the following in the objectives for palliative care: to offer a support system to help the family cope during the patient's illness and in their own bereavement. The provision of palliative care increases as the person nears the end of life and includes support for the family during this entire period. After the patient dies, bereavement counseling for family and friends is also important (26). It provides outpatient services for the bereaved faced with psychological, social, physical and other problems, on the basis of the biopsychosocial model proposed by Engel (27).

The biopsychosocial model evaluates all the factors contributing to both illness and patienthood, rather than giving primacy to biological factors alone. This is the first outpatient service for the bereaved that provides psychological and social care and psychiatric treatment in Japan. This service is currently provided by two psychiatrists and two psychologists for those who have lost their spouse, parent, child or sibling to cancer.

Subjects and Procedure

We conducted a retrospective survey of people consulting the outpatient services for the bereaved of SMUIMC for 30 months between April 2007 and September 2009. Bereaved individuals were defined as first-degree relatives (spouse, parents and children) and siblings of the deceased who had died of cancer.

In this investigation, we mainly used patient background data, regarding age, gender, relationship to the deceased, cancer site of the deceased, reason for consultation, the period before consultation and psychiatric diagnosis, stored in databases, as well as we referred to medical records as necessary. Psychiatric diagnoses were evaluated according to DSM-IV-TR (9).

Statistical analyses were conducted using the SPSS 17.0 package. The differences among the data were compared by an analysis of means using χ^2 test.

This study was approved by the Institutional Review Board of SMUIMC (08-029).

Table 1. Characteristics of the patients

	Total ($n = 51$), n (%)
Age (years)	
Mean ± SD	51.3 ± 14.7 (median:49)
Range	17–76
Gender	
Male	7 (13.7)**
Female	44 (86.3)**
Relationship to deceased	
Spouse	26 (51.0)
Parent	16 (31.4)
Child	7 (13.7)
Sibling	2 (3.9)
Employment status	
Full time	23 (45.1)
Part time	4 (7.8)
Housewife	21 (41.2)
Retired	1 (2.0)
Student	2 (3.9)
Living arrangement	
Alone	19 (37.2)
Not alone	32 (62.8)
History of any psychiatric disorder	
Present	2 (3.9)
Absent	49 (96.1)
Cancer site of deceased	
Lung	12 (23.5)
Pancreas	7 (13.7)
Stomach	6 (11.8)
Hematopoietic	5 (10.0)
Brain	5 (10.0)
Head and neck	3 (6.9)
Breast	3 (6.9)
Colon	3 (6.9)
Female genitalia	2 (4.0)
Unknown	2 (4.0)
Others	5 (10.0)

**Differences between groups were statistically evaluated with χ^2 test ($P < 0.01$).

Table 2. Characteristics of consultation

Reason for consultation (multiple choices)	n (%)
Distress	32 (62.7)
To talk to someone	7 (13.7)
Involved in trouble	5 (9.8)
Physical and psychiatric symptoms	3 (5.9)
Difficulty in concentrating	3 (5.9)
Others	4 (8.0)
Period	13.14 ± 22.43 months

Period: mean time between the loved one's death and the first consultation.

RESULTS

Characteristics of the Patients

During the period of investigation, 949 patients consulted the Department of Psycho-Oncology. Of these patients, 51 (5.4%) had relatives who had died of cancer, which had led them to consult bereaved family services. Their ages ranged from 17 to 76 years (mean ± SD: 51.3 ± 14.7; median: 49). There were 7 males (13.7%) and 44 females (86.3%). There was a significant difference among the consultees between the numbers of males and females ($P < 0.0001$; Table 1).

The most common relationship to the deceased was as a spouse ($n = 26$, 51.0%), followed by parent ($n = 16$, 31.4%), child ($n = 7$, 13.7%) and a sibling ($n = 2$, 3.9%).

Among the background characteristics of the patients, the most common cancer site in the deceased was lung ($n = 12$, 23.5%), followed by pancreas ($n = 7$, 13.7%) and stomach ($n = 6$, 11.8%).

Characteristics of Consultation

The most common reason for consultation was distress from the bereavement, which was recognized in 22 patients (62.7%). Seven patients (13.7%) wanted to talk to someone. Five patients (9.8%) needed help because they had trouble with their relatives, friends and neighbors after the death of a loved one. Three patients (5.9%) showed physical and psychiatric symptoms like insomnia and generalized fatigue. Three patients (5.9%) had difficulty in concentrating on their work (Table 2).

The mean time between the loved one's death and the first consultation (period) ranged from 1 to 108 months ($n = 51$, mean ± SD: 13.1 ± 3.2, median: 5.0), with 24.5% of consultations being carried out within 1 month, 44.9% within the following 12 months and 22.4% within the following 24 months.

Psychiatric Diagnosis

Psychiatric diagnoses of these patients are summarized in Table 3. Over 80% of the bereaved who consulted 'outpatient services for the bereaved' received a psychiatric diagnosis.

Major depression, the most common diagnosis, was observed in 20 patients (39.2%). It was also the most common diagnosis in consultation both within 1 year after the death and over 1 year after the death. There were no significant differences in the ratio of major depression to other psychiatric disorders with regard to the period before the start of consultation (within 1 year after the death and over

Table 3. Psychiatric diagnoses of the patients

Psychiatric diagnosis (multiple choices)[a]	Total ($n = 51$), n (%)	The period before consultation (months)	
		0–12 ($n = 34$), n (%)	>12 ($n = 17$), n (%)
Major depressive disorder	20 (39.2)	15 (44.1)	5 (29.4)
Adjustment disorder	14 (27.5)	9 (26.5)	5 (29.4)
Bereavement reaction	6 (11.8)	5 (14.7)	1 (5.9)
Dissociative disorder	1 (2.0)	1 (2.9)	0 (0)
Generalized anxiety disorder	2 (3.9)	0 (0)	2 (11.8)
Post-traumatic stress disorder	1 (2.0)	1 (2.9)	0 (0)
Others	2 (3.9)	0 (0)	2 (11.8)
No diagnosis	7 (13.7)	4 (11.8)	3 (17.6)

[a]Psychiatric diagnosis is defined by DSM-IV (9).

Table 4. Psychiatric intervention

Psychiatric intervention (multiple choices) ($n = 51$)	n (%)
Psychotropic medication	31 (60.8)
Psychological intervention	43 (84.3)

1 year) ($P = 0.24$). Adjustment disorder was the next most common diagnosis and was observed in 14 patients (27.5%), and bereavement reaction was the third most common and was observed in 6 patients (11.8%).

Other psychiatric diagnoses were generalized anxiety disorder ($n = 2$, 4.0%), post-traumatic stress disorder (PTSD) ($n = 1$, 2.0%), dissociative amnesia ($n = 1$, 2.0%) and schizophrenia ($n = 1$, 2.0%). Seven patients (13.7%) had no diagnosis.

Six patients (11.8%) exhibited the complication of dissociative amnesia during the treatment, with major depression ($n = 2$, 4.0%), adjustment disorder ($n = 2$, 4.0%) or bereavement reaction ($n = 2$, 4.0%). Three patients (5.9%) exhibited the complication of panic disorder during the treatment, with major depression, adjustment disorder and bereavement reaction (data not shown).

Psychiatric Interventions

Thirty-one patients (60.8%) were treated with medication. The following psychotropic drugs were prescribed: benzodiazepines ($n = 8$, 15.7%) or antidepressants ($n = 8$, 15.7%) or, more frequently, the two in combination (benzodiazepines + antidepressants, $n = 14$, 27.5%). One patient (2.0%) was prescribed antidepressants and neuroleptics (Table 4).

Forty-three patients (84.3%) received supportive psychotherapy, cognitive behavioral therapy or unstructured counseling as psychological intervention.

DISCUSSION

This report provides basic information about the bereaved who have lost a loved one to cancer and ask for medical help.

We found that most of the patients who consulted 'outpatient services for bereaved families' at SMUIMC were women. Their characteristics are similar to those of individuals in a study of the background characteristics of relatives of cancer patients (6,7). There are several reasons why women tend to consult bereaved family services. The presence of psychosocial problems or distress is predictive of consultation behavior in women, but not in men (28). Men tend to approach the provision of support negatively even though they perceive themselves as being hurt by the death of a loved one (29,30).

The lung was the most common cancer site and the stomach was the third most common cancer site among the deceased patients; this result is consistent with the most common causes of death among men in Japan (1), reflecting the high proportion of female spouses referred to the outpatient clinic for the bereaved, and it is similar to the findings in a study of the relatives of cancer patients (6,7).

In this study, over 80% of the bereaved who asked for medical help had psychiatric diagnoses. Major depression was the most common psychiatric diagnosis, followed by adjustment disorder. This indicates that most of the bereaved who asked for medical help need psychiatric and/or psychological intervention. Treatment of major depression, especially antidepressant therapy, among the bereaved with bereavement-related depression has been identified as being effective (31). Untreated major depression after bereavement carries the extra burden of prolonging the pain and suffering associated with grief (32). Therefore, more attention should be paid to these diagnoses without dismissing them as 'reasonable given the circumstances' (33). Early detection and appropriate recognition of depression in the bereaved should be encouraged. In addition, adjustment disorders are

often responsive to psychological interventions and positive changes in medical status. The distress that these subjects complained at consultation was not only about their loss, but also from another distress that was an offshoot of the death. This might also be a cause of these psychiatric disorders.

Some patients developed dissociative amnesia in addition to other psychiatric symptoms. Dissociative disorder was not recognized in a previous study of the bereaved who had lost a loved one to cancer. Similar symptoms are included in the criteria for the diagnosis of PTSD, such as an inability to recall an important aspect of the trauma (9). However, six patients did not fulfill the diagnostic criteria for PTSD. They suffered from the symptoms of dissociative amnesia because they could not remember certain things even though they wanted to, which could make them grieve even more. Further studies of dissociative amnesia in the bereaved might be required.

This study has several limitations. First, it was only conducted at one institution, the Comprehensive Cancer Center, and so institution bias may be a problem. Second, this study covered only 51 cases where bereaved family services were used. Further studies are necessary to investigate the findings in more detail. Third, this study was a retrospective study. A prospective study is necessary for more detailed investigation.

In conclusion, we investigated basic characteristics and psychiatric disorders among the bereaved who have lost a loved one to cancer and asked for medical help, using the DSM-IV criteria. The observations that most of the patients who consulted 'outpatient services for the bereaved' were women and over 85% of the patients received a psychiatric diagnosis are important findings. Almost 40% of the diagnoses involved major depression, which is highly responsive to pharmacologic interventions in psychiatric populations. Additionally, about one-third of the diagnoses were adjustment disorders, which are often responsive to psychological interventions and positive changes in medical status. This information is important for both physicians and psychologists since the bereaved who have lost a loved one to cancer often consult and ask for help in clinical settings. In addition, we have to improve our ability to screen for and recognize these factors among the bereaved at an early stage. The present results revealed that appropriate care is necessary for the bereaved who have lost family members to cancer and ask for medical help, and we have to recognize them in clinical settings.

Funding

This study was supported by the Third-Term Comprehensive 10-Year Strategy for Cancer Control and Research of the Japanese Ministry of Health, Labour and Welfare and Grant-in-Aid for Scientific Research.

Conflict of interest statement

None declared.

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