



## BEHAVIORAL AND PSYCHOLOGICAL MANIFESTATIONS OF BRAIN TUMORS

### Radiology

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### ABSTRACT

**Introduction** - Primary brain tumors may present with neuro-psychiatric symptoms in a few cases. This study tries to evaluate the prevalence and predictors of various behavioral and psychological manifestations (BPS) of diagnosed cases of primary brain tumors.

**Methodology** - We conducted a cross-sectional questionnaire based study among consenting patients diagnosed with primary brain tumors at a Government Medical College and Hospital at Faridabad, Haryana. The behavioral and psychological symptoms were assessed through the Neuropsychiatric Inventory (NPI) having a severity assessor and a Caregiver Distress Scale.

**Results** - Behavioral and psychological symptoms were present in 36 (72%) out of 50 randomly selected subjects. The commonest symptoms were anxiety, irritability and dysphoria. BPS, their severity and caregiver distress were significantly associated with tumors of size greater than 4 cm, located in frontal/temporal and parietal regions, exhibiting midline shift and mass effect ( $p < 0.05$ ). Caregiver distress was also predicted by psychotic and behavioral type of symptoms as compared to mood symptoms ( $p < 0.05$ ).

**Conclusion** - Neuropsychiatric symptoms may be the primary presentation and the only clue to the presence of a brain tumor. Clinicians must have a high index of suspicion in patients with new-onset psychiatric symptoms, having atypical presentations and not responding to standard treatment.

### KEYWORDS:

Brain tumors; Psychiatric symptoms; Neuropsychiatric; Behavioral symptoms

### Introduction

The brain tumors are classified primarily based on their histopathological characteristics or anatomical location. Primary brain tumors originate from brain tissues while secondary brain tumors are the ones that metastasize to numerous locations throughout the brain. Hence, neuropsychiatric symptoms are more often associated with metastatic tumors (1). Primary brain tumors usually present with symptoms due to mass effect (2). However, some patients with intrinsic primary brain tumors may experience neurological, cognitive, and psychiatric symptoms that greatly affect daily life (3).

The primary brain tumors are relatively common with an annual incidence of 9 per 100000, compared to 8.3 per 100000 for metastatic brain tumors (2). Gliomas are the most common primary brain tumors, accounting for 40%-55% of all brain tumors. The studies of behavioral and psychiatric symptoms (BPS) originating due to brain tumors date back to the 1930's (4). Keschner reported that approximately 80% patients with brain tumors have psychiatric symptoms, while only 15% had these symptoms as the first clinical manifestation (5).

Neuropsychological symptoms are common in brain tumors and are often multiple. Since nomenclature and parameters of psychiatric disorders change constantly and frequently, it is often difficult to assess these symptoms consistently. Also, it is difficult to predict the symptoms based on the location or vice versa. These symptoms may take form of changes in personality and behavior, mood lability, hallucinations, psychosis, apathy, and motor disturbances (3). The available literature is mostly individual case based. Since, it is rare for primary brain tumors to initially present with neuro-psychiatric symptoms, this study tries to evaluate various behavioral and psychological manifestations of diagnosed cases of primary brain tumors with an established Neuropsychiatric Inventory. We also tried to evaluate the predictors associated with behavioral and psychological symptoms in patients with brain tumors.

### Methodology

We conducted a cross-sectional questionnaire based study among the patients presenting to the outpatient department of a Government Medical College and Hospital at Faridabad, Haryana. The study was conducted after obtaining approval from the Institutional Ethics Committee. Written informed consent form approved by Institutional

Ethics Committee was used before recruiting study subjects.

The study was conducted in the psychiatry and radiology departments of the associated hospital. The participants diagnosed with primary brain tumors were considered for inclusion. Brain tumors were detected and diagnosed using cross-sectional radiological imaging techniques like Contrast Enhanced Magnetic Resonance Imaging (CEMRI) and/or Contrast Enhanced Computed Tomography (CECT) of head. Characterization of the lesion was based on Imaging findings accompanied with pre/post operative histopathological correlation whenever possible.

The inclusion criteria were patients in the age group of 15-60 years, of both sexes, diagnosed with primary brain tumors, having a single and relatively well defined lesion, and willing to give written informed consent either pre-operatively or within one month of operation. The exclusion criteria were patients having any past psychiatric disorder as per DSM-5 (before 6 months of diagnosis of brain tumor), substance use disorder diagnosed as per DSM-5 except nicotine, having multiple tumors and/or secondary metastatic tumors (6). We also excluded patients with Mini Mental State Examination (MMSE) score of less than 21, as cognitive impairment may predispose to BPS (7).

A sample of randomly selected 50 patients diagnosed with primary brain tumors were considered for recruitment in the study. The sample size was considered based on relative rarity of the primary brain tumors (approximately 9 per 1,00,000 population). The study universe was patients referred to radiology department for brain imaging due to various possible reasons, from any of the hospital departments. Those diagnosed with primary brain tumors, meeting the inclusion and exclusion criteria were recruited for the study. These patients were referred to the psychiatry department for detailed evaluation.

The subjects were interviewed by the 2<sup>nd</sup> and the 3<sup>rd</sup> author in detail regarding the socio-occupational details and clinical history. The behavioral and psychological symptoms were assessed through the Neuropsychiatric Inventory (NPI). The NPI is a standard and validated tool to provide a brief assessment of neuropsychiatric symptomatology in routine clinical practice settings over the last one month (8). The NPI includes 10 neuropsychiatric domains with severity assessor (Likert 1 to 3) and a Caregiver Distress Scale (Likert 0 to 5) for

evaluating the psychological impact of neuropsychiatric symptoms reported to be present. The scores of NPI were used to determine the overall severity and distribution of BPS among the patients with brain tumors. Midline shift and mass effects were determined through clinical history and radiological findings.

The data collected for all participants was analyzed using SPSS software (20th version). Confidence interval of 95% was used. For descriptive data, frequency and percentages were used. A simple table was prepared using the NPI scores highlighting the distribution and severity of BPS. Categorical variables were compared through chi square test and ANOVA. Pearson correlation was used for continuous variables. Unpaired t test was used to compare the differences of mean of various parameters.

**Results**

A total of 57 patients were screened and considered for inclusion in the study. Three of them had MMSE scores less than 21 and were excluded. Two had history of psychiatric disorders and were seeking treatment. Two had alcohol dependence syndrome and had to be excluded. Hence, a total of 50 randomly selected subjects completed the study.

Table 1 shows the distribution of socio-demographic parameters, clinical parameters and NPI symptoms. The mean age of study group was 46.60 years. Most of the brain tumors were either glioblastoma, astrocytoma or meningioma (70%), located primarily in supratentorial areas like parietal, temporal and frontal regions. Tumors ranged from 2 cm to 8 cm in size, and approximately one-fourth exerted mass effect. We found that NPI symptoms were present in 36 patients (72%) with brain tumors. The commonest symptoms were anxiety, irritability and dysphoria, followed by agitation and apathy. The mean NPI symptom severity score was 9.28 (out of 30) while the mean caregiver distress score was 14.88 (out of 50).

Table 2 shows the correlation of presence of NPI symptoms with tumor related parameters. It highlights that Behavioral and Psychological symptoms were significantly common in tumors of size greater than 4 cm (Image 1), located in frontal/temporal and parietal regions (Image 2), exhibiting midline shift and mass effect (p<0.05). Sex of patients, type of tumor and medical co-morbidities did not affect NPI symptoms.

**Table 1 - Distribution of socio-demographic parameters, clinical parameters and NPI Symptoms**

Parameter		Frequency N (%), N=50	NPI Symptom	Frequency N (%), N=50
Sex	Male	23 (46)	Present	36 (72)
	Female	27 (54)		
Tumor size	2-4 cm	21 (42)	Delusion	14 (28)
	4-6 cm	19 (38)		
	6-8 cm	10 (20)	Hallucination	7 (14)
Location	Parietal	15 (30)		
	Temporal	12 (24)	Agitation	21 (42)
	Frontal	8 (16)		
	Occipital	7 (14)	Dysphoria	27 (54)
	Brainstem	5 (10)		
	Cerebellum	3 (6)	Anxiety	30 (60)
Type of tumor	Glioblastoma	16 (32)		
	Astrocytoma	13 (26)	Euphoria	17 (34)
	Meningioma	12 (24)		
	Brainstem glioma	2 (4)	Apathy	22 (44)
	Craniopharyangioma	2 (4)		
	Medulloblastoma	2 (4)	Disinhibitions	14 (28)
	Pituitary adenoma	3 (6)		
Mass effect	Yes	13 (26)	Irritability	29 (58)
Midline shift	Yes	12 (26)		
Comorbidity	Yes	8 (16)	Aberrant motor behavior	16 (32)
Age (years)	Mean ± S.D	46.60 ± 8.31		

NPI Severity Score (maximum of 30)	Mean ± S.D	9.28 ± 6.70
Caregiver Distress Score (maximum of 50)	Mean ± S.D	14.88 ± 11.15

NPI - Neuropsychiatric Inventory, S.D - Standard Deviation

We were interested in evaluating the correlation between severity of symptoms and caregiver distress with clinical (tumor related) parameters and NPI symptoms. Table 3 shows that severity of NPI symptoms and caregiver distress also correlated with tumors of size greater than 4 cm, located in frontal/temporal and parietal regions, exhibiting midline shift and mass effect, presence of psychotic and behavioral symptoms compared to mood symptoms, and having multiple symptoms of NPI (p<0.05).

**Table 2 - Correlation of NPI Symptoms with clinical (tumor related) parameters**

Parameter		NPI Symptoms Present n/N (%)	P-value
Sex	Male	16/23 (70)	0.755
	Female	20/27 (74)	
Tumor size	2-4 cm	12/21 (57)	0.040*
	4-8 cm	24/29 (82.7)	
Location	Parietal + Temporal + Frontal	29/35 (82.8)	0.009*
	Occipital + Brainstem + Cerebellum	07/15 (46.7)	
Type of tumor	Glioblastoma	12/16 (75)	0.904
	Astrocytoma	10/13 (26)	
	Meningioma	9/12 (76.9)	
	Brainstem glioma	1/2 (50)	
	Craniopharyangioma	1/2 (50)	
	Medulloblastoma	1/2 (50)	
	Pituitary adenoma	2/3 (66.6)	
Mass effect	Yes	12/13 (92.3)	0.036*
	No	24/37 (64.8)	
Midline shift	Yes	12/12 (100)	0.014*
	No	24/38 (63.1)	
Comorbidity	Yes	6/8 (75)	0.837
	No	30/42 (71.4)	

\* - Significant at p-value < 0.05

N- Frequency distribution of a parameter, n - Number of subjects having NPI symptom in that parameter

NPI - Neuropsychiatric Inventory

Co-morbidities include hypertension, diabetes mellitus and other significant medical illnesses.

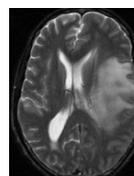


Image 1 - Anaplastic Astrocytoma: Large left cerebral mass lesion in temporo-parietal region with perilesional edema and mass effect

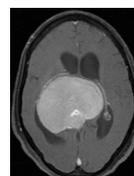


Image 2 - Meningioma: Large enhancing midline mass lesion with both supra and infratentorial components extending into bilateral temporal and thalamic regions with mass effect.

Table 3 - Correlation of severity and caregiver distress with clinical (tumor related) parameters and NPI symptoms

Parameter		Mean/Mean square\$ /Pearson correlation# (Symptom Severity score)	Correlation with severity of symptoms (P-value)	Mean/Mean square\$ /Pearson correlation# (Caregiver distress)	Correlation with caregiver distress (P-value)	
Sex	Male	9.57±8.01	0.784	15.43±13.23	0.749	
	Female	9.04±5.74				
Age (years)		0.235 <sup>#</sup>	0.100	0.126 <sup>#</sup>	0.382	
Tumor size	2-4 cm	4.48±3.81	0.000*	6.81±5.64	0.000*	
	4-8 cm	12.76±6.17				
Location	Parietal + Temporal + Frontal	10.60±7.13	0.032*	10.69±12.16	0.10	
	Occipital + Brainstem + Cerebellum	6.20±4.29				
Type of tumor	Glioblastoma	22.246 <sup>§</sup>	0.831	49.034 <sup>§</sup>	0.898	
	Astrocytoma					
	Meningioma					
	Brainstem glioma					
	Craniopharyngioma					
	Medulloblastoma Pituitary adenoma					
Mass effect	Yes		16.23±4.78	0.000*	27.08±8.44	0.000*
	No		6.84±5.45		10.59±8.52	
Midline shift	Yes		18.17±3.88	0.000*	30.17±7.40	0.000*
	No		6.47±4.59		10.05±6.96	
Comorbidity	Yes		12.50±8.26	0.139	20.63±14.24	0.113
	No		8.67±6.28		13.79±10.30	
NPI symptom group	Psychotic	Yes	12.14±6.55	0.000*	19.97±11.22	0.000*
		No	5.33±4.61		7.86±6.22	
	Mood	Yes	9.83±6.68	0.079	11.83±11.11	0.061
		No	4.00±2.16		5.00±1.82	
	Behavioral	Yes	10.92±6.59	0.002*	17.61±11.09	0.002*
		No	4.00±3.97		6.09±5.95	
Number of symptoms			0.832 <sup>#</sup>	0.000*	0.803 <sup>#</sup>	0.000*

\$- Mean square with in groups, #- Pearson correlation

NPI - Neuropsychiatric Inventory

NPI symptom group - Psychotic (hallucination, delusion, agitation), Mood (euphoria, dysphoria, anxiety, apathy), Behavioral (irritability, aberrant motor behavior, disinhibitions)

## Discussion

Behavioral and psychiatric manifestations are a part and parcel of various brain tumors. Still, there is controversy regarding different tumor parameters such as location, size, type of tumor etc. in relation to BPS symptoms. A few studies conducted in the past have tried to evaluate the BPS symptoms in association with brain tumors, but the results have been varying and inconsistent (1, 9). Changes in psychiatric nomenclature over the years and use of unreliable tools has complicated the picture further. Most of the literature in this field is based on individual case reports (10). So, this study aimed to assess the various behavioral and psychiatric symptoms, their predictors, severity and caregiver distress in association with brain tumors.

We found that approximately 70% patients with brain tumors had neuro-psychiatry morbidity during the past month. Similarly, a study reported that approximately 80% patients with brain tumors have psychiatric symptoms (5). Mardaga et al reported 90% prevalence of BPS in brain tumor patients in a conference paper (11). However, no other literature could be found regarding the same. Anxiety (60%) was the most common symptom followed by irritability (56%) dysphoria (54%) and agitation (42%) in our study. Madhusoodanan et al also reported mood symptoms to be the most common, being reported in 36% of the cases (12). Most of the previous studies have reported anxiety and depressive symptoms to predominate in patients with BPS (1,2,13). This has been hypothesized as a normal psychological reaction to a serious illness, apprehension before undergoing chemotherapy or operative procedure, and has biological and biochemical bases (14,15).

Our study showed that prime predictor of BPS symptoms were tumor size (>4 cms), mass effect, midline shift, and location (parietal, temporal and frontal) as compared to the tumors of size (<than 4 cms), without mass effect & midline shift and of other location (occipital, brainstem and cerebellar region) respectively. The type of tumor and co-morbid medical disorders had no significant difference in BPS symptoms. Other studies have reported higher incidence of depression and memory disturbances in left hemispheric tumors, many other studies have refuted this association (16, 17). However, the association between specific areas in the brain and psychiatric manifestations can be seen, such as psychotic symptoms and pituitary tumors, anorexia and hypothalamic tumors (12).. In another study done by Lampl and Barak, psychiatric disorders were diagnosed in 44% of meningiomas with convexity. They also obtained a statistically significant correlation between edema volume and the presence of coexisting psychiatric disorders, but not between the tumor's mass volume and the psychiatric symptoms (18). Seddighi et al showed that tumor location was significantly associated with depressive and anxiety symptoms (13).

Quality of life also appears to be affected in brain tumor patients with psychiatric symptoms (16,17,19,20). Further, psychiatric symptoms also impact the distress among caregivers. The patients with greater tumor size, mass effect, midline shift, having multiple symptoms in psychotic and behavioral domains had significantly more severe symptoms and caregiver distress as compared to those who didn't. But the location, type of tumor and comorbidity had no significant effect on their severity scores and caregiver distress. For the first time, it was shown that that psychotic and behavioral symptoms caused greater severity of caregiver distress in comparison to the patients with only mood symptoms. The number of symptoms also positively correlated with severity scores and caregiver distress. Charkavliuk et al. analyzed 271 patients with brain tumors to evaluate the prevalence of psychiatric symptoms and psychotropic treatment and their relation to quality of life. They concluded that psychiatric symptoms such as depression and anxiety may significantly hamper the quality of life (19).

Our study is one of a very few studies which have assessed primary brain tumors and associated neuro-psychiatric symptoms. It has focused only on primary brain tumors which are more common than secondary metastatic tumors. It has also evaluated the tumor related predictors associated with these symptoms. Relatively small sample size, random selection of patients and unequal distribution of different tumors (in regard to location, type and size) are the main limitations of the study.

### Conclusion

We may conclude that brain tumors mostly present with neurologic features, however, sometimes psychiatric symptoms may be the only clue to the presence of a brain tumor. Vice versa, tumors of size greater than 4 cm, located in frontal/temporal and parietal regions, exhibiting midline shift and mass effect are an important predictor of impending neuropsychiatric manifestations.

It is vital for clinicians to have a high index of suspicion of brain tumor in patients with new-onset psychiatric symptoms, having atypical presentations and not responding to standard treatment. Neuroimaging should be considered in such patients who are young and have no past or present history of psychiatric disorders. Still, there are lacunae's in research in this indispensable area of brain tumors and their different psychiatric and behavioral manifestation, and the extent to which they affect daily functioning and family life.

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Conflicts of Interest - We have no conflicts of interest and nothing to declare.

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