

PREDICTING MAJOR DEPRESSION IN BRAIN TUMOR PATIENTS

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SUMMARY

Very few studies have been performed utilizing DSM criteria to diagnose major depressive disorder (MDD) in adult brain tumor patients. This study aimed to diagnose MDD in this population using DSM-IV criteria.

Eighty-nine adult brain tumor patients were examined in an ambulatory neuro-oncology clinic setting using a structured psychiatric interview which followed current DSM-IV diagnostic criteria for MDD. This sample was interviewed and evaluated on a one-time basis. The patients were referred for evaluation on a consecutive basis. Multiple regression was used to model critical independent variables to predict MDD.

Twenty-eight percent of the sample ($N = 89$) were found to have major depressive disorder using DSM-IV criteria. Key predictors of MDD included frontal region of tumor location ($p = 0.001$), combined sadness and lack of motivation symptoms ($p = 0.0001$), and family psychiatric history ($p = 0.006$). The multiple regression models account for 37% of variance in predicting MDD ($R^2 = 0.37$).

A substantially higher incidence of MDD was found in this sample of adult brain tumor patients compared with other adult, ambulatory cancer patients previously evaluated with DSM criteria. The incidence of MDD was about triple that found in other published studies using DSM criteria. Copyright © 2002 John Wiley & Sons, Ltd.

INTRODUCTION AND LITERATURE REVIEW

An estimated 16,500 new patients were newly diagnosed with primary malignant brain (and other nervous system) tumors in the year 2000. For this same year, an estimated 13,000 individuals died from these tumors (ACS-2000). Standard treatment of primary brain tumors generally involves surgery in combination with radiation and/or chemotherapy. The degree of residual tumor following surgery has been shown to be an important predictor of survival (Shapiro, 1986). Radiation therapy has been found to double survival time, with recent advances in radiation therapy producing more focused delivery and less tissue damage and neurologic sequelae of treat-

ment (Nelson *et al.*, 1986; Scharfen *et al.*, 1992). Chemotherapy has also been shown to extend survival in primary brain tumor patients, with recent research focusing on the permeability of the blood–brain barrier in the delivery of chemotherapy to this patient population (Brain Tumor Collaborative Group, 1986; Inamura *et al.*, 1994). The usual psychiatric complications of cancer, with adjustment disorders being more frequent than organic mental disorders can be expected to be reversed in primary brain tumor patients. In a study of inpatient psychiatric consultations in a sample of primary brain tumor patients, 41% were diagnosed with organic mental disorders, vs. 26% being diagnosed with adjustment disorders (Passik and Ricketts, 1998). Delirium is a common psychiatric problem in primary brain tumor patients. It has been diagnosed in 25% of an inpatient sample of oncology patients, and in 85% of terminal cancer patients (Massie *et al.*, 1979, 1983). Direct causes include primary brain tumor, and indirect causes include

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infection, nutrition, electrolyte imbalance, and metabolic encephalopathy due to organ failure (Breitbart and Cohen, 1998). Dementia, unlike delirium in primary brain tumor patients, has a temporal onset which is subacute or chronic (Passik and Ricketts, 1998). Dementia has been sometimes found to have a radiation-induced etiology in a percentage of primary brain tumor patients. This has been found to be fatal in a large proportion of patients who develop such a syndrome (De Angelis *et al.*, 1989).

Primary brain tumor patients treated with radiation usually must be administered glucocorticoids to control cerebral edema induced by the radiation. Mood and anxiety syndromes may result from these drugs as well as delirium (Breitbart *et al.*, 1993; Boston Collaborative Drug Surveillance Program, 1972). An additional factor complicating organic mental status of patients with primary brain tumors is the threat of seizure disorders. For patients with brain metastases, seizures are the presenting symptoms in 20% of cases (Paillas and Pellet, 1975). Approximately 30–40% of such patients will experience a seizure at some point secondary to the development of brain metastases (Paillas and Pellet, 1975). This necessitates administering prophylactic anticonvulsants, which is complicated in that they also have sedating effects on the brain and can interact negatively with the steroids (Vermeulen and Aldenkamp, 1995; Passik and Ricketts, 1998).

Coping with the emotional challenges of brain tumors is a formidable task for all of these patients. Some previous studies have emphasized cognitive aspects over emotional ones (Weitzner and Meyers, 1997; Scheibel *et al.*, 1996). Others have focused on quality of life of brain tumor patients instead of emotional and cognitive aspects (Sneeuw *et al.*, 1997; Giovagnoli *et al.*, 1996; Weitzner *et al.*, 1996). A few articles have focused more directly on emotional reactions and adjustments to brain tumors (Salander *et al.*, 1996; Irle *et al.*, 1994). However, even these articles have not generated systematic data based on DSM-IV criteria (American Psychiatric Association, 1994). Given the relative absence of systematic, combined psychiatric/neurocognitive data on this population, the present study was performed. We hypothesized that in comparison with other studies using DSM interview criteria, brain tumor patients would show a higher incidence of major depression than patients with other types of cancer.

METHODS

Patients. Patients for this study were all in treatment for primary malignant brain disease in the UCLA Neuro-Oncology Program (NOP). The study included 89 consecutively referred patients to the psychiatrist and neuropsychologist on the NOP team. These referrals were made as part of the multi-disciplinary model of the clinic and were not made because of a special need for psychiatric care. Thus, these 89 patients were fully representative of the larger clinic matrix. All of these patients had previous treatment with surgery and/or radiotherapy. Sixty-six percent of the study patients were receiving single or multi-agent chemotherapy at the time of this study. None were receiving radiation therapy. Mean age of the patient group was 43.2 yr, with a range of 18–76 yr. The study patient/sex ratio compares very closely to that of the NOP matrix (i.e., Study, males 55% vs. NOP 54%). In terms of educational level, 32.9% had high school or less education, 47.4% had some college or a college degree, and 19.7% had education beyond a college degree. Males represented 55% ($N = 49$) and females 45% ($N = 40$) of the study population. Most of the patients were not employed (57.9%) at the time of interview and testing, while the remainder were employed full time (27.6%), or part time (14.5%). The majority of the patients (61.8%) were married/cohabiting, while the remainder were never married, separated/divorced, or widowed. Range of Karnofsky Performance Scale (KPS) ratings were from 40 to 100%. Breakdowns showed: 38%, KPS = 100; 26%, KPS = 90; 10%, KPS = 80; and 26%, KPS < 80.

Disease and treatment. Table 1 shows tumor locations and tumor types. The majority of patients in the present study matrix had frontal lobe tumors (42.6%) of the glioblastoma multiforme (GBM) type (43.8%). These tumor location sites and pathologic types were compared to the general population matrix of the NOP. The study sample compares closely to the clinic population on tumor location (Study, 42.6% frontal lobe tumors vs. 42% for the NOP) and on pathologic type (Study, 43% Glioblastoma vs. 38% for the NOP).

The patients in this study matrix had received multiple and varied treatments. These included:

Table 1. (a) Tumor location

Location	Left (<i>N</i>) (%)	Right (<i>N</i>) (%)	Total (<i>N</i>) (%)
Frontal	18 (20.7)	20 (23.0)	38 (42.6)
Temporal	10 (11.5)	7 (8.0)	17 (19.1)
Parietal	5 (5.7)	10 (11.5)	15 (16.9)
Brain stem			9 (10.1)
Other			10 (11.2)

(b) Tumor pathological type

Pathological type	Total (%)
Glioblastoma multiforme	43.8
Anaplastic astrocytoma	13.4
Low grade astrocytoma	8.9
Low grade oligodendroglioma	7.9
Anaplastic oligodendroglioma	3.4
Gemistocytic astrocytoma	3.4
Anaplastic mixed glioma	3.3
Meningioma	2.2
Pilocytic astrocytoma	2.2
Anaplastic oligoastrocytoma	1.1
Cyst aspiration	1.1
Ependymoma	1.1
Germinoma	1.1
Glioma	1.1
Hemangiopericytoma	1.1
Low grade mixed oligoastrocytoma	1.1
Lymphoma	1.1
Medulloblastoma	1.1
Pineoblastoma	1.1
Total	100.0

neurosurgical debulking (73%), regional radiotherapy (73%), chemotherapy—previous or current (79%), whole brain irradiation (17%), gamma knife radiotherapy (6%). In addition, 32.5% of the patients in the study group (29/89) were on steroids at the time of their interviews. This included 27 patients on Decadron and 2 patients on Prednisone.

Measures/Procedures

Patients were evaluated using a structured psychiatric interview incorporating DSM-IV criteria and a brief neuropsychological screening battery emphasizing complex attention processes. The structured psychiatric interview, performed by the team psychiatrist (D.F.), was three pages in length, focusing on: review of symptoms (depres-

sion, sleep, and mood), past psychiatric history, family psychiatric history, and social history. In addition, the psychiatrist rated: family support, overall patient distress, and overall patient functional level, and provided a DSM-IV diagnosis (diagnoses) if one existed (American Psychiatric Association, 1994). To evaluate the presence of absence of a major depressive disorder, all of the criteria from the DSM-IV manual were included in the structured psychiatric interview. This included all of the nine key symptoms. The psychiatrist also evaluated whether these symptoms met criteria for a mixed episode (manic), whether these symptoms were due to a direct physiological effect of a substance, or medical condition, whether these symptoms cause clinically significance distress and whether bereavement was also present. In this fashion, all criteria for a DSM-IV diagnosis of major depression were considered.

The neuropsychology screening battery was composed of four standardized instruments. These included: (1) Trailmaking Test, forms A & B, a test of visual-motor and visual conceptual tracking (Davies, 1968); (2) Symbol Digit Modalities Test, a test measuring integration of different verbal and perceptual nonverbal processes, and psychomotor speed (Smith, 1982); (3) Digit Span, a subtest from the Wechsler Adult Intelligence Test—Third Edition, involving attention and immediate memory (Wechsler, 1997), and (4) Repeating Phrases, a subtest from the Boston Diagnostic Aphasia Battery measuring immediate memory for two difficulty levels of verbal stimuli (Goodglass and Kaplan, 1983). The tests were chosen from the many available ones using the following criteria: (1) brevity and ease of administration in the clinic setting of the NOP; (2) availability of objective scoring criteria; (3) availability of normative standards across the broad age range of patients in this study; and (4) demonstrated reliability and validity in clinical research. The diagnosis of major depression was determined by the project psychiatrist. He carefully differentiated between subclassifications of depressive etiologies, including medical/pharmacologic co-factors in making his diagnosis. No sub-threshold diagnoses of major depression were included in the determination of prevalence rates of major depressive disorder (MDD). For this diagnosis to be made in this study, at least five of the symptoms had to be present, plus the other four key criteria in the DSM-IV diagnosis had to be met or accounted for. Thus, the diagnosis was made only when this

Table 2. Independent variable definitions

Independent variable	0	1
Frontal lobe tumor	All other locations	Tumor is diagnosed in the frontal lobe without any presence in neighboring regions.
Right hemisphere tumor	Tumor is diagnosed in the left hemisphere or both hemispheres	Tumor is diagnosed in the right hemisphere.
Lack of motivation and sadness symptoms	At most, one of the symptoms is present	Both symptoms present
Previous psychiatric history	No prior hospitalization and no Suicide attempts	Prior hospitalization and/or suicide attempt.
Family history	No history of suicide, depression, or hospitalization	Family history of at least one of the following: suicide, depression, or hospitalization
Age	Birth date after 12/31/1955	Birth date on or before 12/31/1955
Life partner	No partner: divorced, widowed, or unavailable	Married or living with a partner.

threshold was determined. Family members were always present and included in the diagnostic interview process. Family support ratings were made by the psychiatrist upon observation of the patient–family interaction, and patient distress was rated both by the patient and family member.

In addition, organic mental disorder was differentiated in this study from MDD via the use of DSM#293.83 (mood disorder due to a medical condition). This was found in a smaller proportion of this population ($N = 6$, 8% of sample).

STATISTICAL ANALYSES

Data analysis was performed in three stages. First was descriptive statistics, mainly calculating percentages of study variables including patient characteristics, disease and treatment factors, and clinical findings. Second, data mining procedures were performed to discover independent variables that merit statistical comparison and eliminate irrelevant variables (Fayyad *et al.*, 1996). Due to the substantial number of patient, disease, and treatment variables, a set of computer algorithms were utilized to discern relevant patterns of relationships within the dataset. Third, once a final set of relationships between variables were found, they were tested using classical statistics. Specifically, a hierarchical logistic multiple regression was performed, and an analysis of variance using the dependent variable, clinical diagnosis of major depression, was also performed. A binary encoding of the diagnosis variable ($296.2 \times$ or $296.3 \times$ DSM-IV diagnoses codes) was recorded

Table 3. Self-reported symptoms: depression

Symptom	% Present
Energy loss	68.4
Concentration problem	68.4
Weight change	57.9
Sadness	52.6
Sleep disorder	51.3
Motoric slowing	50.0
Motivation loss (Diminished interest in activities)	48.9
Guilt	25.0
Death ruminations	9.2

as 1 (yes for MDD diagnosis), and all other diagnoses codes were recorded as 0 (no diagnosis of MDD). Binary encoding, also used for each independent variable, is summarized in Table 2.

RESULTS

Table 3 shows patients' reported symptoms of depression. These emanate from the criteria for a DSM-IV diagnosis of MDD, which were incorporated into the study psychiatric interview. Five or more of these symptoms need to be endorsed to establish this diagnosis. As Table 3 shows, these do not add up to 100% because, by definition, patients will endorse more than one symptom. Six of the nine possible symptoms were endorsed by 50% or more of the patients.

In terms of neurocognitive status, a substantial percentage of the patient sample were found to

have disabilities. More specifically, 60% were found to have clinically significant psychomotor slowing (defined as less than 10th percentile on one or both administrations of the Symbol Digit Modalities Test). With respect to attention and concentration, 55% had clinically significant difficulties with sustaining attention and/or shifting perceptual sets (defined as less than the 24th percentile on one or both portions of the Trailmaking Test). In contrast, immediate memory functioning was found to be comparatively less impaired than the other areas of cognitive functioning. Here 41% were found to have immediate memory problems (defined as more than or equal to one standard deviation below the mean on the Digit Span sub-test of the Weschler Adult Intelligence Scale-III). A more complete elaboration of the neurocognitive data will be presented in a separate manuscript. Table 4 reflects the percentage of patients who were given a diagnosis of MDD (28%). Also in Table 4 are data regarding tumor location comparing patients diagnosed with an MDD (28%), $N = 25$; entire study sample $N = 89$).

The structured psychiatric interview assessed prior psychiatric history in the study patients as well as in their families. Patients' psychiatric history consisted of: (1) psychiatric hospitalization, and/or; or (2) suicide attempts. Family psychiatric history included: (1) depression history, and/or; (2) hospitalization, and/or; (3) suicide. With regard to the patients, the data showed a relatively large incidence of prior counseling/psychotherapy experience (40%); Four percent of the study patients reported prior psychiatric hospitalization, and 8% reported a

history of prior suicide attempts. Family histories documented a relatively large incidence of reported depression (32.9%), and drug use (23.7%). Prior psychiatric hospitalization was reported in 15.8% of families; suicide attempts were reported in 13.2% of families.

Table 5 amplifies one key aspect of self-reported symptoms critical for making the diagnosis of major depression—that of sleep symptomatology. Table 5(a) classifies sleep problems into subtypes, with difficulty falling asleep being most frequent (52%), continuity disturbance (multiple frequent awakenings) being next (40.6%), and early morning awakenings, being least frequent (31.6%). Here again, these do not necessarily add up to 100% because often patients will report more than one category of problems. Table 5(b) also reflects the range of hours of sleep. Table 5(b) shows the majority of patients to be sleeping within a range of 8–9 hr (54.1%), while a smaller group reported less (5–7 hr, 21.6%). A minority of patients reported hyposomnic sleep (2–4 hr, 12.7%) and an equivalent minority reported hypersomnic sleep (10+ hrs, 12.6%).

Table 6 is a multiple regression analysis predicting MDD using seven independent variables. These seven independent variables are described in the Methods section under Statistical Analyses (see Table 2). Using ANOVA, the total regression significantly accounted for substantial variance in identifying those variables which predict MDD ($F = 6.75, p = 0.0000$). Of the seven independent variables, three entered the regression as highly significant predictors of the dependent variable. These included: frontal region

Table 4. Psychiatric diagnosis of major depression disorder (MDD)

Tumor location	Patients with MDD ($N = 25$)	Entire patient group ($N = 89$)
Left cerebrum	7 (28%)	37 (41%)
Right cerebrum	13 (52%)	36 (40%)
Others*	5 (20%)	16 (18%)
Frontal lobe	11 (44%) (of 25 patients with MDD)	27 (30%) (of entire patients group of 89)

25 of 89 patients (28%) given diagnosis of MDD.

*Including: cerebellum, brain stem, corpus callosum, & spinal cord.

Table 5.

(a) Sleep problems

Type	% Present
Difficulty falling asleep	52.0
Continuity disturbance	40.6
Early morning awakening	31.6

(b) Range of hours of sleep

Number of hours	%
2–4	12.7
5–7	21.6
8–9	54.1
10+	12.6

($r = +0.32$, $p = 0.001$), sadness and lack of motivation ($r = +0.49$, $p = 0.0001$), and family psychiatric history ($r = +0.26$, $p = 0.006$). In terms of total variance accounted for by the regression, $R^2 = 0.37$.

DISCUSSION

The key hypothesis of this study was that brain tumor patients would demonstrate a higher

incidence of MDD compared with DSM criteria-based studies of patients with other types of cancer. A comprehensive review of the scientific literature found seven studies of ambulatory cancer patients assessed for MDD, which used DSM criteria (see Table 7). Comparing these findings with those of the present study, where 28% of the patients were diagnosed with MDD (using DSM criteria), it appears that the key hypothesis was supported. Although Table 7 shows seven studies which linked DSM criteria to depression in cancer patients, only four of the seven studies appear to link DSM criteria directly to MDD (Massie *et al.*, 1979; Massie and Holland, 1987; Derogatis *et al.*, 1983; Lansky *et al.*, 1985), with the ranges of these four studies being from 4.5 to 9%. Thus, the present study showed rates of MDD to be triple that of the highest end of the previously published studies. In addition, the present study is the only one using DSM criteria to diagnose MDD specifically in brain tumor patients.

Comparing the incidence of MDD in the present study (28%) with that found in the general US population (3%) is even more striking. The data

Table 6. Multiple regression analysis. Predicting major depressive disorder

Variables	Coefficients	t stat	p-value
Right hemisphere	-0.065	-0.722	ns
Frontal region	0.317	3.417	0.001
Sadness and motivation	0.490	4.635	0.000
Psychiatric history (patients)	-0.321	-1.717	ns
Psychiatric history (family)	0.264	2.814	0.006
Patient age	0.013	0.143	ns
Marital status	-0.156	-1.759	ns

Table 7. Psychiatric studies of depression in cancer patients using DSM criteria

Reference	N	Female/male	Patient types	Method	Percentage depressed
Massie <i>et al.</i>	334	189/145	Hospitalized + ambulatory, all stages & sites	Interview, DSM-III criteria	49% depressed 5% extreme 24% severe 75% mild-moderate
Massie and Holland	546	Not cited	Hospitalized + ambulatory, all stages & sites	Interview, DSM-III criteria	9% major depression 26% adjustment disorder with depressed mood
Derogatis <i>et al.</i>	215	110/105	50% Hospitalized, 50% ambulatory, all stages	DSM-III criteria, psychometric testing	6% major depression 12% adjustment disorder with depressed mood
Morton <i>et al.</i>	48	0/48	Largely ambulatory, oropharyngeal, geriatric	DSM-III criteria	40% depressed
Lansky <i>et al.</i>	500	500/0	85% Ambulatory, 43% survivors without evidence of disease, 34% early stage	DSM-III criteria, psychometric testing	5.3% using psychometric testing 4.5% using DSM-III criteria
Jenkins <i>et al.</i>	22	22/0	Ambulatory breast cancer patients, with recent local recurrence	DSM-III criteria, psychometric testing	32% depressed 27% anxiety + depression 45% depressed or anxious
Sneeuw <i>et al.</i>	556	556/0	Ambulatory, stage I & II breast cancer	DSM-III criteria, psychometric testing	4.5% depressed

shows the present study patients are 9 times more likely to have major depression than the general US population (Burke and Regier, 1999). The rate of MDD (28%) vs. organic mood syndrome (in this study mood disorder due to medical conditions 8%) is striking and unexpected. The investigators conclude this difference is due to the fact that the study patients were ambulatory and functioning at reasonably high levels as evidenced by the high Karnofsky ratings. If the study population had reflected patients with generally lower Karnofsky ratings, then they would have been more terminally ill, more likely to show organic mood disorders vs. MDD.

The data in Table 3 concerning self-reported symptoms of depression suggest several issues to consider. First, many of these symptoms such as energy loss, concentration problems, weight change, and motoric slowing are also part of the physical symptoms caused by the brain disease. This presents an important potential confound to the study conclusion regarding etiology/prevalence of MDD. Physical disability and mood disorder are very difficult to differentiate in this and other populations of seriously medically ill patients. As presented in the literature review, medical treatments such as corticosteroids and radiation further complicate this very complex diagnostic problem. These symptoms, however, should not cause the clinician to ignore or discount the possible presence of depression, as the symptom of sadness was endorsed by 52.6% of the patients. It is noteworthy that the least frequently endorsed symptom in this group was death ruminations (9.2%), perhaps indicating that problems with living overshadow concerns about the potential for death. This finding adds greater impetus for the clinician to actively intervene into problems of living that threaten quality of daily life.

The study data on sleep problems is important in several aspects. Sleep disturbance has long been recognized as 'one of the most consistent symptoms of depressive illness' (Kales *et al.*, 1975). In addition, insomnia is the most frequently found subtype of sleep disturbance. This was demonstrated in the present study where insomnia (i.e. difficulty falling asleep) was the most frequently reported subtype of sleep disturbance (52%). The normal range of sleep hours has been found to be 5–8 h per night (Webb, 1970). However, a 20% incidence of some form of sleep disorder has been reported in a presumably normal population

(Rayban and Detre, 1969). The incidence of sleep disturbances appears to increase with age and with the presence of significant levels of anxiety or depression. In contrast, the data from the present study indicate that a substantial portion of the study sample fell outside this range (12.7% less than 5 h, 12.6% more than 9 h). This suggests that the clinician closely query the brain tumor patient about his/her sleep patterns. Several features can affect sleep patterns with brain tumor patients. These include: current radiation therapy (increase sleep); use of Decadron (decrease sleep); and use of autoconvulsants (increase sleep). These serve as examples of factors that modify sleep, but are not an exhaustive list of these factors. Improvement in sleep may be especially important in management and containment of MDD.

The results from the multiple regression are perhaps the most important findings in this study. First and foremost, these data show this set of variables to predict a significant amount of the variance (37%) in the dependent variable. Examining the three significant independent variables, they demonstrate the validity of the 'Biopsychosocial Model' (Engle, 1975). Here, biological factors (such as tumor location, psychological factors (such as mood states) and social factors (such as family environment) must all be jointly considered to understand a complex patient outcome such as MDD among brain tumor patients. However, when family is considered as a variable it may also have genetic and biological concomitants in addition to being a 'social' variable. Given the robust significance of each of these three independent variables, the clinician is advised to carefully consider contributions from each dimension (medical, psychological, and social) in his/her understanding and management of the emotional status of the adult brain tumor patient.

In conclusion, a few caveats are necessary to consider with regard to this study. The relative contributions of several (independent) variables to MDD have been systematically identified. This does not mean, however, that this is an exhaustive list of clinically meaningful variables which may be associated with outcome. A second caveat is the absence of another psychiatrist to validate the diagnoses of the project psychiatrist (DF). All cases were discussed in depth with the project senior consultant (DW) and neuro-oncologist (TC), but no formal inter-rater reliability statistic was calculated. A third caveat is the absence of a

control group in this study design. Recognizing this, the investigators attempted to compare these findings on depression rates with those from other studies of adult ambulatory cancer patients, and also from the general population. A fourth caveat is the cross-sectional nature of the study design. The investigators are cognizant of the fact that brain tumor patients are often in a constant state of emotional flux. However, given the absence of data about depression in this population, our study is a valid initial step to understand this complex phenomenon.

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