Psychiatric aspects of brain tumors: A review

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Abstract

Infrequently, psychiatric symptoms may be the only manifestation of brain tumors. They may present with mood symptoms, psychosis, memory problems, personality changes, anxiety, or anorexia. Symptoms may be misleading, complicating the clinical picture. A comprehensive review of the literature was conducted regarding reports of brain tumors and psychiatric symptoms from 1956-2014. Search engines used include PubMed, Ovid, Psych Info, MEDLINE, and MedScape. Search terms included psychiatric manifestations/symptoms, brain tumors/neoplasms. Our literature search yielded case reports, case studies, and case series. There are no double blind studies except for post-diagnosis/-surgery studies. Early diagnosis is critical for improved quality of life. Symptoms that suggest work-up include: new-onset psychosis, mood/memory symptoms, occurrence of new or atypical symptoms, personality changes, and anorexia without body dysmorphic symptoms. This article reviews the existing literature regarding the diagnosis and management of this clinically complex condition.

Key words: Brain tumors; Psychiatric symptoms; Neuropsychiatric; Behavioral symptoms; Diagnosis; Management; Neuroimaging

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Core tip: Psychiatric symptoms may rarely be the only presentation of a brain tumor. Any type of psychiatric symptoms can occur with brain tumors. Unfortunately, the symptoms generally do not have any localizing value. New onset psychosis, mood or memory symptoms, occurrence of new or atypical symptoms, personality changes and anorexia without body dysmorphic symptoms, suggest a work up including neuroimaging. Early diagnosis is
critical for improved quality of life for the patient.

INTRODUCTION
The majority of large studies discussing brain neoplasms and psychiatric symptoms date back to the 1930’s. Since psychiatric nomenclature and disease parameters change constantly, it is difficult to analyze this topic in a consistent manner.

Brain tumors are relatively common with an annual incidence of 9 per 100000 for primary brain tumors and 8.3 per 100000 for metastatic brain tumors. Brain tumors may be classified based on their histopathologic characteristics or anatomical location. There are two types of tumors: ones that are primary, originating from the brain tissue, and ones that metastasize to numerous locations throughout the brain. Because of this, metastatic tumors often present with more neuropsychiatric symptoms. The most common primary brain tumors are gliomas, which are divided into several types: astrocytomas, oligodendrogliomas, and ependymomas. The groups of brain tumors that are not from the glial tissue include meningiomas, schwannomas, craniopharyngiomas, germ cell tumors, pituitary adenomas, and pineal region tumors. Majority of all brain tumors are gliomas, accounting for 40%-55%. Tumors metastasizing to the brain account for 15%-25% of all brain tumors.

Most brain tumors present with specific neurologic signs due to mass effect. However, in rare cases they may present primarily with psychiatric symptoms. A study by Keschner et al reported that 78% of 530 patients with brain tumors had psychiatric symptoms. However, 18% of the 530 presented only with these symptoms as the first clinical manifestation of a brain tumor. Due to the neuronal connections of the brain, a lesion in one region may manifest a multitude of symptoms depending on the function of the underlying neuronal foci. Symptoms of brain lesions depend on the functions of the networks underlying the affected areas. For instance, a significant association has been found between anorexia symptoms and hypothalamic tumors, a probable association between psychotic symptoms and pituitary tumors, memory symptoms and thalamic tumors, and mood symptoms and frontal tumors.

Management of brain tumors consists of surgical resection of the tumor, stereotactic radiosurgery, radiotherapy, and chemotherapy. Treatment of the psychiatric symptoms caused by brain tumors depends on the presenting symptoms and includes antidepressants, antipsychotics, mood stabilizers, and anxiolytics. Although there may be an association between some tumor locations and psychiatric symptoms, it is difficult to predict the symptoms based on the location or vice versa. This paper will explore the diverse manifestations, diagnosis, and management of brain tumors that present primarily with psychiatric symptoms.

LITERATURE REVIEW
A comprehensive review of the literature was conducted regarding reports of brain tumors and psychiatric symptoms from 1956-2014. Search engines used include PubMed, Ovid, Psych Info, MEDLINE, and MedScape. Search terms included psychiatric manifestations/symptoms, brain tumors/neoplasms. Our literature search yielded case reports, case studies, and case series. There are no double blind studies except for post-diagnosis/surgery studies.

We found 172 cases with psychiatric symptoms. Psychiatric symptoms were assigned to 7 main categories: depressive symptoms, apathy, manic symptoms, psychosis, personality changes, eating disorders, and a miscellaneous category for the less frequently encountered symptoms. Each category will be discussed. Some reports may be included in more than one category due to combination of symptoms.

Depression (Table 1)
Depression may be seen in different stages (before, during or after diagnosis/treatment) of brain tumors. Depression was reported in 2.5%-15.4% of primary brain tumors[8]. According to Mainio et al, depression was found in 44% of all brain tumor patients, primary and metastatic, and was associated with functional impairment, cognitive dysfunction, reduced quality of life, and reduced survival. It was also noted that depression was more commonly found in frontal lobe tumors. More specifically left frontal lobe tumors were more frequently associated with depression and akinesia.

Apathy (Table 2)
Apathy must be distinguished from major depressive disorder and chronic fatigue syndrome. Patients presenting with apathy when asked about their mood, state that they are not depressed, but instead have chronic fatigue and lack of motivation. This may be associated with a functional disconnection between the frontal lobe and paralimbic areas, or damage in these areas. Levy et al suggests that apathy is common in neurodegenerative disorders and is independent of depression. The diagnostic criteria for apathy suggested by Starkstein et al include lack of motivation, diminished goal-directed behavior (lack of effort, or dependency on others to structure activity), diminished goal-directed cognition (lack of interest in learning new things or in new experiences, or lack of concern about one’s personal problems), or diminished emotions (unchanging affect, or lack of emotional responsivity to positive or negative events).
### Table 1  Brain tumors and depressive symptoms\(^{(41)}\)

| Ref. | Psychiatric symptoms | Tumor location | Tumor type | Remarks |
|------|----------------------|----------------|------------|---------|
| Zivković et al\(^{(55)}, 2014\) | Depression, impairment in memory, motivation, concentration, insomnia, increased appetite, headaches | Parietal lobe | Epidermoid tumor | Subsequent neurological symptoms led to CT scan and diagnosis of the brain tumor |
| Assefa et al\(^{(49)}, 2012\) | Depression, anxiety, insomnia, headache, nausea, vomiting, unilateral abducens palsy | Parasellar and retrosellar areas of the petrous apex, temporal lobe | Meningioma | Neurologic deficit with psychiatric symptoms |
| Ondúlek et al\(^{(34)}, 2011\) | Depression, anxiety, headache | Left temporal lobe | Glial tumor | Persistent headache led to neurologic consult and CT, and diagnosis of the brain tumor |
| Cheema et al\(^{(53)}, 2010\) | Depression, anhedonia, low energy, insomnia, suicidal ideations | Left frontal and temporal lobe | Glioblastoma | Duration of psychiatric symptoms of 10 yr make the association of glioblastoma questionable and possibly unrelated to brain tumors |
| Bunevicius et al\(^{(46)}, 2008\) | Depression, Parkinsonian symptoms | Right fronto-temporal lobe | Meningioma | Subsequent neurological symptoms led to CT scan and diagnosis of the brain tumor |
| Bunevicius et al\(^{(40)}, 2008\) | Depression, psychosis | Left temporal lobe | Intra-cerebral cyst | Refractory symptoms |
| Habermeyer et al\(^{(47)}, 2008\) | Depression, delirium | Right frontal lobe | Glioblastoma multiforme | Psychiatric and neurological symptoms at initial presentation |
| Oreskovic et al\(^{(43)}, 2007\) | Depression, attention deficit hyperactivity disorder | Suprasellar and pineal regions | Germ cell tumor | Good prognosis with chemotherapy and radiation |
| Moise et al\(^{(49)}, 2006\) | Depression, headache, memory loss | Right thalamus | Glioblastoma multiforme | Partial improvement of symptoms with surgical treatment and antidepressants |
| Madhusoodanan et al\(^{(27)}, 2004\) | Recent depressive symptoms, anger and agitation | Left parietal | High grade glial neoplasm with sporadic cells | Resolution of depressive symptoms after surgery, chemotherapy and radiation therapy |
| Kohler et al\(^{(51)}, 2001\) | Depressive symptoms refractory to antidepressants, following surgical resection of left frontal neurocytoma | Left lateral ventricle, left frontal encephalomalacia | Neurocytoma | Good response to ECT |
| Ghaziuddin et al\(^{(31)}, 1999\) | Depressed mood, mania, suicidal ideation, irritability, guilt, grandiosity, early insomnia, olfactory hallucinations | Brainstem (ponto-mesencephalic) | Astrocytoma | Improvement with ECT |
| Kaplan\(^{(41)}, 1997\) | Progressive depression and anxiety | Right frontal and parietal | Unknown | |
| Kugaya et al\(^{(47)}, 1996\) | Depressed mood, agitation, depersonalization, ideas of reference, suicidal ideation | Ependymal | Cyst | Partial removal of cyst led to complete resolution of symptoms |
| Griffith\(^{(50)}, 1995\) Filley et al\(^{(50)}, 1995\) | Depression, Severe depression, extensive weight loss | Olfactory area | Esthesioneuroblastoma | |
| Chipkevitch et al\(^{(30)}, 1993\) | Atypical anorexia nervosa, depression | Hypothalamus | Squamous cell carcinoma | |
| Fulton et al\(^{(35)}, 1992\) | Reduced communication, depression, seizures, neurologic signs | Right frontal lobe | Astrocytoma | Poor response to steroid treatment |
| Goodman et al\(^{(45)}, 1992\) | Late-onset depressive symptoms, left-sided Horner’s syndrome | Several bi-frontal masses | Unknown | |
| Ko et al\(^{(33)}, 1989\) | Depressive symptoms, emotional lability, amnesia for recent events | Multiple metastatic left frontal-parietal lesions | Origin in right lung | No surgical intervention |
| Tanaghow et al\(^{(40)}, 1989\) | Depressed mood, social withdrawal, personal neglect, apathy | Anterior corpus callosum | Unknown | |
| Upadhyaya et al\(^{(45)}, 1988\) Greenberg et al\(^{(35)}, 1988\) | Depression and delusions, Treatment-resistant depression with delusions | Third ventricle | Colloid cyst | Good response of psychiatric symptoms to ECT |
| Goldstein et al\(^{(45)}, 1988\) Summerfield\(^{(45)}, 1987\) | Depression, psychosomatic symptoms | Left frontal-parietal, Cerebellum | Meningioma | Good response to ECT |
| Ghadirian et al\(^{(30)}, 1986\) | Depression and anxiety followed by visual hallucinations | Right temporal lobe | Meningioma | |
### Table 2: Brain tumors and apathy

| Ref. | Psychiatric symptoms | Tumor location | Tumor type | Remarks |
|------|----------------------|----------------|------------|---------|
| Aydin et al\(^{[5]}\), 2013 | Loss of self-generated behavior, irritability, disinhibition, impulsivity | Midline subfrontal region | Meningioma | Psychiatric and neurologic symptoms with consequent diagnosis of brain tumor |
| Filley et al\(^{[9]}\), 1995 | Apathy, social-withdrawal, poor self-care | Bifrontal | Benign meningioma | |
| Filley et al\(^{[9]}\), 1995 | Apathy, irritability, anemia, right hemiparesis | Left frontal lobe and genu of corpus callosum | Immunoblastic lymphoma | |
| Filley et al\(^{[9]}\), 1995 | Apathy, amnesia, poor affect | Thalamic and fornical columns | Gonadotropic cell pituitary adenoma | |
| Fulton et al\(^{[3]}\), 1992 | Loss of interest, poor concentration, withdrawal, lack of communication, neurologic signs | Left frontal lobe involving corpus callosum | Unknown | |
| Tanaghow et al\(^{[50]}\), 1989 | Depressed mood, social withdrawal, personal neglect, apathy | Anterior corpus callosum | Unknown | |
| Burkle et al\(^{[5]}\), 1978 | Depression, hypersonmia, anhedonia, low energy, poor concentration, memory lapses | Third ventricle with obstruction of lateral ventricles | Colloid cyst | |
| Avery\(^{[5]}\), 1971 | Euphoria, drowsiness, and apathy | Tuberculum sellae | Meningioma | Some residual psychiatric disturbance following resection |
| Avery\(^{[5]}\), 1971 | Depression, apathy | Right cribriform plate | Meningioma | Post-op manic episode before resolution of symptoms |
| Avery\(^{[5]}\), 1971 | Depression, apathy | Right cribriform plate | Meningioma | Improvement after surgery |
| Avery\(^{[5]}\), 1971 | Apathy, change in work behavior | Cribiform plate | Meningioma | Improvement after surgery |

Adapted from Trends in Brain Cancer Research. New York: Nova Science Publishers Inc., 2006.

### Table 3

**Manic symptoms**

In addition to depression, patients with brain tumors can also present with other mood symptoms, such as mania. There are reports which show that while
depression was associated with left frontal tumors, mania was found more commonly with right frontal tumors presenting with characteristics such as euphoria and underestimation of the significance of their illness\(^{11}\). Right hemisphere lesions have been reported to present as manic symptoms\(^{15-19}\).

**Psychosis (Table 4)**

Another common psychiatric presentation of brain tumors is hallucinations and psychosis. Madhusoodanan et al\(^{41}\) reported that while mood symptoms are the most common, being reported in 36% of the cases, psychotic symptoms were found in 22% of patients. In these cases of psychotic symptoms, the tumors were found in cerebral cortical, pituitary, pineal and posterior locations. Among these, pituitary gland was the most common location for psychotic symptoms. However, in another study, temporal lobe tumors were closely related to psychotic manifestations\(^{40}\).

**Personality changes (Table 5)**

Frontal lobe lesions and ventricular cysts may present with personality changes. This may include disinhibition, hypersexuality, and aggressive behaviors.

**Eating disorders (Table 6)**

Weight loss and decreased appetite are associated with different types of malignancies, and in patients with brain tumors it may be among the first warning signs. This may be mistaken for symptoms of anorexia nervosa, particularly in young females, and can lead to a misdiagnosis. A review by Madhusoodanan et al\(^{40}\) on associations between tumor locations and psychiatric symptoms concluded that while anorexia symptoms may be a result of tumors in numerous locations in the brain, hypothalamic neoplasms most commonly present as anorexia symptoms.

**Miscellaneous symptoms (Table 7)**

There are some cases of patients with brain tumors who present with a more ambiguous psychiatric history and progression of illness. Feng et al\(^{20}\) described an 86-year-old female who presented with anomic aphasia. The patient reportedly had difficulty naming familiar objects and people for month. Her neurological exam was normal and she did not have any symptoms related to psychiatric symptoms to perphenazine.

### Table 3  Brain tumors and manic symptoms\(^{41}\)

| REF. | Psychiatric symptoms | Tumor location | Tumor type | Remarks |
|------|----------------------|----------------|------------|---------|
| Bhatia et al\(^{40}\), 2013 | Visual hallucinations, grandiosity, excessive talking, elated mood | Third ventricle | Neuroepithelial cyst | Psychiatric symptoms and diagnosis of brain tumor with no development of neurologic symptoms |
| Yetimalar et al\(^{40}\), 2007 | Personality change, psychomotor agitation, enhanced talkativeness and sex drive, decreased need for sleep | Pons | Cavernous angioma | Neurologic symptoms developed after the brain tumor was diagnosed |
| Ghaziuddin et al\(^{40}\), 1999 | Depressed mood, mania, suicidal ideation, irritability, guilt, grandiosity, early insomnia, olfactory hallucinations | Brainstem (ponto-mesencephalic) | Astrocytoma | Improvement with ECT |
| Mazure et al\(^{40}\), 1999 | Late-onset manic episode with psychotic features; no neurologic signs | Right temporal lobe | Glioblastoma multiforme | Good and rapid response of psychiatric symptoms to perphenazine |
| Filley et al\(^{40}\), 1995 | New-onset manic symptoms | Bitemporal | Glioblastoma multiforme | Neurinoma |
| Mark et al\(^{40}\), 1991 | Treatment-resistant bipolar disorder | Acoustic nerve | Neurinoma | Symptoms resolved completely after tumor resection |
| Greenberg et al\(^{40}\), 1988 | Manic symptoms | Brainstem | Metastases, origin unknown | |
| Jamieson et al\(^{40}\), 1979 | Mania | Right occipital, temporal and parietal lobes | Metastatic tumors-unknown primary source | |
| Schertzer et al\(^{40}\), 1974 | Recurrent manic episodes | Frontal | Unknown | Meningioma |
| Avery\(^{40}\), 1971 | Mania, euphoria | Offactory nerve | Unknown | Some residual psychiatric disturbance following resection |

Adapted from Trends in Brain Cancer Research. New York: Nova Science Publishers Inc., 2006. ECT: Emission computed tomography; CT: Computed tomography.
Table 4  Brain tumors and psychotic symptoms

| Ref.       | Psychiatric symptoms                                                                 | Tumor location          | Tumor type                | Remarks                                                                 |
|------------|----------------------------------------------------------------------------------------|-------------------------|---------------------------|-------------------------------------------------------------------------|
| Krayem et al[91], 2014 | Psychosis, auditory hallucinations, self-injurious behavior                              | Right temporal lobe    | Astrocytoma               | Psychosis developed either from tumor recurrence or right temporal brain tissue loss post-surgery |
| Kaloshi et al[95], 2013 | Visual and auditory hallucinations, spasmodic laughter, minimal spontaneous speech       | Cerebellum              | Glioneuronal              | Partial improvement of symptoms with surgery                             |
| Arasappa et al[90], 2013 | Lethargy, anhedonia, persecutory delusions, and third person auditory hallucinations    | Fourth ventricle        | Choroid plexus papilloma  | Improvement with surgery                                                  |
| Canuet et al[92], 2011 | Schizophrenia-like psychosis                                                            | Right parietal lobe     | Meningioma                | Psychosis developed 6 yr after initial surgery with tumor recurrence. Gradual improvement with antipsychotics |
| Bunevicius et al[83], 2008 | Schizophrenia                                                                          | Left temporal lobe      | Anaplastic oligodendrolioma | Improvement with surgery                                                  |
| Bunevicius et al[84], 2008 | Depression, psychosis                                                                  | Left temporal lobe      | Intra-cerebral cyst        | Refractory symptoms                                                       |
| Bunevicius et al[84], 2008 | Schizophrenia                                                                          | Left temporal lobe      | Glioblastoma multiforme   |                                                                         |
| Parisis et al[84], 2003 | Peduncular hallucinosis (complex visual hallucinations), sleep impairment                | Cerebellar metastases   | Metastases                | Mechanism thought to be extrinsic compression of posterior midbrain-pons by mass edema |
| Rueda-Lara et al[85], 2003 | Delusions, hallucinations                                                               | Pituitary               | Hormone producing adenoma | Partial improvement of symptoms with surgical treatment and antidepressants |
| Maiuri et al[87], 2002  | Hallucinations                                                                         | Posterior thalamus      | Glioblastoma multiforme   |                                                                         |
| Miyazawa et al[88], 2001 | Headaches and psychotic symptoms                                                       | Pineal                  | Pineal meningioma         | Improvement with surgery                                                  |
| Miyazawa et al[88], 2001 | Headaches and psychotic symptoms                                                       | Pituitary               | Unknown                   | Improvement with steroid/hormone treatment                               |
| Craven[89], 2001      | Acute psychotic episode                                                                 | Pineal                  | Germinoma                 |                                                                         |
| Vardet et al[90], 2000 | Psychotic symptoms and cognitive deterioration                                           | Right temporo-parietal ganglia | Germinoma |                                                                         |
| Mordecai et al[91], 2000 | Psychotic and obsessive-compulsive symptoms, left-sided weakness, diabetes insipidus, decline in academic functioning | Bilateral basal ganglia | Germinoma |                                                                         |
| Werring et al[92], 1999 | Visual hallucinations, palinopsia, posterior headache                                    | Occipital               | Tuberculoma               |                                                                         |
| Carson et al[93], 1997 | Pediatric psychosis - hallucinations, aggression, violence                              | Third ventricle          | Choroid plexus papilloma  |                                                                         |
| Bal 209, 1996 | Persecutory delusions, auditory and visual hallucinations, fluctuating levels of consciousness followed by grand-mal seizures | Cerebellopontine angle | Meningioma |                                                                         |
| Filley et al[94], 1995 | Psychotic symptoms (perceptual disturbances)                                            | Temporal                | Low-grade oligoastrocytoma |                                                                         |
| Okada et al[95], 1992 | Positive and negative psychotic symptoms                                                | Left basal ganglia       | Unknown                   | Positive symptoms resolved after surgical resection, but negative symptoms persisted |
| Trabert et al[96], 1990 | Symptoms of anorexia followed by seizures and psychosis                                  | Temporo-basal           | Angioma                   |                                                                         |
| Nagaratnam et al[97], 1990 | Paranoid delusions                                                                       | Left frontal lobe       | Venous angioma            |                                                                         |
| Ko et al[98], 1989 | Paranoid ideation, irritability, short-term memory difficulties                        | Left parieto-occipital lesion | Origin in right kidney | No surgical intervention due to advanced stage                           |
| Dyck[99], 1985         | Auditory hallucinations                                                                 | Sylvian fissure          | Lipoma                    |                                                                         |
| Binder[100], 1983      | Sudden behavioral changes followed by paranoid delusions; no focal neurologic signs     | Right lateral ventricle | Meningioma                | Complete resolution of symptoms after surgical intervention             |
| Binder[101], 1983      | New-onset rage attacks on background of chronic schizophrenia                            | Bilateral occipital     | Meningioma                | Resolution of rage attacks after surgical removal                        |
| Dunn et al[102], 1983  | Peduncular hallucinations                                                                | Midbrain compression    | Cystic craniopharyngioma  | Prompt resolution after drainage of cyst                                 |
| Soulairac et al[103], 1979 | Peduncular hallucinosis                                                                 | Right temporal           | Astrocytoma               |                                                                         |
| Buchanan et al[104], 1975 | Pressured speech, hypomania, persecutory delusions                                     | Lateral ventricle        | Meningioma                |                                                                         |
| Blustein et al[105], 1972 | Thought disorder, auditory hallucinations                                              | Left parieto-occipital lobe | Porencephalic cyst        |                                                                         |

Adapted from Trends in Brain Cancer Research. New York: Nova Science Publishers Inc., 2006.
follow-up showed resolution of her pathological laughter condition, insidiousness of the disease process, vague symptoms are a rare occurrence. The rarity of this Brain tumors as the primary cause of psychiatric modifications was diagnosed. Two weeks post-operative follow-up showed resolution of her pathological laughter and hemiparesis.

**DIAGNOSIS**

Brain tumors as the primary cause of psychiatric symptoms are a rare occurrence. The rarity of this condition, insidiousness of the disease process, vague symptomatology, variety of signs pointing to several causative factors all contribute to the diagnostic challenges. Diagnosis of psychiatric symptoms being secondary to brain tumors starts from having the clinical suspicion. Early diagnosis is critical with regards to further treatment and better quality of life.

A thorough medical history and physical examination may assist in the diagnosis. Subtle clues that could otherwise be missed include neurologic signs: apraxia, visual field deficits, and anomia. Personality changes, sleep disturbances, apathy, weight loss, anorexia, or

![Table 5](https://www.wjgnet.com)

| Ref.                  | Psychiatric symptoms                        | Tumor location       | Tumor type               | Remarks                          |
|----------------------|---------------------------------------------|----------------------|--------------------------|---------------------------------|
| Lajara-Nanson et al, 2000 | Personality changes and hypersexual behavior | Ventricular          | Ventricular cyst         | Improvement with surgery        |
| Paul et al, 2000      | Personality changes, memory impairment, poor concentration | Extramedullary with infiltration of the cerebral dura | Plasmacytoma                  |                                  |
| Fahy et al, 1995      | Frontal lobe symptoms in absence of neurological signs | Frontal              | Meningioma               |                                  |
| Jones, 1993          | Personality changes, aggressive behavior, and emotional lability | Ventricle            | Ventricular cysts        | Improvement with surgery        |
| Fulton et al, 1992    | Personality changes, walking difficulties, incontinence, neurologic signs | Frontal lobe         | Multiple metastases      | Poor response to steroid treatment |
| Fulton et al, 1992    | Bizarre, disinhibited behavior, neurologic signs | Multiple left orbito-frontal and right thalamus | Astrocytoma                  | Poor response to steroid treatment |
| Fulton et al, 1992    | Withdrawn, inappropriate behavior, neurologic signs | Bilateral            | Unknown                   | Poor response to steroid treatment |
| Lobowsky, 1984       | Personality changes and emotional lability | Ventricle            | Ventricular cysts        | Improvement with surgery        |
| Barbizet et al, 1982  | Rage attacks, Bulimia, uninhibited and brutal sexual behavior, periods of depression with suicide attempts | Fronto-temporal       | Astrocytoma               |                                  |

Adapted from Trends in Brain Cancer Research. New York: Nova Science Publishers Inc., 2006.

![Table 6](https://www.wjgnet.com)

| Ref.                  | Psychiatric symptoms                        | Tumor location       | Tumor type               | Remarks                          |
|----------------------|---------------------------------------------|----------------------|--------------------------|---------------------------------|
| Vad Winkler et al, 2009 | Eating disorder                           | Pituitary gland      | Craniopharyngioma        | Improvement with surgery        |
| Vad Winkler et al, 2009 | Eating disorder                           | Third ventricle      | Craniopharyngioma        | Developed pituitary deficiency after surgery |
| Houy et al, 2007      | Anorexia nervosa                           | Frontal side of the right sylvian valley | Cavernous hemangioma     | Improvement with surgery        |
| Lin et al, 2007       | Anorexia nervosa                           | Hypothalamic region, third ventricle, pineal region, lateral ventricle, corpus callosum | Unknown                  |                                  |
| Wolańczyk et al, 1997 | Anorexia nervosa, delusions, catatonia     | Right parietal lobe  | Arachnoid cyst           |                                  |
| Chipkevitch et al, 1993 | Atypical anorexia nervosa, depressive symptoms | Hypothalamus        | Teratoma                  |                                  |
| Berek et al, 1991     | Anorexia nervosa                           | Third ventricle      | Teratoma                  |                                  |
| Trabert et al, 1990   | Symptoms of anorexia followed by seizures and psychosis | Temporo-basal        | Angioma                   |                                  |
| Climo, 1982           | Anorexia nervosa                           | Hypothalamus         | Craniopharyngioma        |                                  |
| Weller et al, 1982    | Anorexia nervosa                           | Pineal gland         | Pinealoma                 |                                  |
| Goldney, 1978         | Anorexia nervosa                           | Hypothalamus         | Craniopharyngioma        |                                  |
| Swan, 1977            | Anorexia nervosa                           | Hypothalamus         | Pinealoma                 |                                  |
| White et al, 1977     | Anorexia nervosa                           | Hypothalamus         | Glioma                    |                                  |
| Heron et al, 1976     | Anorexia nervosa                           | Hypothalamus         | Unknown                   |                                  |
| Daly et al, 1973      | Anorexia nervosa                           | Hypothalamus         | Ectopic pinealoma         |                                  |

Adapted from Trends in Brain Cancer Research. New York: Nova Science Publishers Inc., 2006.
Table 7 Brain tumors and miscellaneous symptoms

| Ref. | Psychiatric symptoms | Tumor location | Tumor type | Remarks |
|------|----------------------|----------------|------------|---------|
| Feng et al[28], 2013 | Anomic aphasia | Left temporal lobe | Glioblastoma multiforme | No resolution of aphasia after surgical treatment |
| Hoffmann et al[20,32], 2012 | Crying, spitting, biting self and others, mutism, withdrawal, sleepiness, anergia, bipolar affective disorder | Pituitary gland | Craniopharyngioma | No resolution of symptoms after surgery |
| Wong et al[30], 2012 | Attacks of sensory overload and unusual familiarity | Left temporal lobe | Epidermoid tumor | |
| Rosenzweig et al[38], 2010 | Epilepsy, paroxysmal ictal phonemes | Left superior temporal gyrus | Angiocentric glioma grade I | Resolution of symptoms after surgery |
| Tsutsumi et al[23], 2008 | Abnormal laughter, left-hemiparesis | Right frontal lobe | Glioblastoma multiforme | Resolution of psychiatric symptoms after surgical treatment |
| Sokolski et al[31], 2003 | Breakthrough manic symptoms with mild nausea and dizzy spells, daily derealisation episodes with olfactory auras | Right medial temporal, displacing right ventricle and right hippocampus | Grade IV invasive astrocytoma | Improvement of psychiatric symptoms with surgical resection |
| Burns et al[24], 2003 | New-onset pedophilia | Right orbito-frontal | Unknown | |
| Daigneault et al[32], 1999 | Aggression, precocious puberty and worsening seizures | Hypothalamic | Hamartoma | |
| Konovalov et al[33], 1998 | Korsakoff’s syndrome | Third ventricle | Colloid cyst | Complete resolution after surgical resection |
| Caplan et al[34], 1992 | Intractable seizures followed by coprolalia, compulsive behaviors, aphasia | Left anterior temporal | Ganglioma | Symptoms subsided after surgical resection |
| Ko et al[35], 1989 | Expressive aphasia, short-term memory difficulties, no focal neurologic signs | Multiple metastatic left fronto-parietal lesions | Origin in right lung | |
| Ko et al[36], 1989 | Deteriorating memory and disorientation to time and place, behavioral changes, visual agnosia, aphasia, self-neglect | Left parietal extending to temporal lobe with midline shift | Unknown-surgery | |
| Ribeiro et al[37], 1989 | Bonnet syndrome, blindness | Posterior parasagittal | Meningioma | |
| Durst et al[38], 1988 | Koro | Corpus callosum | Lipoz or dermoid tumor | |
| Binder[39], 1983 | Behavioral changes, confusion with neurological signs developing after 24 h | Left thalamic | Glioblastoma multiforme | |
| de Bures et al[40], 1982 | Aggressive behavior, cognitive impairment on background of chronic alcohol abuse and head injuries | Left temporal | Astrocytoma | |

Adapted from Trends in Brain Cancer Research. New York: Nova Science Publishers Inc., 2006.

Faltering concentration may be the first presentation of the illness. Further clues that suggest the presence of brain tumors may include psychiatric symptoms that do not fall into distinct diagnostic categories or atypical symptoms, symptoms that are refractory to treatment, and recurrence of previously controlled symptoms where other contributory factors (such as non-adherence to treatment, acute stressors, or medication changes) have been ruled out[1].

Neuroimaging is the primary diagnostic modality used to visualize the presence of brain tumors. CT and MRI are used for anatomical assessments. Magnetic resonance spectroscopy is used for the relative quantification of metabolites in different brain locations. Studies of neuronal activity related to local cerebral blood flow are done by functional MRI (fMRI). Positron emission tomography and single-photon emission computed tomography provide images by use of radionuclides[22]. For the purpose of this article, we will focus on the anatomical assessments that are routinely used in clinical practice. CT remains the modality of choice for trauma and acute hemorrhage. Its other advantages include: greater availability, fewer contraindications, and less expense. MRI offers higher resolution and is useful in evaluating necrosis, hemorrhage, cysts, tumors, and white-matter changes. It is generally superior to CT in visualizing brain tumors or other soft-tissue lesions. Functional studies are mostly used in the research setting and presently do not appear to have major advantages over CT and MRI for routine clinical setting. This may change with further refinements and clinical utility[21].

Madhusoodanan et al[1] recommended that neuroimaging be considered in the following conditions: new-onset psychosis, new-onset mood/memory symptoms, occurrence of new or atypical symptoms, new-onset personality changes, and anorexia without body dysmorphic symptoms. Conditions wherein neuroimaging may or may not be required include recurrence of previously controlled psychiatric symptoms and patients that are refractory to treatment[1].

Neuropsychological testing is useful in evaluating
cognitive and neuropsychological dysfunction, in documenting changes pre- and post-treatment, and in monitoring the effectiveness of rehabilitative efforts[27].

MANAGEMENT

Removal of the tumor may completely resolve the psychiatric or behavioral symptoms. Otherwise, decreasing the size of the tumor or halting its growth may also decrease these symptoms. Additionally, treating the acute mass effects such as increased intracranial pressure or hydrocephalus may improve cognitive functioning and decrease behavioral symptoms[28].

Neuropsychiatric and behavioral symptoms can persist or worsen after these interventions. Pharmacological and psychotherapeutic measures can be instituted to improve the functioning and quality of life[23].

Pharmacological management follows general therapeutic principles of tumor-free patients with similar symptoms. However, patients with brain tumors may have increased susceptibility for delirium, seizures, medication side effects, and drug-drug interactions.

Antidepressants may be beneficial in patients presenting primarily with depressive symptoms. Selective serotonin reuptake inhibitors (SSRIs) have a favorable side effect profile and less potential to cause delirium. Maprotiline and bupropion appear to have higher risk for seizures[29]. Methylphenidate has also been shown to be effective in patients with secondary depression. It was well tolerated and did not appear to have an increased risk for seizures. It was also found to be effective in patients with apathy syndrome aside from depression[25].

Mood stabilizers are useful in treating manic symptoms. Lithium may cause delirium and lower seizure threshold. Valproate, carbamazepine, oxcarbazepine, benzodiazepines, and gabapentin, having anticonvulsant properties, may be preferable alternatives[26]. A recent review explored possible neuroprotective effects of lithium in patients with brain cancer, especially when treated with radiation. Possible targets of lithium may include excitotoxicity, excessive apoptosis, reduced neurogenesis, and senescence of growth and regeneration. This effect has been shown in preliminary studies, but more research is required to confirm its benefits and clinical utility[29].

Antipsychotics may be used for treating psychotic syndromes with hallucinations, delusions, and disturbances in thought content and processes. First-generation antipsychotics were more widely used. Lower potency antipsychotics like chlorpromazine and thioridazine may be associated with increased risk for seizures and delirium. High-potency antipsychotics such as fluphenazine and haloperidol have lesser risk for seizure and delirium. First-generation antipsychotics like haloperidol and fluphenazine have a higher potential for extrapyramidal symptoms. This can be minimized by lowering the dosages or the addition of antiparkinsonian agents such as benzotropine or trihexyphenidyl. However, addition of these agents also increases the risk for anticholinergic delirium. The second-generation antipsychotics may be preferred because of lower incidence of some of these side-effects. Effectiveness of these agents has been noted in some case reports[26,27]. However, clozapine and olanzapine are also associated with higher risk for seizures and delirium[29].

Other treatment modalities include electroconvulsive therapy (ECT). This may be given consideration in cases of refractory depression. Brain tumors without increased intracranial pressure (ICP) or edema can be treated safely with ECT[29,30] when appropriate precautions have been taken. Daily neurological evaluations are of paramount importance as deterioration may be subtle. High-risk patients are those with presence of large mass or multiple masses, increased intracranial pressure, edema, or mass effect. In these patients, ECT may be considered only if they are severely ill, or there is risk for harm to self or others, and other options have failed. Measures to reduce edema and the increase in ICP should be undertaken. Regardless of the risks of ECT, all patients undergoing this treatment should have ongoing consultation with the neurologist/neurosurgeon. Additionally, changes in the lesion should be taken into account during maintenance treatments, as low-risk patients may progress to high-risk[23].

Psychotherapy is also an important treatment modality. This helps to improve overall functional status, interpersonal and psychosocial stressors, and emotional and cognitive status. Anxiety and depressive symptoms are frequently present and may benefit from supportive and cognitive therapy, and psychoeducation. This is supported by a study which found that the presence of depressive symptoms was the most important predictor of quality of life among patients with brain tumors[31,32]. It is also important to improve coping strategies and identify maladaptive defenses that may interfere with somatic treatments[2].

DISCUSSION

Diagnosis and treatment of psychiatric symptoms of brain tumors are challenging. At initial presentation, patients may have a variety of symptoms or a clinical picture that do not fit into a diagnostic category. Symptoms may be vague, such as apathy syndrome or personality changes, or symptoms that are refractory to treatment. Psychiatric symptoms may be the only presenting symptoms of a brain tumor. These symptoms tend not to be localized to specific anatomical regions and tumors are not confined to specific subdivisions. Tumors also exert effects by pressure, edema, and diaschisis (affecting connections to distant areas of the brain). Thus, psychiatric symptoms generally have no localizing value. A possible exception as previously discussed, is hypothalamic tumors that present with anorexia without distorted body image. Neuroimaging, pituitary hormone levels, and ophthalmologic evaluation
are recommended based on the symptomatology to rule out the presence of a tumor.[1,4,9]

Various studies describe the impact of tumor location and the variety of symptoms. Dorsolateral tumors lead to difficulties with organization and planning. Orbital-frontal tumors cause disinhibition, and medial frontal tumors cause apathy and abulia. Frontal tumors may exhibit personality changes in the patient. Diencephalic and pituitary lesions lead to vegetative symptoms. More specifically, diencephalic lesions manifest hyper-somnic and hyperphagic variants of depressive disorders.[8,10,35,36]

A thorough history and physical examination, high degree of clinical suspicion, and neuroimaging are keys to the diagnosis. A review[27] was conducted on the clinical- and cost-effectiveness of structural imaging (by use of CT or MRI) in patients with psychosis, especially that of first-episode psychosis. It concluded that structural neuroimaging adds little clinical information not suspected on history and physical examination that would influence management. Routine neuroimaging is not recommended.

Brain tumors may be primary or secondary, and are treated accordingly either by surgery, radiation, or chemotherapy. After the treatment of the tumor, psychiatric symptoms may either resolve or persist. From our clinical experience, we advocate that the treatment of psychiatric symptoms may begin before the treatment of the brain tumor, to improve the quality of life and coping skills. The psychotropics may be tapered gradually and discontinued after the tumor treatment. If psychiatric symptoms recur, psychotropics may be reinstated.

Studies of anxiety, depression, and somatic symptoms in brain tumors are complicated because it is unclear whether they are caused by the tumor or is a psychological response to the stress secondary to the diagnosis or treatment. Compounding the clinical conundrum is the lack of large controlled studies evaluating the psychiatric symptoms of brain tumors or their treatment modalities. Due to the relative rarity of this presentation and the wide array of manifestations, information regarding treatment is mostly derived from case reports or case series. Furthermore, the descriptions of psychiatric symptoms are not uniform in the literature. All these factors contribute to the difficulties in the analysis and extrapolation of available information. Treatment options include pharmacotherapy, psychotherapy, and ECT as discussed earlier.

A review that attempted to delineate the role of antidepressants in patients with brain tumors was unable to make recommendations due to lack of appropriate studies and cautions about the assumption of efficacy in this patient population[30]. With regards to safety, a study of SSRIs in patients with glioblastoma multiforme found neither any increased toxicity nor adverse effects on survival[39]. Methylphenidate has shown some evidence of efficacy in improving cognitive function and motivation. The side effects were minimal[24]. However, a more recent prospective, placebo-controlled trial of prophylactic d-threo-methylphenidate did not show any improvement in quality of life, with the main outcome measure being improvements in fatigue[40]. Continued treatment for persistent psychiatric symptoms is also complicated by the potential for delirium and seizures, possible side effects, drug-drug interactions, and status of the tumor and its treatment. Steroids may be associated with depression and psychosis. It is important that the treatment should be based on a multi-disciplinary team approach. Clinical specialists involved in the treatment should work closely and be aware of these issues with continued treatment, rehabilitation, and quality of life.

CONCLUSION
Psychiatric symptoms may be the only presenting feature of brain tumors. Thorough history and medical examination with a high index of suspicion are important for early diagnosis. Neuroimaging should be considered in patients presenting with new-onset psychosis or mood/memory symptoms, occurrence of new or atypical symptoms, personality changes, and anorexia without body dysmorphic symptoms. Treatment is geared towards the tumor, its complications, and the psychiatric symptoms. Management of persistent psychiatric symptoms is based on extrapolation of limited evidence, assessment of risk vs benefits, and understanding of potential complications related to the disease and concomitant therapy. Further investigation is needed to improve our understanding of the mechanisms by which tumors produce psychiatric symptoms. This may lead to improved understanding of the mechanisms of psychiatric disorders, advanced diagnostic modalities, better categorization of symptom constructs, and prospective trials for the management of the psychiatric symptoms in patients with brain tumors. With improvements in imaging techniques and diagnostic categorization of psychiatric symptoms, studies of correlation of anatomic location or neuronal functional groups and psychiatric symptoms may yield associations not previously found.

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