

# Neuropsychological Disorders in Patients with Brain Tumor

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## Abstract

**Background:** Very few studies have utilized specific criteria to assess mental disorders in brain tumor patients. This study aimed to diagnose mental disorders in this population using DSM-IV (depression, sleep, and mood) criteria.

**Methods:** From March 2007 to July 2009, the surgically treated patients with intracranial neoplasm were included in the study. These patients were examined in an ambulatory neuro-oncology clinic setting using a structured psychiatric interview which followed current DSM-IV diagnostic criteria.

**Results:** This study is based on the clinical data of 89 patients with brain tumor. The mean age was 42.2 years old. Fifty five percent (55 %) of the patients were male. In our study, the prevalence of mild depression was about 30% for males and 38% for females. Before tumor operation, severe anxious as well as severe obsessive-compulsive symptoms were present in 14% of males. In females, 29% of the subjects had reported to have severe anxiousness and 25% severe obsessive symptoms.

**Conclusion:** Depressive symptoms as well as anxious and obsessive psychopathology were shown to be prevalent signs among patients with brain tumor. The associated factors are tumor location, patient's premorbid psychiatric status, cognitive symptoms and adaptive or maladaptive response to stress.

**Key Words:** Brain Tumor, Psychological, Treatment

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## Introduction

Primary brain tumor has a great, often dramatic impact on the life of patients and their families [1, 2]. Brain tumor, being both a malignancy and a progressive neurodegenerative disease, has a direct effect on the patient's cognitive, neurological and psychic functions, causing focal cerebral dysfunction at the site of the tumor lesion [3]. In addition, treatment of the tumor, i.e. surgery, radiotherapy, chemotherapy and immunotherapy, may be neurotoxic and cause dysfunction of the sub cortical white matter [4].

The main literature in the field of neuropsychiatry symptoms for brain tumor patients has been based on individual case reports and retrospective case series [3]. In addition, studies focusing on psychiatric symptoms in brain tumor patients are mainly descriptive, and the number of cases in the study populations is small [5, 6]. Quality of life (QOL) in brain tumor patients has not yet been extensively studied; the first studies were initiated as recently as in the 1990s' [7, 8]. Since many studies of QOL in brain tumor patients are either retrospective or cross-sectional in nature, the effects of tumor characteristics and treatment as well as patients' emotional and

cognitive impairments are difficult to estimate over time [6].

This study is a prospective project in which mental disorders among brain tumor patients are evaluated. The purpose of this study is to examine mental disorders in relation to tumor characteristics and patients' psychosocial factors among brain tumor patients.

## Materials and Methods

In this study, the subjects were the consecutive patients with brain neoplasm who referred to the clinic of neurosurgery and underwent surgical procedure from March 2007 to July 2009. These referrals were made as part of the multi-disciplinary model of the clinic and were not made as a special need for psychiatric care. All the subjects were treated with surgery and/or radiotherapy. Our exclusion criteria were as follows: age more than 60 or less than 18 years; presence of any previous mental problem more than one year prior to the diagnosis of the tumor; Karnofsky score of less than 60; severe dysfunction of patients' somatic condition; confusion due to raised intracranial pressure; tumor induced motor aphasia; and the patient's or the

**Table 1.** The frequency of the side and site of the brain tumors in the patients.

Location No (%)	Right No (%)	Left No (%)	Total No (%)
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 (10.2)
Others	2 (2.3)	8 (8.9)	10 (11.2)

family's refusal to participate in the study. Informed consent was signed by the patients and their first degree relatives.

The collected data included name, surname, file number, age, sex, duration of the illness, marital state, employment, education, Karnofsky scale [9], location of the tumor and pathology. The psychological investigations were performed by the psychology team. Patients were evaluated using a structured psychiatric interview incorporating DSM-IV criteria and a brief neuropsychological screening battery which emphasized complex attention processes [9]. The structured psychiatric interview focused on the review of symptoms past psychiatric history, family psychiatric history, and social history. In addition, the psychiatrist rated: family support, overall patient distress, overall patient functional level, and provided a DSM-IV diagnosis if existed. To evaluate the presence or absence of a major depressive disorder, all the criteria from the DSM-IV manual were included in the structured psychiatric interview. The psychiatrist also evaluated the following: whether these symptoms were due to a direct physiological effect of a substance, or a medical condition; whether these symptoms caused clinically significant distress; whether bereavement was present. In this fashion, all the criteria for a DSM-IV diagnosis of mental disorders were considered. The patients were evaluated at three time points.

The subjects were assessed within 1-3 days before operation (i.e. during the admission for the surgical operation of a brain tumor). Then, the follow-up measurements for psychiatric symptoms were performed three months after the operation. Psychiatric symptoms were assessed using two structured screening instruments: the Crown-Crisp Experiential Index (CCEI), and the Beck Depression Inventory (BDI) [10, 11]. Chi square test was used to assess the qualitative variables, and Mann Whitney test was used to analyze the quantitative factors.

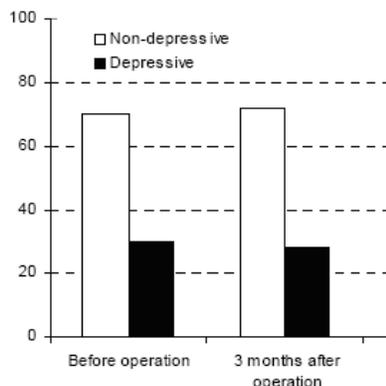
## Results

In this study, 98 patients with intracranial brain tumor were referred to the clinic of neurosurgery from March 2007 to July 2009 and were surgically treated. The mean age of the patient group was 42.2 years with a range of 18–60 years. Fifty five percent (55 %) of the patients were male. Male to female ratio was 1.2. In terms of educational level, 51.8% had high school diploma or less, 38.5% had a college degree, and 9.7% held a post graduate degree. Most of the patients were not employed (67.9%) at the time of the interview and testing, while the remainders were employed full time (17.6%), or part time (24.5%). The majority of the patients (61.8%) were married, while the remainders were never married, separated/divorced, or widowed.

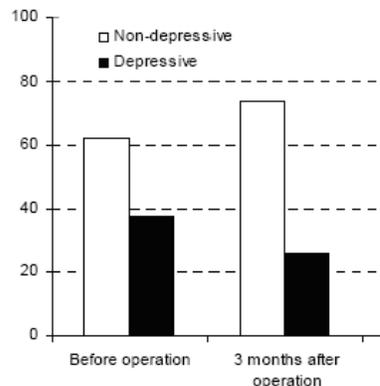
Range of Karnofsky Performance Scale (KPS) ratings was from 60 to 100%. In our cases, 28% had KPS=100; 26% had KPS=90; 15% had KPS=80; and 31% had KPS=70.

**Table 2.** The frequency of the pathologic type of brain tumors in the patients.

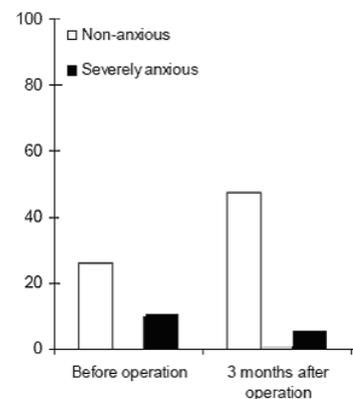
Pathologic Type	No (%)
Glioblastoma multiforme	27 (39.3)
Anaplastic glioma	11 (20.2)
Low grade glioma	9 (13.5)
Meningioma	15 (16.8)
Ependymoma	4 (4.5)
Germinoma	2 (2.2)
Hemangioma	2 (2.2)
Lymphoma	3 (3.4)
Medulloblastoma	3 (3.4)
Pituitary Adenoma	8 (8.9)
Metastasis	5 (5.6)
Total	89 (100)



**Figure 1.** Bar diagram of the frequency of depression in male patients before and 3 months after operation.



**Figure 2.** Bar diagram of the frequency of depression in female patients before and 3 months after operation.



**Figure 3.** Bar diagram of the frequency of anxiety in male patients before and 3 months after operation.

The majority of the patients in our study had frontal lobe tumors (42.6%) of the glioblastoma multiform (GBM) type (43.8%). The location and side of the tumors are summarized in table 1. The most common pathologic type was glioblastoma multiform (39.3%), followed by meningioma (16.8%). Table 2 demonstrates the relative frequency of the pathologic tumor types of the patients.

In this study, the patients had received multiple and varied treatments. The treatments included: neurosurgical debulking (85 %); regional radiotherapy (68%); chemotherapy (32.2%); whole brain irradiation (17.3%); and gamma knife radiotherapy (4.6%). In addition, 82.5% of the patients' group were on steroids at the time of their interviews.

The prevalence of depressive symptoms was assessed with Beck Depression Inventory (BDI). The level of anxiety according to CCEI, and the level of obsessive-compulsive symptoms (OBS) in the CCEI were assessed separately for male and female patients.

In the male patients, the prevalence of at least mild depression (BDI) prior to operation was 30%, while it was 25.6% (Fig) 3 months after the operation.

In the female patients, 37.8% were shown to be at least mildly depressed before tumor operation. However, at three months after operation, 26% of the females were found to have at least mild depression (Fig2).

The prevalence of depressive symptoms before operation and in follow-up assessments was not statistically significant between genders.

Before tumor operation, the prevalence of major depression (BDI scores 14 or over) was 10.4% for males and 19.7% for females. At three months after operation the prevalence of major depression was 12.8% for males, and 6.7% for females.

Before tumor operation, 14.7% of the male patients were severely anxious, while the corresponding proportion was 6.8% at three months after the operation. In the female patients, 28.7% of the subjects had reported to be severely anxious before tumor operation. However, the rate of severe anxiety was 17.6 % in the female group three months after the operation.

The level of anxiety differed significantly between the genders at three months ( $p=0.015$ ) after tumor operation, but not before.

In this study, 14.5% of the males were severely obsessive (OBS) before tumor operation. However, the proportion of severely obsessive males decreased to 9.3% at three months after tumor operation. Among females, the prevalence of severe obsession was 25.6% before tumor operation, and it increased at three months after tumor operation up to 38.7%. The gender difference was found to be statistically significant only at three months after operation ( $p= 0.022$ ).

Considering the anxiety level according to CCEI which was assessed before the tumor operation, the patients with a tumor in the right hemisphere were shown to have higher anxiety scores ( $5.75\pm 3.32$ ) compared to those with a tumor located in the left hemisphere ( $3.59\pm 3.12$ ,  $p = 0.032$ ) Corresponding differences in the level of anxiety were not found in three months and in one year after the operation. Furthermore, a statistically significant decline in

anxiety levels from brain surgery to the follow-up assessments was found in patients with a right hemisphere tumor ( $p = 0.015$ ), while no significant difference between measurements was observed among patients with left hemisphere tumors. The changes over time in the level of obsession (OBS) by the CCEI were investigated according to lateralization and anterior/posterior location of the tumor. In the female patients who had a primary brain tumor in the left anterior hemisphere, a statistically significant increase was observed in the level of obsession between preoperative and three-month postoperative measurements ( $p=0.007$ ). No corresponding increase in the level of obsession was found in females or males if the tumor was located in any other region of the brain.

Another finding was that at preoperative measurements, the level of obsession was notably high among patients with the tumor in the right anterior hemisphere (right anterior vs. left anterior  $p=0.021$ , right anterior vs. right posterior ( $p=0.055$ ), and it remained notably high (the mean obsession scores  $> 8.0$ ) also in the subsequent measurements.

Assessment of the depression association with tumor location showed that patients with a tumor located anteriorly in the hemispheres had a trend for higher depression (BDI) scores ( $9.4 \pm 8.7$ ) before tumor operation compared to those with a tumor in posterior regions of the brain ( $5.7 \pm 6.0$ ,  $p=0.057$ ) This difference in the level of depression was, however, not found at three months after the surgery.

The decrease of the depression level among the patients with an anterior tumor was statistically significant from the mean  $\pm$  SD scores  $9.4 \pm 8.7$  before surgery to the scores  $6.1 \pm 5.2$  at three months after the operation ( $p= 0.049$ ).

A corresponding decrease between preoperative and postoperative measurements was not found if the tumor was located in the posterior regions of the brain. ( $p=0.34$ )

In the patients with a high-grade glioma in the right hemisphere, the decline of the anxiety scores by CCEI ( $4.7 \pm 2.0$ ) was statistically significant between measurements before tumor operation and at three months after the operation ( $2.4 \pm 1.5$ ,  $p=0.018$ ).

No differences in the level of anxiety were found in the patients with a glioma (low-grade or high-grade), those with a meningioma in the left hemisphere or those patients with a meningioma in the right hemisphere.

The level of depression did not differ between the histological subgroups, being independent of the malignant or benign status of the tumor. However, an overtime change was observed in the depression

level of the patients with a pituitary adenoma whose depression scores decreased significantly during the follow-up from 6.7 to 2.4, ( $p=0.019$ ).

The prevalence of depression was studied in our patients. The mean (SD) BDI score for males was 6.9; the corresponding score for females was 8.9. At three months after tumor operation, the decrease of the mean of depressive scores were statistically significant in the whole database ( $p= 0.031$ ).

## Discussion

In general, a human is a biopsychosocial entity in which psyche, soma and the social environment are in a subtle and complex interrelation between each other. The central nervous system is responsible for the regulation of this entity, and a brain tumor, causing brain dysfunction, has a direct, biological impact on all human functions [12]. Patients with a primary brain tumor can experience their disease in a more comprehensive way than indicated by their clinical symptoms due to the tumor [13]. This is because this serious illness causes a psychological reaction, a typical, individual response in each patient [12], and malignancy per se causes dysregulation of the hypothalamic-pituitary-adrenal axis and changes in immune system [14].

Although psychiatric symptoms are based on location of damage in the brain, psychiatric symptoms in brain tumor patients are different from those patients with infarct, injury or infection in the brain [15]. In stroke patients, psychiatric symptoms are more studied and destruction of neurons is seen, while in brain tumor patients deficits are mainly based on the more gradual displacement and plasticity of neuronal structures [16]. Psychiatric symptoms can be the first and only signs of primary brain tumor and between 1% and 2% of patients with a psychiatric disorder may have unrecognized brain neoplasm [17, 18].

Depressive symptoms as well as anxiousness and obsessive psychopathology were shown to be prevalent signs among neurosurgical patients with a primary brain tumor in our patients.

In our study, the prevalence of at least mild depression before tumor operation was as high as 30% for males and 38% for females. Although the proportion of depressed patients decreased significantly after tumor operation, the prevalence of at least mild depression was still notably high. Before tumor operation, severe anxiousness symptoms as well as severe obsessive-compulsive symptoms were present in 14% of the male patients. In females, 29% had reported to have severe anxiousness and 25% severe obsessive symptoms. However, the

prevalence of severe anxiousness decreased both in females and in males to 14% and 4% respectively during the follow-up. Contrary to anxiety symptoms, the prevalence of severe obsession increased significantly up to the three-month measurement point in female patients, while it decreased during the follow-ups in male patients.

Assessment of the tumor lateralization association with the anxiety of patients before tumor operation showed that the level of anxiety was substantially higher in the patients with a tumor in the right hemisphere compared to those with a left hemispheric tumor.

Furthermore, the level of anxiety decreased significantly three months after tumor operation in the patients with a right hemispheric tumor.

While investigating the level of obsession in relation to tumor location, it was found that in the female patients with a tumor in the left anterior region of the brain the obsession scores were significantly increased three months after operation. However, in the patients with a tumor in the right anterior location, severe obsession was already present before tumor operation as well as at the follow-ups.

The association of depression with tumor location and with the patients' functional outcome was also investigated. The anterior location of the tumor of the patients was associated with higher preoperative depressive scores compared to the scores of the patients suffering from a posterior location of the tumor. In addition, depression was found to be significantly correlated with the patients' decreased functional outcome before tumor operation and at follow-ups.

Among patients with a primary brain tumor, depression was shown to be a major psychiatric symptom, and in all likelihood it complicated the course of the disease before and after operation. In addition, obsessive and compulsive symptoms in females appeared to increase as early as at three months after operation among those with a tumor in left anterior location of the brain. Severe obsession was found especially in female patients with a tumor in the right anterior location of the brain at all the measurement points.

In earlier literature, depression among cancer patients was considered to be a normal psychological reaction to a serious illness [19].

Nowadays, there is growing evidence that depression in cancer patients is not merely an appropriate psychological reaction, but that it has biological and biochemical bases [14].

The pathophysiology behind the depression in cancer patients is most probably multifactorial in its origin. As suggested by several researchers, deregulations of the hypothalamic-pituitary-adrenal axis and changes in cytokine levels in the brain may lie behind the association between depression and cancer [14, 19]. Further, depression in cancer patients complicates coping with the disease, causes worsening the quality of life and interferes with adherence to medical treatment [20].

The prognosis of cancer patients may worsen particularly due to depression as depression often prevents patients from complying with treatment regimens and other health-promoting behaviors [21]. Both obsessive-compulsive symptoms and depression are known to decrease the quality of life in the patients [22, 23].

Patients in psychiatric settings may present with such medical conditions as brain tumors, which may or may not be associated with neurological symptoms. In some cases, patients may only have psychiatric symptoms such as mood changes, psychotic symptoms, panic attacks, changes in personality, or memory difficulties. Brain tumors may be detected in patients at their first presentation to mental health services or sometimes in patients with well-established psychiatric diagnoses. In this study, we showed that in some cases brain tumors can be neurologically silent and only present atypical psychiatric symptoms. We emphasize the need for neuroimaging studies in patients with atypical changes in mental status, even without neurological signs or symptoms. Our findings remain exploratory due to small sample size, but they suggest that psychological problems develop over time and are due to a combination of neurological and psychosocial problems that ensure initial treatments. The factors suggested to be associated with psychiatric symptoms among brain tumor patients are tumor location, patient's premorbid psychiatric status, tumor-associated cognitive symptoms and adaptive or maladaptive response to stress, usually all in combination [3]. Treating these problems may reduce the complications in patients with brain tumors.

## Acknowledgment

None

## Conflicts of Interest

We have no conflicts of interest and nothing to declare.

## Author's Contributions

SA operated the patients and collected the surgical and pathologic data and wrote the manuscript. SAS operated the patients, analyzed the data, prepared tables, figures and performed the literature review. AF did the neurological evaluation and gathered the reference. NS performed the neuropsychological exam and categorized the mental disorders of the patients.

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