Depression and functional outcome in patients with brain tumors: a population-based 1-year follow-up study

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Object. The authors analyzed changes in depression and contemporary functional states by using valid tools in a population-based study sample during a 1-year follow-up period.

Methods. The study population consisted of 77 patients with a solitary primary brain tumor treated surgically at the Oulu Clinic for Neurosurgery. Each patient’s depressive status, according to the Beck Depression Inventory (BDI), and functional outcome, based on the Karnofsky Performance Scale (KPS), were evaluated before the tumor was surgically treated as well as 3 months and 1 year after surgery. Before surgery 27 patients (35%) had BDI scores indicating the presence of depression. These scores were significantly higher in patients with a history of depression (p = 0.017) and in those with a lower functional outcome (p = 0.015). In the entire study sample the severity of depression decreased statistically significantly (p = 0.031) at 3 months postsurgery. A lower functional status (KPS score ≤ 70) in patients was significantly associated with high depression scores at the 3-month (p = 0.000) and 1-year (p = 0.005) assessments. The decrease in the level of depression was significant in patients with an anterior tumor (p = 0.049) and those with a pituitary adenoma (p = 0.019).

Conclusions. Affective disorders among patients with brain tumors must be considered immediately after surgery, especially in persons with a depression history and in those with a coincident physical disability.

Key Words • primary brain tumor • depression • functional outcome

Depression as a neuropsychiatric symptom among patients with a primary brain tumor is common, varying from 15 to 38% in different study populations. Nevertheless, it is difficult to differentiate which of the depressive symptoms are caused by the neuropsychological effects of the tumor and which are the patient’s psychological reactions to the stress caused by serious disease. It is therefore important to measure depression by using a clinically valid method such as that in the study by Wellisch and colleagues. These authors evaluated depression by using the Diagnostic and Statistical Manual for Mental Disorders, ed 4, criteria for MDD in patients with brain tumors and found in their cross-sectional study that 28% of the patients (89 patients) had MDD. Factors predictive of depression included frontal location of a tumor, combined symptoms of sadness and lack of motivation, and history of psychiatric disorder in the family.

Affective symptoms in patients with primary brain tumors have been focused on in recent years for several reasons. In general, the prevalence of depression in physically ill patients completing self-administered questionnaires has varied up to 60% in different populations. The duration of survival in patients harboring brain tumors, apart from those with glioblastoma multiforme, is expected to be longer because of the effects of modern radiotherapy and chemotherapy. In addition, depression and emotional distress are known to be the main variables that can decrease the quality of life in patients with brain tumors. It is also known that depression predicts cancer progression and death in patients with different types of cancer and in patients with high-grade gliomas.

The literature on depression in patients with primary brain tumors has focused mainly on a single measurement; for example, the assessment of depression has been performed only in the tumor surgery perioperative period, despite the knowledge that the mood state in patients fluctuates. The sex difference in the prevalence of depression in patients with brain tumors is contradictory. Some researchers have found no sex difference, whereas authors of epidemiological studies have reported that the prevalence of depression in female patients is approximately twice that in male individuals in the general population. Pringle and colleagues reported that female patients with a left-sided tumor had a significantly higher incidence of depression than males, although no sex difference was demonstrated if the tumor was located in the right hemisphere. It has also been proposed that female patients with brain tumors do not suffer depression more often than males but that they are more likely to report the symptoms.

Depressive symptoms in patients with brain tumors ac-

Abbreviations used in this paper: BDI = Beck Depression Inventory; CCEI = Crown–Crisp Experiential Index; CT = computerized tomography; HPA = hypothalamic-pituitary-adrenal; KPS = Karnofsky Performance Scale; MDD = major depressive disorder; MR = magnetic resonance; SD = standard deviation.
According to tumor histological features have not been studied much. It has been reported that 16 months after tumor surgery, patients with high-grade gliomas tended to have a more severe depression than those with other tumor types, for example, low-grade gliomas or meningiomas. In contrast, Irle and associates found that 2 to 10 days after tumor surgery the patients with a glioma and a meningioma demonstrated no difference in their emotional state. In a study by Pringle and colleagues depression was assessed before and after tumor surgery. These authors reported that patients with a meningioma had higher preoperative levels of depression as measured using the Hospital Anxiety and Depression Scale than those with a glioma, a glioblastoma multiforme, an astrocytoma, or brain metastasis. On postoperative assessment, the severity of depression in the patients decreased despite the tumor histological features.

Many researchers in this field have pointed out the difficulty in differentiating affective disorders from symptoms caused by decreased functional states in patients, both of which usually occur concomitantly in patients harboring brain tumors. Furthermore, methodologically sound studies with repeated measurements over a long enough period following brain tumor surgery are lacking.

In the present follow-up study we addressed changes over time in the incidence and severity of depression and the functional state in patients with brain tumors. Special attention was also focused on such sociodemographic factors as patient sex and depression history. The advantage of our study design lay in our ability to measure the depression status and functional outcome in patients at one preoperative and two postoperative assessments.

**Clinical Material and Methods**

**Patient Population**

The study population consisted of 77 patients (30 male and 47 female) with a solitary primary brain tumor treated surgically at the Oulu Clinic for Neurosurgery, Oulu University Hospital, between February 1990 and March 1992. Epidemiologically, the cohort is a comprehensive and unselected population sample given that the Oulu Clinic for Neurosurgery performs all brain tumor resections in its catchment area. The mean age before surgery was 48.5 ± 11.3 years (SD) in male patients and 45.9 ± 11.7 years in female patients (p = 0.149, z = -1.443, Mann-Whitney U-test). Sociodemographic information was collected during admission to the hospital for tumor surgery.

**Tumor Characteristics**

Preoperative MR images or CT scans were obtained to render a neuroimaging-based diagnosis. Anatomical classification of the brain based on the system of Matsui and associates was used to define the tumor location as was done in the study by Salo and colleagues. The distance of the tumor from the apex of the frontal lobe was determined by calculating from each CT scanning or MR imaging slice the ratio of the distance between the anterior part of the tumor and the apex of the frontal lobe to the anteroposterior diameter of the entire brain. The mean of these percentages was used to describe the distance from the apex of the frontal lobe to the tumor. There were 39 patients (51%) in whom the tumor was located anteriorly and 25 patients (32%) in whom the tumor was located posteriorly. The anterior or posterior location of the tumor was not defined in 13 cases (17%) because of the lesion’s infratentorial position. Complete tumor data have been reported earlier.

Histological grading was based on the World Health Organization classification system. Tumors were categorized as follows: 23 meningiomas (29.8%), 16 Grade I and II gliomas (20.8%), 15 Grade III and IV gliomas (19.5%), 12 vestibular schwannomas (15.6%), seven pituitary adenomas (9.1%), and four other tumors (5.2%; hemangiopericytoma, malignant lymphoma, craniopharyngioma, and an undefined tumor).

**Assessment of Functional Status**

Each patient’s overall functional state was analyzed according to the KPS before tumor operation as well as 3 months and 1 year after surgery. This scale indicates a person’s ability to work, perform physical activity, and care for the self, and has been used to assess functional status in patients with brain tumors. One trained physician assigned scores from 0 (dead) to 100 (healthy) at 10-unit intervals for each level. In the present study patients were divided into two categories according to KPS score: those with KPS scores greater than 70 and those with scores of 70 or less.

**Assessment of Depression**

Depressive symptoms were evaluated using the BDI, a widely accepted screening instrument for symptoms corresponding to the diagnostic criteria for depressive disorders outlined in the *Diagnostic and Statistical Manual for Mental Disorders, ed 4*. The BDI has been used to evaluate depressive symptoms in patients with primary brain tumors. Depression was considered to be present if the BDI score was 10 or greater. Patients were also asked if they had a history of depressive periods. Former episodes were evaluated using the depression scale from the CCEI, a clinical self-rating diagnostic scale used to differentiate healthy persons and psychoneurotic patients at a statistically significant level. The CCEI has been used in studies on patients with psychiatric or somatic diseases and has been validated for the general Finnish population. Patients completed both questionnaires during admission for the surgical procedure for the brain tumor, once within 1 to 5 days of surgery when the patient was unaware of the tumor’s malignancy, and again at 3 months and 1 year postsurgery. A trained psychologist administered both indices.

**Statistical Analysis**

Values are presented as the means ± SDs. The statistical significance of group differences in continuous variables was analyzed using the Mann-Whitney U-test (two groups) and the Kruskal-Wallis test (two groups) and those in categorical variables by using the Pearson chi-square test or the Fisher exact test. Differences between measurements for continuous variables were assessed with the Wilcoxon signed-rank test (two repeated measurements) and the Friedman test (two repeated measurements). Our correlation analyses included the Spearman rank-order correlation. We performed our analyses with commercially available statistical software (SPSS for Windows, version 10; SPSS, Inc., Chicago, IL).
Depression and functional outcome in patients with brain tumor

TABLE 1

<table>
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<tr>
<th>Parameter</th>
<th>Entire Study Population</th>
<th>No. (%)</th>
<th>Mean BDI Score</th>
<th>p Value</th>
<th>No. of Depressed Patients (%)</th>
<th>p Value</th>
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<td>0.241‡</td>
<td>9 (33.3)</td>
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<td>5.9 ± 5.9</td>
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<td>7 (25.9)</td>
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<td>≤70</td>
<td>26 (33.8)</td>
<td>10.9 ± 8.6</td>
<td>0.015‡</td>
<td>13 (48.1)</td>
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<td>&gt;70</td>
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<td>14 (51.9)</td>
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* Represents those with a BDI score greater than or equal to 10.
† Chi-square test, compared with patients whose BDI score was less than 10.
‡ Mann–Whitney U-test, compared with patients whose BDI score was less than 10.
§ Kruskal–Wallis test, compared with patients whose BDI score was less than 10.

Results

Table 1 shows the mean BDI scores according to the sociodemographic and clinical characteristics of patients with a primary brain tumor before surgery. Twenty-seven patients (35%) had scores indicating depression. Among all patients, the mean BDI score before tumor surgery was 8.1 ± 7.5. At the follow-up assessments 3 months and 1 year after tumor surgery the mean depression scores were 5.7 ± 4.8 and 5.7 ± 6.2, respectively. In the entire study sample, mean depression scores decreased statistically significantly (p = 0.031, z = −2.157, Wilcoxon signed-rank test) at 3 months after surgery compared with the corresponding scores before surgery. The mean depression scores in patients did not differ by sex, age, or marital or employment status at assessment times before surgery.

Patients with a history of depression demonstrated a significantly higher incidence of depression according to the BDI scores, and the proportion of these depressed patients was significantly greater than those having no history of depression. Furthermore, 13 of the patients (50%) with a lower functional status (KPS score ≤70) had depression, whereas only 14 of those (27%) with KPS scores greater than 70 were depressed.

As seen in Fig. 1, at the preoperative assessment there was no sex difference in the severity of depression in patients. Among the male population the mean depression scores showed statistically significant decrease (p = 0.047, z = −1.989, Mann–Whitney U-test) by 12 months postoperatively, whereas among the female population the scores decreased statistically significantly (p = 0.046, Wilcoxon signed-rank test) immediately following tumor surgery—8.7 to 6.1, and −0.545, respectively). Furthermore, at 3 months post-surgery the mean depression scores were statistically significantly higher in patients with a history of depression (p = 0.006, Mann–Whitney U-test), although the corresponding association was not present 1 year after the operation.

Table 2 shows the mean BDI scores according to the functional outcome and depression history at 3 months and 1 year after tumor surgery. A lower functional status (KPS score ≤70) was significantly associated with an increased incidence of depression at both follow ups (r = −0.140, and −0.545, respectively). Furthermore, at 3 months post-surgery the mean depression scores were statistically significantly higher in patients with a history of depression (p = 0.006, Mann–Whitney U-test), although the corresponding association was not present 1 year after the operation.

Table 3 presents the mean BDI scores according to the tumor location. Among patients with an anteriorly located tumor the mean depression score before surgery was greater compared with those harboring a posterior tumor. Moreover, in patients with an anterior tumor the mean BDI scores decreased statistically significantly (p = 0.049, Wilcoxon signed-rank test) immediately following tumor surgery—from 9.4 ± 8.7 to 6.1 ± 5.2. A corresponding decrease between preoperative and postoperative assessments was not found in patients harboring a tumor located in the posterior regions of the brain.

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Figure 2 shows the depression scores according to tumor histological characteristics preoperatively and at 3 months and 1 year postsurgery. There was no significant difference in the severity of depression between the histological subgroups either before or after surgical treatment of the tumor. On follow up in patients with a Grade III or IV glioma, the difference between higher preoperative and lower postoperative depression scores tended toward statistical significance (p = 0.084, Friedman test for repeated measurements). In patients with a pituitary adenoma, the mean BDI score decreased statistically significantly from 6.7 to 2.8 (p = 0.019, Friedman test for repeated measurements).

Discussion

We found in the present study that before tumor surgery every third patient with a primary brain lesion was suffering from actual depression according to the standardized BDI. Thus, the prevalence of depression in the current study sample was approximately six times greater than that in the general Finnish population. This finding coincides with the results of recent clinical studies of patients with brain tumors in which the prevalence of depression varied from 28 to 37%. In contrast, another study in patients with high-grade gliomas physician-determined depression was prevalent in 15% in the early postoperative state, whereas self-reported depressive symptoms were demonstrated in 93% of patients immediately after brain tumor surgery. Our results showed that 74% of patients with depression also had a history of depressive episodes. It is already known that depression is a recurrent disorder. In general, every second person with a depressive period in his or her life is at risk for a new depressive episode. After two depressive periods the risk for a new episode is 70%, and after three periods the risk is 90%. Furthermore, a premorbid psychiatric disorder in patients with brain tumors is known to be associated with adaptive or maladaptive responses to stress. It is understandable that a serious somatic disease posing the threat of death is psychologically stressful. At the same time many stressful events such as hospitalization and a neurosurgical operation occur in the patient’s life. Authors of recent literature have pointed out that stress can be a pathogenic factor for depression by causing disturbances in the HPA axis. Perhaps patients with an elevated risk of depression because of a history of a psychiatric disorder are liable to experience a new depressive episode following tumor diagnosis. Despite the earlier affective status, the depression scores in our study decreased significantly by 1 year postsurgery. A decreased incidence of depression following tumor surgery has been documented in earlier studies in patients with gliomas and meningiomas. In contrast, Litofsky and colleagues reported an increase in the incidence of depression compared with preoperative levels, that is, 15 to 22% at the 3- and 6-month follow ups, respectively, in patients with high-grade gliomas. In our study depression incidence remained the same before surgery and at 3 months postoperation in patients harboring high-grade gliomas.

Association of Depression With Functional Outcome

Depression has a significant effect on functional outcome and quality of life in patients with brain tumors. As reported by Huang and colleagues, however, few authors have focused particularly on functional outcomes in these pa-

<table>
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<td>no. of patients</td>
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<td>KPS score</td>
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<td>≤70</td>
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<td>8.8 ± 6.4</td>
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<td>&gt;70</td>
<td>57 (82.6)</td>
<td>5.1 ± 4.3</td>
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<tr>
<td>correlation (r)</td>
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<tr>
<td>correlation (r)</td>
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<td>0.000†</td>
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* Mann–Whitney U-test. † Spearman rank-order correlation.
Depression and functional outcome in patients with brain tumor

Depression According to Patient Sex and Tumor Location

Decreased depression scores after tumor surgery were seen in both male and female patients, although the level of depression was higher in female patients. Moreover, the proportion of depression in women was twice that of men, which agrees with Finnish epidemiological data. Note, however, that we found that depression levels decreased significantly for up to 1 year in men, whereas a similar decrease was apparent in women by 3 months postsurgery. These findings are interesting and require additional study given that sex differences in recovery from depression have been studied infrequently.

In our study patients with a tumor located anteriorly in a hemisphere had higher mean depression scores before surgery compared with scores in patients harboring a tumor in a posterior region. After surgery no difference in the level of depression was found regardless of anterior/posterior location. In addition, the level of depression decreased significantly between preoperative and 3-month posts operative assessments in patients with an anterior tumor. In a previous cross-sectional study a frontal lesion location was a highly significant predictor for an MDD after surgery in patients with a primary brain tumor. Furthermore, in the study by Irle and colleagues, patients with lesions in the ventral frontal cortex or in the temporoparietal cortex reported significantly worse mood states postoperatively than those with lesions in other regions of the brain. Thus, in patients with brain tumors the cortical interconnection with limbic structures is asserted to be more important than the specific lesion location for the development of neuropsychiatric symptoms. The occurrence of these symptoms probably originates from frontal and/or limbic release or disconnection syndromes. In the literature, data on the relationship between depression and brain lesion location in general has been contradictory. These findings are interesting and require additional study.

Depression in Patients With Different Types of Tumors

Our database consisted of primary brain tumors with different histological subgroups. The level of depression did not differ between these subgroups regardless of whether the tumor type was malignant or benign. Unfortunately, in the present study we were unable specifically to evaluate patients whose clinical status resembled apathy and to differentiate them from depressed patients. Obviously, the issue requires further study. Altogether, we assert that biological theories could primarily explain the cause of depression in patients with primary brain tumors.

TABLE 3
Depression scores in 64 patients with a primary brain tumor, according to tumor location

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of Tumors (%)</th>
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<tr>
<td>tumor location</td>
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<td>anterior</td>
<td>39 (50.6)</td>
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<tr>
<td>posterior</td>
<td>35 (32.5)</td>
<td>5.7 ± 6.0</td>
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<tr>
<td>p value*</td>
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<td>0.057</td>
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* Mann–Whitney U-test.

FIG. 2. Bar graph illustrating the mean BDI scores in the patients with brain tumor, according to tumor histological features before surgery (dark gray bars) and at 3 months (white bars) and 1 year (light gray bars) post surgery.
of Pringle and colleagues, who found higher preoperative depression scores in patients with meningiomas compared with those in patients harboring a tumor with malignant histological features. In our study, however, the level of depression in specific histological subgroups varied among the different assessments; for example, in patients with a pituitary adenoma the level of depression decreased significantly during the entire follow up. Korali and colleagues, in a recent retrospective study of patients with a different type of pituitary adenoma, did not find an increased risk of developing lifetime psychopathology compared with the general population. In this same study, however, patients with a pituitary adenoma and any diagnosis of a psychiatric disorder during the 12-month period before the study had a significantly increased risk of major depression. Formerly, an increased incidence of psychiatric disorders was found in patients with different types of pituitary adenoma; for example, depression and anxiety symptoms have been significantly associated with Cushing syndrome. Nowadays dysregulation of the HPA axis is thought to play an important role in the origins of depression. Although the number of cases in our subgroup of patients with pituitary adenoma was small and we could not evaluate the type of adenoma in these patients, the theory of dysregulation in the HPA axis in the origins of depression might explain, at least in part, the findings in this study. We emphasize that our findings must be considered preliminary and thus additional research using larger databases is urgently needed.

Study Limitations

One of the limitations of our study was the heterogeneous tumor sample. There were also a small number of cases within the histological subgroups and thus our findings are putative in nature, although our database represents a comprehensive and large sample of the Finnish population. Unfortunately, a psychiatric diagnosis based on any structured diagnostic interview was not available in this study, and our database did not include information on any psychotherapeutic or pharmacological treatment of the patients. Changes that have occurred over time in clinical neurosurgical care and depression treatment as well as their potential impact on patient recovery are worth investigating in future studies. For example, the pharmacotherapeutic treatment of depression has improved tremendously during the past decade: tricyclic antidepressive agents that were formerly commonly prescribed have been replaced with selective serotonin reuptake inhibitors, serotonin and noradrenaline uptake inhibitors, monoamine oxidase inhibitors, noradrenergic and specific serotonergic antidepressants.

Conclusions

Given the accompanying prospects of brain tumor, a psychological crisis is an understandable patient reaction, and it is important to treat the disorder as soon as the patient’s physical condition allows. The psychological approach must consist of crisis therapy with supportive elements and psychoeducational methods. Affective disorders in patients with brain tumors must be considered immediately after surgery, especially in patients with a history of depression and in those with a physical disability. In clinical practice, referral for consultation to Consultation-Liaison services is worth considering in planning for the treatment of depression. Physicians should direct special attention to recognizing depression in patients with pituitary adenomas and in those with primary tumors located anteriorly in the brain hemisphere.

References


A. Mainio, et al.
Depression and functional outcome in patients with brain tumor