



Study of Association of Various Psychiatric Disorders in Brain Tumors

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AJNS 2022;17:621–630.

Abstract

Background Brain tumors may be associated with high morbidity, and psychiatric symptoms may be an early manifestation. It is important to address mental symptoms as early as possible because they are prone to develop psychiatric comorbidities in future. If untreated, these situations may worsen and lead to burden upon caregivers.

Methods A total of 176 brain tumor patients between January 2021 and January 2022 constituted the sample size. All recently diagnosed cases of brain tumor with age equal to or more than 18 years who can comprehend and answer questionnaires were included. Patients with a long history of brain tumor or who had a history of a psychiatric illness other than presenting symptoms or any other serious medical illness were excluded.

Results Twenty-seven percent of brain tumor patients had psychiatric symptoms. Depressive symptoms were the most common, associated with 24% of patients, followed by anxiety disorders. Psychiatric disorders were more common in supratentorial compared to infratentorial tumors. Psychiatric symptoms seem to be associated more commonly with malignant tumors and peritumoral edema. Among malignant tumors, depressive symptoms tend to be related with high-grade glioma, and among benign tumors, they were more common in meningioma. No predilection to laterality and anatomical lobe involvement is reported.

Conclusion Screening of psychiatric disorders should be a routine in brain tumor patients. An integrated approach is required to treat brain tumor patients. Healthcare professionals should be more vigilant about the onset of psychiatric symptoms and the need of palliative care to improve the quality of life.

Keywords

- psychiatric
- SCAN
- brain tumors
- depressive disorders
- anxiety

article published online
October 28, 2022

DOI <https://doi.org/10.1055/s-0042-1757437>.
ISSN 2248-9614.

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Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Key Messages

- Depressive symptoms are the most common psychiatric disorder followed by anxiety or panic disorders associated with brain tumors.
- Psychiatric disorders are more common in supratentorial tumors compared to infratentorial tumors.
- No predilection to laterality and anatomical lobe involvement reported.
- Among malignant tumors, depressive symptoms tend to be related with high-grade glioma, and among benign tumors, it is more common in meningioma.

Introduction

Brain tumors have an annual incidence of 9 per 1,00,000 for primary tumors and 8.3 per 1,00,000 for metastatic tumors.¹ Brain tumors may be associated with high morbidity including neuropsychiatric sequelae. It may manifest as mood, personality, or cognitive changes. If neglected or untreated, these situations may worsen further and lead to burden upon caregivers.^{2,3} Not just as a part of sequelae, psychiatric symptoms may be the early manifestation of brain tumors and in some cases, the only presentation of a brain tumor.^{4–6} The incidence of depressive symptoms in brain tumor patients has been recorded with a wide range across different studies. Some reported it to be less than 10%, whereas other studies showed that 50 to 80% can have associated depressive symptoms.^{7,8} It is important to address mental health symptoms as early as possible because brain tumor patients are prone to develop psychiatric comorbidities in future. The distressing revelation of their diagnosis, the perception of their death, and losing of loved ones manifest as emotional and behavioral changes. In addition, brain tumor patients with psychiatric disorders may not have just diminished quality of life but overall survival also decreases.^{9,10} Hence, identifying high risk patients early is crucial to provide adequate palliative care. Brain tumors can alter functions of the neural framework vital for synchronizing emotions, behaviors, and personality.^{11,12} These tumors with associated edema can further cause inflammatory changes that are often correlated with psychiatric manifestations due to more mass effect.^{9,13} Therefore, some patients being treated for psychiatric disorders will eventually be detected with a brain tumor.^{7,14} Considering the higher occurrence of psychiatric manifestations in brain tumors and probability of missing the diagnosis of tumor at an early stage, this study is planned to understand the psychiatric illnesses likely to be associated with brain tumors and its characteristics (location, radiological, and histopathological features). Most of the previous studies have evaluated psychiatric disorders as a comorbid condition developed secondarily to diagnosis during the course of the disease, but our study is intended to evaluate the association of psychiatric symptoms that pre-exist the diagnosis of brain tumor.

Methods

A total of 176 consecutively diagnosed brain tumor patients between January 2021 and January 2022 constituted the study sample size. All recently diagnosed cases of primary or metastatic brain tumor with age equal to or more than 18 years who can comprehend and answer verbal/written questionnaires were included. Patients with long history of brain tumor or who had history of previous psychiatric illness other than presenting symptoms/current substance abuse or any other serious medical illness were excluded. The study was carried out in accordance with the latest version of the declaration of Helsinki.¹⁵ The nature and purpose of the study was explained to the participants and written informed consent was obtained either by the participant himself or his next of kin. The study was approved by the institution's ethics committee (Protocol No. 309 MC/EC/2021). All participants were evaluated preoperatively soon after the brain tumor was diagnosed. Demographic and tumor characteristics of the participants were assessed on a self-designed semistructured Performa by interviewing the participants and exploring the medical records along with neuroradiological investigations. Histopathological investigations were collected postoperatively.

Assessment of Psychiatric Symptoms

WHO Schedules for Clinical Assessment in Neuropsychiatry

We used the WHO Schedules for Clinical Assessment in Neuropsychiatry (SCAN) Version 2.1¹⁶ for evaluating psychiatric symptoms. The clinical interview was carried out by an experienced psychologist who was officially trained at designated SCAN training centers. He was blinded to radiological features of brain tumor. "The Schedules for Clinical Assessment in Neuropsychiatry (SCAN) is a semi-structured clinical interview which has been developed and tested globally with good validity and reliability."¹⁷

Assessment of Tumor Characteristics

Radiological Evaluation

The radiological diagnosis of the brain tumor was carried out by magnetic resonance imaging. Tumor location, laterality, size, and peritumoral edema were determined by an independent radiologist and a neurosurgeon. Anatomical locations were classified in relation to lobe as frontal (including frontal part of corpus callosum), temporal (including insular and medial part of sphenoid wing), parietal, occipital, ventricle (all intraventricular tumors), and more than one lobe. Tumors were also broadly classified as supratentorial or infratentorial and extra-axial or intra-axial. Tumor size was calculated by measuring maximum unidimensional diameter (cm) on the T1-W images. Peritumoral edema was classified into three grades based on hyperintensity seen around tumor on T2-fluid-attenuated inversion recovery images. Patients were categorized as grade 1 if the

edematous area was less than tumor mass, as grade 2 if the edematous and tumor mass were equal, and as grade 3 if the edematous area was larger than the tumor mass.¹⁸

Pathological Evaluation

Histopathological grading was done according to the WHO classification¹⁹ by independent pathologists who were blinded to the study.

Statistical Analysis

Discrete data was expressed in the form of proportions. Difference in proportion was analyzed using chi-squared test. Logistic regression was used to predict presence of psychiatric disorder on the basis of independent factors. The level of significance was 95% for all statistical analysis.

Results

Patients Characteristic

A total of 176 patients were enrolled in the study. The age of patients ranged from 18 to 73 years with mean age of 41.80 ± 14.30 years. ► **Table 1** gives the summary of patients' characteristic.

Distribution of Psychiatric Disorders

All patients were evaluated preoperatively and 27% (47 out of 176) of them had psychiatric disorders. Among various psychiatric disorders, obsession, depressive symptoms, manic episode, anxiety/panic attack, and alcohol dependence

were identified to be associated with brain tumors either in isolation or combined form. Depressive symptoms were the most common psychiatric disorder associated with brain tumors, presented in 24% of patients. Anxiety or panic attack was present in 8.5% of patients followed by manic episodes in 2.8%. (► **Table 2**).

Age and Gender versus Psychiatric Disorders

Majority of patients (13.6%) with psychiatric disorders were in the age group of 41 to 60 years. About 29% of males and 24% of females had psychiatric disorders in brain tumors. Depressive symptoms (27.8%) and panic attack (11.4%) were more common in patients aged between 41 and 60 years of age. Depressive symptoms were more common in males and anxiety/panic attack was more common in females. There was no statistically significant association between age and gender of patients with the presence of psychiatric illness (p -value > 0.05).

Laterality versus Psychiatric Disorders

Different psychiatric disorders were equally distributed in right- and left-sided brain tumors. No significant association existed between laterality of brain tumors and the presence of psychiatric disorders (p -value > 0.05).

Tumor Size versus Psychiatric Disorders

Psychiatric disorders were present in 31% of patients with tumor size more than 4 cm. Among patients with tumor size more than 4 cm, 24% patients had depressive symptoms,

Table 1 Association of psychiatric disorders with tumor characteristics

Variables			Psychiatric disorders		Total	p-Value
			Yes	No		
Laterality		Left	18	33	51	$\chi^2 = 3.125$ p -Value = 0.505
		Mid-line	9	36	45	
		Right	18	55	73	
		Multicentric	2	5	7	
Tumor size		≤ 4 cm	11	50	61	$\chi^2 = 2.941$ p -Value = 0.086
		> 4 cm	36	79	115	
Edema		Present	37	84	121	$\chi^2 = 8.318$ p -Value = 0.05
		Absent	10	45	55	
Location	Lobe	Frontal	14	28	42	$\chi^2 = 11.614$ p -Value = 0.071
		Temporal	13	20	33	
		Parietal	5	13	18	
		Occipital	0	2	2	
		Ventricle	3	12	15	
		More than one lobe	8	16	24	
		Others	4	38	42	
	Compartment	Supratentorial	46	104	150	$\chi^2 = 6.831$ p -Value = 0.009
		Infratentorial	1	25	26	
	Brain parenchyma	Extra-axial	17	55	72	$\chi^2 = 0.358$ p -Value = 0.549
		Intra-axial	30	74	104	

Table 2 Distribution of psychiatric disorders

Variables		Psychiatric disorders			No psychiatric disorders (%)	
		Depression (%)	Manic episode (%)	Anxiety/panic attack (%)		
Laterality	Left	14 (24.1)	1 (1.7)	10 (17.2)	33 (56.9)	
	Mid-line	9 (18.4)	1 (2)	2 (4.1)	36 (73.5)	
	Right	17 (21.8)	2 (2.6)	3 (3.8)	55 (70.5)	
	Multicentric	2 (25)	1 (12.5)	0 (0)	5 (62.5)	
Tumor size	≤ 4 cm	11 (17.2)	0 (0)	3 (4.7)	50 (78.1)	
	> 4 cm	31 (24)	5 (3.9)	12 (9.3)	79 (61.2)	
Edema	Present	32 (18.9)	5 (3.0)	13 (7.7)	84 (49.7)	
	Absent	10 (17.2)	0 (0)	2 (3.4)	45 (77.6)	
Location	Lobe	Frontal	13 (28.3)	2 (4.3)	2 (4.3)	28 (60.9)
		Temporal	11 (27.5)	3 (7.5)	6 (15)	20 (50)
		Parietal	5 (26.3)	0 (0)	1 (5.3)	13 (68.4)
		Occipital	0 (0)	0 (0)	0 (0)	2 (100)
		Ventricle	3 (18.8)	0 (0)	0 (0)	12 (75)
		More than one lobe	6 (23.1)	0 (0)	4 (15.4)	16 (61.5)
		Others	4 (9.1)	0 (0)	2 (4.5)	38 (86.4)
	Compartment	Supratentorial	41 (24.7)	4 (2.4)	15 (9)	104 (62.7)
		Infratentorial	1 (3.7)	1 (3.7)	0 (0)	25 (92.6)
	Brain parenchyma	Extra-axial	17 (21)	2 (2.5)	6 (7.4)	55 (67.9)
		Intra-axial	25 (22.3)	3 (2.7)	9 (8)	74 (66.1)

Note: A total of 64 psychiatric disorders were present in 176 brain tumor cases. In some patients, more than one psychiatric disorder were present.

followed by anxiety in 9.3% of patients. No significant association existed between tumor size and the presence of psychiatric disorders (p -value = 0.08).

Peritumoral Edema versus Psychiatric Disorders

About 30.6% of patients with peritumoral edema had associated mental symptoms compared to 18% of patients without edema. Among patients with grade II peritumoral edema, one-third (33.3%) of patients had depressive symptoms and 8.3% patients had anxiety (► **Figs. 1** and **2**). Statistically significant association existed between peritumoral edema and the presence of psychiatric disorders (p -value = 0.05).

Anatomical Location of Tumor versus Psychiatric Disorders

Presence of psychiatric disorders in relation to anatomical lobe is as follows: frontal lobe: 33.3% (14/42), temporal lobe: 39.3% (13/33), parietal lobe: 28% (5/18), more than one lobe involvement: 33.3% (8/24), and ventricle: 20% (3/15). Among patients with tumor in frontal lobe, depressive symptoms were present in 28.3% of patients, and anxiety and manic episode each in 4.3% of patients. Among patients with tumor in temporal lobe, depressive symptoms were present in 27.5% of patients, anxiety in 15% of patients, and manic episode in 7.5% of patients (► **Tables 1** and **2**). No statistically significant association noted between anatomical lobe in-

volvement of brain tumors with the presence of psychiatric symptoms (p -value > 0.05).

About 30.6% of patients with supratentorial tumors had psychiatric symptoms compared to 4% of patients with infratentorial tumors (► **Table 1**). Among patients with supratentorial tumor, depressive symptoms, anxiety and manic episode were present in 24.7, 9, and 2.4%, respectively (► **Table 2**). Statistically significant association existed between compartment location of brain tumors with the presence of psychiatric disorders (p -value < 0.05). Psychiatric disorders were more common in intra-axial tumors when compared to extra-axial tumors, but the difference was not statistically significant.

Histopathology versus Psychiatric Disorders

Psychiatric disorders were more commonly associated with malignant tumors when compared to benign brain tumors (30 vs. 23%, respectively). Among malignant brain tumors, 43% of high-grade gliomas were associated with psychiatric symptoms in comparison to 19% of low-grade gliomas (► **Fig. 3**). Among high-grade gliomas, 34% of patients had depressive symptoms and 11.3% had anxiety disorders. However, among low-grade gliomas, depressive symptoms and anxiety were present in 12.5% and 7.5% patients, respectively. Among meningiomas (benign tumor), 27.5% patients had depressive symptoms and 10% had anxiety disorders.

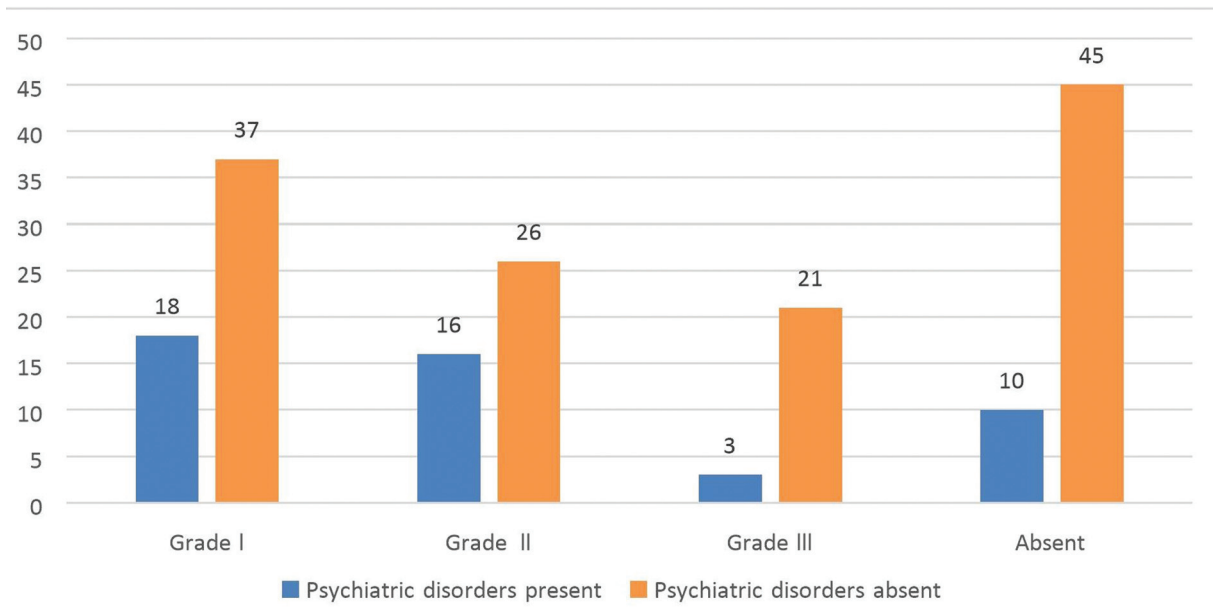


Fig. 1 Association between peritumoral edema and psychiatric disorders.

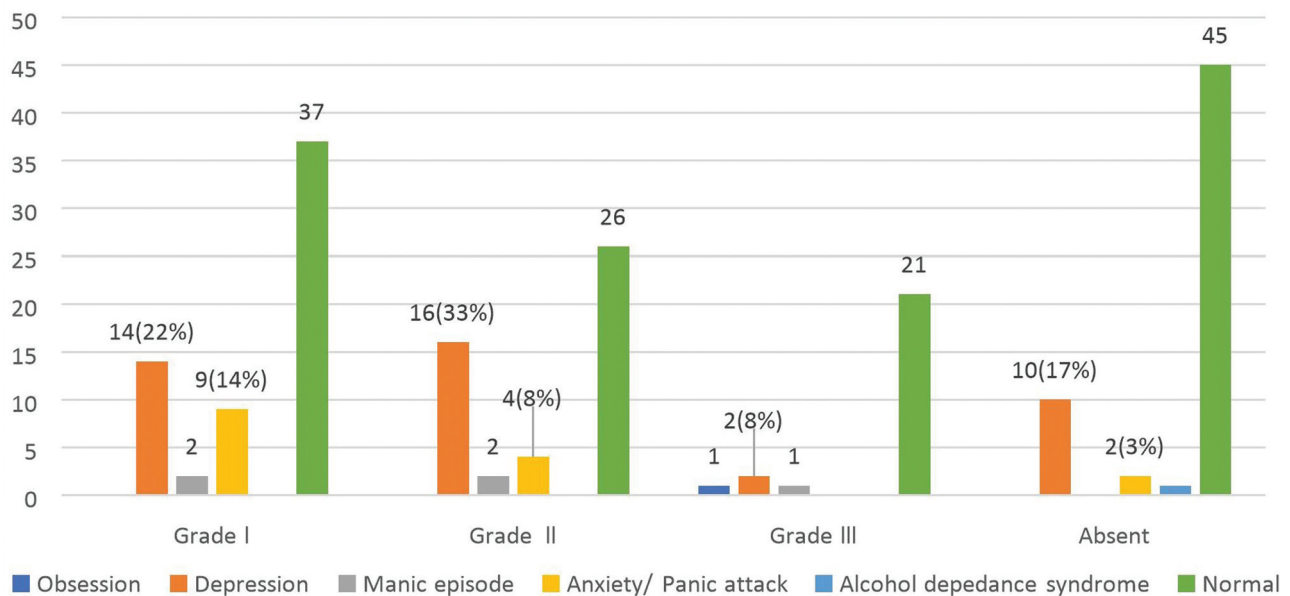


Fig. 2 Distribution of psychiatric disorders in relation to peritumoral edema.

About 25% of pituitary tumors were associated with depressive symptoms (► **Fig. 4**). Statistically significant association existed between the histopathology of brain tumors and the presence of psychiatric disorders (p -value = 0.02).

Logistic Regression for Prediction of Psychiatric Disorders in Brain Tumors

A logistic regression analysis (► **Supplement Table S1**; available in the online version only) was done to predict the psychiatric disorders in brain tumor patients (176 subjects) using age, sex, tumor size, edema, location (extra- vs. intra-

axial, supratentorial vs. infratentorial) and histopathology as predictor. A test of the full model was statistically significant indicating that the predictor as a set reliably distinguishes between yes (presence of psychiatric disorder) and no (absence of psychiatric disorder) outcomes (chi-square: 22.718, p = 0.002, df: 7). Prediction success overall was 70.5% (6.4% for yes and 93.8% for no). The Wald criterion demonstrated that age and location of tumor (supratentorial vs. infratentorial) (p < 0.05) made a significant contribution to prediction. Other predictors were not significant predictors.

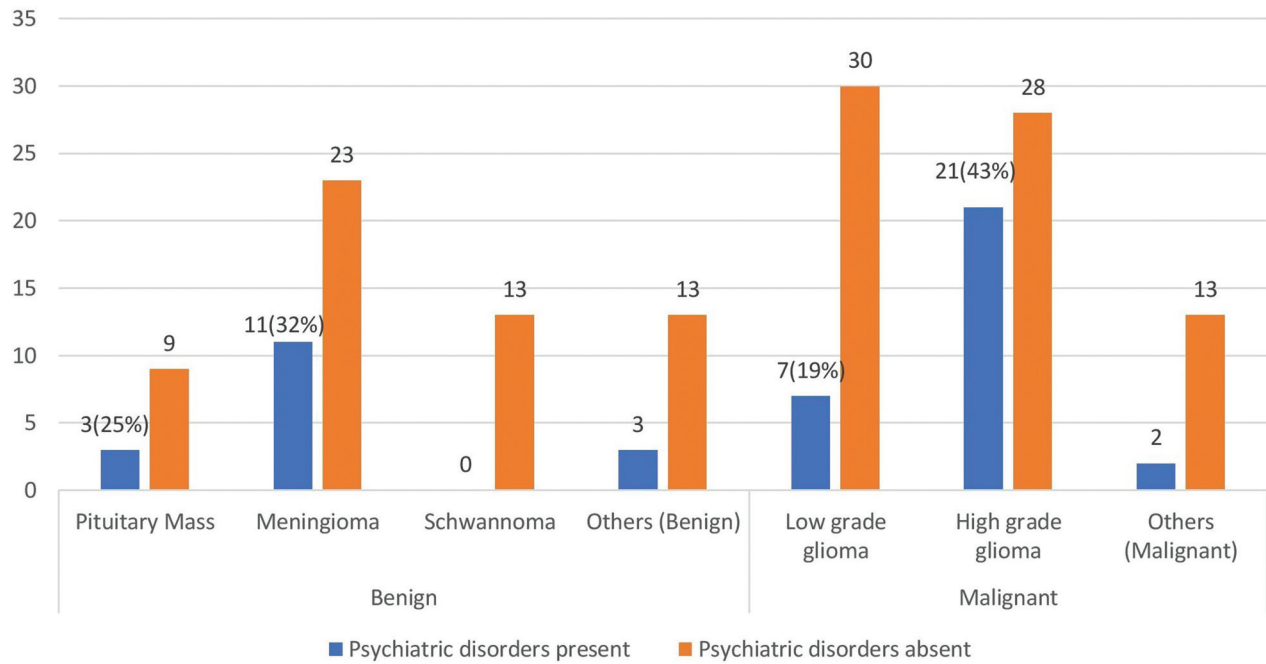


Fig. 3 Association between histopathology and psychiatric disorders.

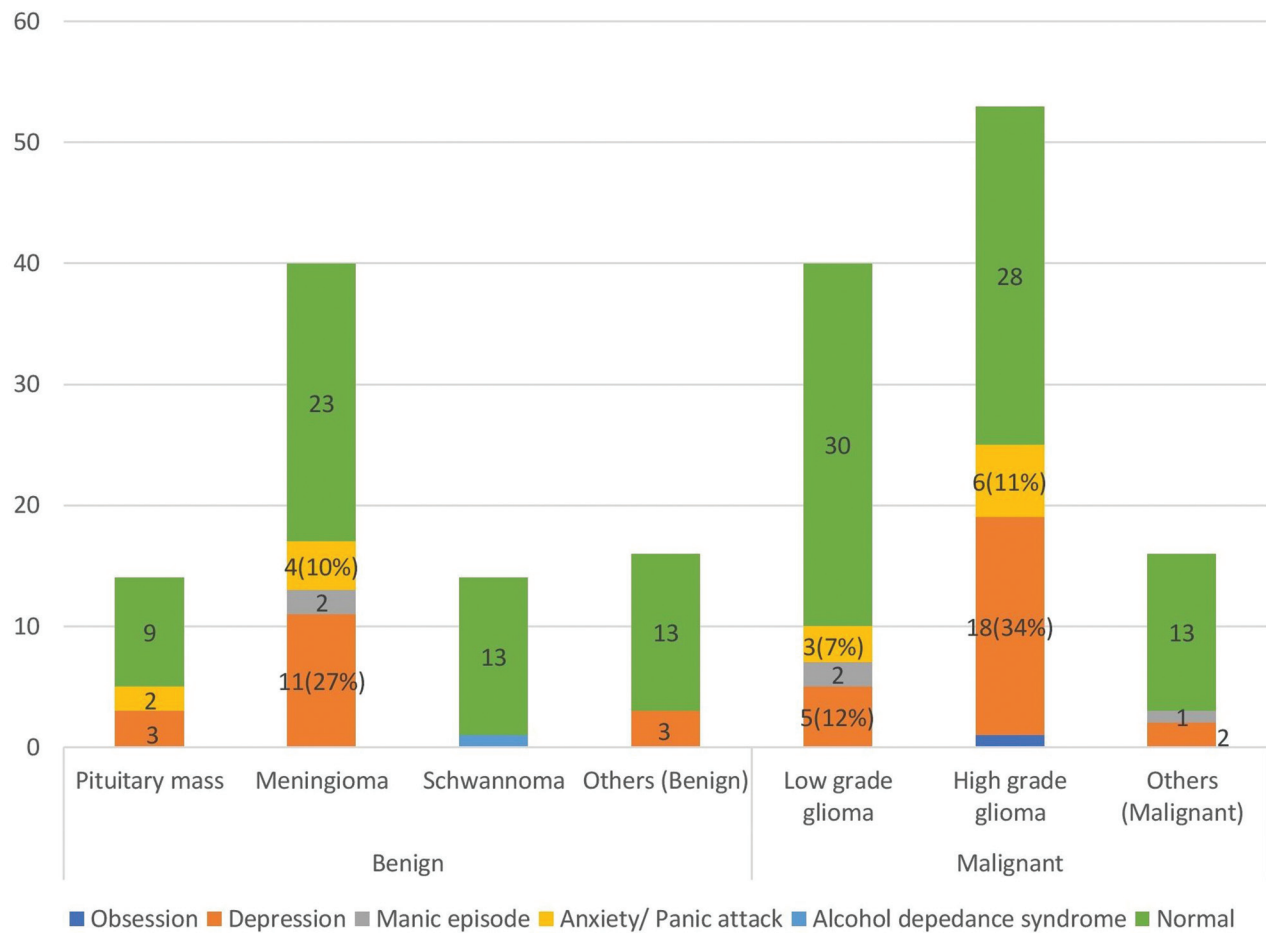


Fig. 4 Distribution of psychiatric disorders in relation to histopathology of tumors.

Discussion

Most of the brain tumors present with symptoms of raised intracranial pressure (headache, vomiting, and decreased vision) or neurological deficits, but infrequently they may present with psychiatric symptoms. But the relationship between psychiatric disorders and brain tumors has remained unclear. Psychiatric disorders are often misinterpreted and undertreated, although it may have considerable influence over the psychological well-being of brain tumor patients.^{9,20} It may lead to behavioral changes, increased suicidal tendency, low treatment adherence, longer recovery, and diminished survival. Moreover, caregivers are also predisposed to develop behavioral and personality changes. Treatment protocols of brain tumor patients such as steroids, chemotherapy, radiation, and surgery further add on symptoms of depression and anxiety.^{9,21} Recognizing and treating these disorders along with brain tumor pathology as integrated approach are crucial to improve the quality of survival period. Early psychiatric intervention can substantially reduce mortality risk and improve symptoms of adjustment disorder while lowering the seizure frequency.^{9,22,23}

In the initial phase of the disease, impairment in neuro-cognition remains subtle and thus likely to evade clinical attention or misdiagnosed as a psychiatric disorder.^{24,25} A neuropsychiatric syndrome, known as “disorders of diminished motivation” (DDM), is proposed to develop from the disorganization of dopaminergic pathways in various part of brain and is characterized by “impairments in goal directed behaviors.” Features of DDM are similar to that of the depressive disorders and thus often misdiagnosed.²⁵ There are no clear guidelines as such to recommend the indications of neuroimaging in psychiatric disorders. However, it is believed that the development of psychiatric symptoms after 40 years of age should raise the suspicion of brain tumor. Headache, seizure, visual impairment, and other neurological signs or symptoms, with psychiatric symptoms, herald the possibility of associated brain tumor. A recent change in character of previous psychiatric symptoms, poor response to treatment, and patients with absence of family history of psychiatric disorders suggest the possibility of underlying mass lesion. Presence of any of these features in a psychiatric disorder warrants neuroimaging.^{7,25}

Most of the studies have reported that women are more likely to be sensitive than men to the same psychological stress, and therefore, more prone to develop depressive symptoms.^{24,26} In contrast to this, we found that most of the patients with associated psychiatric disorders were in age group of 41 to 60 years with male preponderance. Depressive symptoms were more prevalent in males and anxiety/panic attack was more common in females. However, the difference was not statistically significant. As reported in literature, incidence of psychiatric disorders in brain tumor patients is widely ranged from 50 to 80%.^{7,27} Our study showed that 27% of brain tumor patients including benign, malignant and metastatic had psychiatric disorders. Most of them presented in clinical settings with symptoms of headache but change in mood symptoms cannot be

neglected completely, which often goes unnoticed. A recent meta-analysis done in 2010 showed that mood symptoms were the most common psychiatric manifestations and were found in 36% of case reports.¹³ Our study also found that depressive disorders were the most common psychiatric disorder presenting in 24% of brain tumor patients, followed by anxiety or panic attacks in 8.5% of patients.

A recent study evaluated the association of laterality of brain tumor with psychiatric disorders and concluded that left-sided tumors had significantly higher number of depressive disorders compared to the right.²⁸ On the other hand, one study reported that patients with right hemispheric tumors had significantly higher anxiety disorders compared to that of the left hemispheric tumors.²⁹ However, our study showed no predilection of psychiatric disorders to laterality of brain tumors.

The effect of tumor mass volume on the development of psychiatric disorder is still unknown. One recent study evaluated psychiatric manifestations in supratentorial meningiomas and showed that the frequency of psychiatric abnormalities in patients with meningiomas more than 35 cc was higher (66.66%) when compared to tumor volume of less than 35cc.³⁰ In our study, we examined correlation of tumor size (maximum unidimensional diameter) with psychiatric disorders and found that psychiatric disorders were present in 31% of patients having tumor size more than 4 cm compared to 18% of patients with tumor size equal to or less than 4 cm. Depressive disorders and anxiety/panic attacks were more common in patients with brain tumor size more than 4 cm.

Peritumoral edema is often said to be a causative factor for cognitive deficits and somatic symptoms like headache and fatigue. This cognitive dysfunctions in turn lead to depressive symptoms and anxiety, but sometimes it can mask the symptoms of depression in brain tumor patients.⁹ There are only few studies who have studied the association of psychiatric disorders with peritumoral edema. One study suggested that psychiatric disorders in high-grade meningioma patients were strongly associated with the presence of brain edema.³¹ Other study also found that psychiatric abnormalities were present in 73.7% of meningioma patients with peritumoral edema more than 50cc compared to 15.8% of patients with peritumoral edema volume less than 50cc.³¹ To the best of our knowledge, these studies till now were done in meningioma patients. However, this study after taking all types of brain tumor into account found psychiatric disorders to be associated in 30.6% of patients with peritumoral edema compared to 18% of patients without edema. Among patients with grade II peritumoral edema, one-third (33.3%) patients had depressive disorders, 8.3% patients had anxiety and 4.2% patients had manic episode. This association was statistically significant with *p*-value of 0.05. The general belief is that tumors that cause raised intracranial pressure cause more psychiatric disorders. Some authors even speculated that peritumoral edema results in disruption of cortical interconnections to limbic structures, which is more important than the tumor size and location.^{7,32,33}

The association of psychiatric disorders with respect to anatomical lobe involvement is much debated topic. In this study, we found supratentorial tumors to be associated with psychiatric disorders more in comparison to infratentorial tumors (30.6 vs. 4% respectively, $p = 0.009$). Depressive disorders were the most common psychiatric manifestations among supratentorial tumors. The possible explanation could be the disorganized intercerebral connections in supratentorial tumors which is not there in infratentorial tumors unless they cause significant hydrocephalus.

Most of the previous studies in literature suggested that frontal lobe tumors are associated with mood (depressive disorders) and behavior changes.^{34,35} In consistent with these old studies, one recent study also concluded a strong correlation between psychiatric manifestations and location of tumor with temporal lobe meningioma presenting most commonly, followed by frontal lobe tumors.³⁰ However, there are few studies which reported that psychiatric disorders were not found to be associated with any tumor location.^{11,28,36} Most important aspect while considering the location of tumor is a well-known fact that frontal lobe is an area that controls behavior and personality of an individual. Thus, frontal lobe tumors may cause behavioral or personality changes as neurological manifestation that has to be differentiated with psychiatric disorders. In our study, the SCAN tool has purposefully resolved this issue. We found that psychiatric disorders (in total) were present in all anatomical lobes with almost equal frequency and depressive symptoms occurred most frequently among these psychiatric disorders. But this distribution was not statistically significant.

Many studies have been done to look for the development of psychiatric disorders following the diagnosis of brain tumors (glioma). But only few studies have examined the association between the histopathology of tumor and psychiatric abnormalities, based on symptoms of presentation prior to diagnosis.^{37–39} Few studies say that patients with meningiomas tend to have higher predilection to depressive disorders (30%) compared to other tumors like gliomas and schwannomas. It can be even more prevalent than the general population.⁹ However, recently few studies have shown that psychiatric morbidity and cognitive dysfunction are not associated with tumor grading or malignancy.^{28,29,31} But no clear differentiation of symptoms between low- and high-grade gliomas has been made till now. In contrast with the above evidence, our study showed that psychiatric disorders were more commonly associated with malignant tumors when compared to benign brain tumors (30 vs. 23%, respectively). Forty-three percent of high-grade gliomas were associated with psychiatric disorders in comparison to 19% of low-grade gliomas. Among malignant tumors, depressive disorders were more commonly associated with high-grade glioma and among benign tumors, it was more common in meningioma. These differences were statistically significant with p -value of 0.02. More rapid is a tumor growth, the more probable it is to cause psychiatric disorders. However, slow growing tumors (such as meningiomas) may cause adaptive changes in the brain and hence, the

tumor will more likely remain “neurologically silent” and may present only with psychiatric symptoms without any neurological sign and symptoms. In these cases, if neuroimaging not performed early then accurate diagnosis may be delayed and tumor will eventually grow enough to cause neurological deficit.^{31,32,40} Among pituitary tumors, 25% of patients had psychiatric symptoms either in the form of depressive symptoms or anxiety or both. Pituitary tumors are associated with depressive and anxiety disorders and believed to be caused by variation in hypothalamic-pituitary-adrenal axis leading to hormonal dysregulation.⁹

Logistic Regression for Prediction of Psychiatric Disorders in Brain Tumors

On bivariate analysis, age, location (supratentorial vs. infratentorial), edema, and histopathology were significantly associated with the presence of psychiatric disorders in brain tumor cases. However, on multivariate analysis, only age and location (supratentorial vs. infratentorial) were found to be significantly associated with psychiatric disorders.

Strengths and Limitations

Most of the previous studies have used self-reported questionnaires to measure the association of psychiatric disorders, which is not a standardized scale. These questionnaires can be used for screening, but they tend to overestimate the existing rate because it depends on the individual interpretation of questions.⁹ The strength of our study is the use of SCAN tool, which is a structured interview and thus eliminates the chance of missing the diagnosis of psychiatric disorders. It can also reveal whether the psychiatric disorders are directly associated with brain tumor or merely a comorbid condition developed secondarily to diagnosis.⁹ The study has few limitations. First, the sample was collected from only one center. Thus, results may differ from population of different geographic region. Second, we have not taken cognition into account that may be affected in brain tumor patients. Third, the sample size is small, although greater than most previous studies. Multicentric studies with large sample size are required along with cognitive assessment to further characterize these findings.

Conclusion

Screening of psychiatric disorders should be a routine in brain tumor patients. An integrated and multidisciplinary approach should be required to treat brain tumor patients. Healthcare professionals should be more vigilant about the onset of psychiatric symptoms and the need of palliative care of to improve the quality of life.

Authors' Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Anand K. Das, Achal Sharma, Akhilesh Jain, Devendra K. Purohit, Ram K. Solanki, and Ajay Gupta. The first draft of the manuscript was written by Anand K.

Das and all authors commented on previous versions of the manuscript. All authors read and approved the final version of manuscript.

Ethical Approval

The study was approved by the Institution's Ethics Committee (Protocol No. 309 MC/EC/2021).

Data Availability

The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

Funding

None.

Conflicts of Interest

None declared.

Acknowledgements

I acknowledge all our professors and consultants in department of neurosurgery and psychiatry for the guidance and assistance.

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