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REVIEW

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 with neuroimaging 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

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.

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INTRODUCTION

The majority of large studies discussing brain neoplasms and psychiatric symptoms date back to the 1930's[1]. 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[2].

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*[3] 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[1]. 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[4].

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[1].

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[5]. According to Mainio *et al*[6], 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[7]. It was also noted that depression was more commonly found in frontal lobe tumors[8-10]. More specifically left frontal lobe tumors were more frequently associated with depression and akinesia[11].

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[12]. This may be associated with a functional disconnection between the frontal lobe and paralimbic areas, or damage in these areas[13,14]. Levy *et al*[15] suggests that apathy is common in neurodegenerative disorders and is independent of depression. The diagnostic criteria for apathy suggested by Starkstein *et al*[16] 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*[42], 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*[43], 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
Ozdilek *et al*[44], 2011	Depression, anxiety, headache	Left temporal lobe	Glial tumor	Persistent headache led to neurologic consult and CT, and diagnosis
Cheema *et al*[45], 2010	Depression, anhedonia, low energy, insomnia, suicidal ideations	Left frontal and temporal lobe	Glioblastoma multiforme	Duration of psychiatric symptoms of 10 yr make the association of glioblastoma questionable and possibly unrelated
Bunevicius *et al*[46], 2008	Depression, Parkinsonian symptoms	Right fronto-temporal	Meningioma	Subsequent neurological symptoms led to CT scan and diagnosis of the brain tumor
Bunevicius *et al*[46], 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*[48], 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*[50], 2004	Recent depressive symptoms, anger and agitation	Left parietal	High grade glial neoplasm with sporadic cells	Resolution of depressive symptoms after surgery, chemo- and radiation therapy
Kohler *et al*[32], 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[51], 1997	Progressive depression and anxiety	Right frontal and parietal	Unknown	
Kugaya *et al*[52], 1996	Depressed mood, agitation, depersonalization, ideas of reference, suicidal ideation	Ependymal	Cyst	Partial removal of cyst led to complete resolution of symptoms
Griffith[53], 1995	Depression	Olfactory area	Esthesioneuroblastoma	
Filley *et al*[8], 1995	Severe depression, extensive weight loss	Left frontal	Squamous cell carcinoma	
Chipkevitch *et al*[54], 1993	Atypical anorexia nervosa, depression	Hypothalamus	Teratoma	
Fulton *et al*[55], 1992	Reduced communication, depression, seizures, neurologic signs	Right frontal lobe	Astrocytoma	Poor response to steroid treatment
Goodman *et al*[56], 1992	Late-onset depressive symptoms, left-sided Horner's syndrome	Several bi-frontal masses	Unknown	
Ko *et al*[57], 1989	Depressive symptoms, emotional lability, amnesia for recent events	Multiple metastatic left fronto-parietal lesions	Origin in right lung	No surgical intervention
Tanaghow *et al*[58], 1989	Depressed mood, social withdrawal, personal neglect, apathy	Anterior corpus callosum	Unknown	
Upadhyaya *et al*[59], 1988	Depression and delusions	Third ventricle	Colloid cyst	
Greenberg *et al*[29], 1988	Treatment-resistant depression with delusions	Left fronto-parietal	Meningioma	Good response of psychiatric symptoms to ECT
Goldstein *et al*[30], 1988	Depression	Right frontal	Meningioma	Good response to ECT
Summerfield[60], 1987	Depression, psychosomatic symptoms	Cerebellum	Hemangioblastoma	
Ghadirian *et al*[61], 1986	Depression and anxiety followed by visual hallucinations	Right temporal lobe	Meningioma	

Uribe[62], 1986	Depressive symptoms with rage episodes, forgetfulness, disturbance in short-term memory and abstract thinking, later-onset headaches, disorientation, gait unsteadiness, hemiparesis	Left temporo-parietal	Glioblastoma multiforme	
Dietch[63], 1984	Agoraphobia with panic attacks and major depression; later-onset right-sided weakness	Left fronto-parietal	Glioblastoma multiforme	Good response to imipramine, resolution of symptoms after surgery
Maurice-Williams *et al*[64], 1984	Depression, focal seizures	Frontal	Meningioma	Improvement of symptoms after tumor was removed
Fisher *et al*[65], 1983	Depression	Limbic system	CNS lymphoma	
Barbizet *et al*[66], 1982	Rage attacks, Bulimia, uninhibited and brutal sexual behavior, periods of depression with suicide attempts	Fronto-temporal	Astrocytoma	
Lahmeyer[67], 1982	Depression and urinary incontinence	Bilateral frontal	Meningioma	Good response to amphetamines
Littman *et al*[68], 1981	Depression, speech difficulties	Left temporal	Unknown	
Khuan *et al*[69], 1979	Depression, poor work performance	Right thalamus	Unknown	
Burkle *et al*[70], 1978	Depression, hypersomnia, anhedonia, low energy, poor concentration, memory lapses	Third ventricle with obstruction of lateral ventricles	Colloid cyst	
Carlson[71], 1977	Severe depression; prior history of seizures	Frontal	Meningioma	Complete resolution of symptoms after surgery
Carlson[71], 1977	Severe depression	Right frontal	Grade IV astrocytoma	Resolution of symptoms after surgery
Scherrer *et al*[72], 1974	Depression followed by euphoria, then seizures	Frontal	Unknown	
Blustein *et al*[73], 1972	Depression	Right temporal	Grade I astrocytoma	
Avery[74], 1971	Depression, apathy	Right cribriform plate	Meningioma	Post-op manic episode before resolution of symptoms
Avery[74], 1971	Depression, apathy	Right cribriform plate	Meningioma	Improvement after surgery

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

Table 2 Brain tumors and apathy[41]

Ref.	Psychiatric symptoms	Tumor location	Tumor type	Remarks
Aydin *et al*[75], 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*[8], 1995	Apathy, social-withdrawal, poor self-care	Bifrontal	Benign meningioma	
Filley *et al*[8], 1995	Apathy, irritability, anomia, right hemiparesis	Left frontal lobe and genu of corpus callosum	Immunoblastic lymphoma	
Filley *et al*[8], 1995	Apathy, amnesia, poor affect	Thalamic and fornical columns	Gonadotropic cell pituitary adenoma	
Fulton *et al*[55], 1992	Loss of interest, poor concentration, withdrawal, lack of communication, neurologic signs	Left frontal lobe involving corpus callosum	Unknown	
Tanaghow *et al*[58], 1989	Depressed mood, social withdrawal, personal neglect, apathy	Anterior corpus callosum	Unknown	
Burkle *et al*[70], 1978	Depression, hypersomnia, anhedonia, low energy, poor concentration, memory lapses	Third ventricle with obstruction of lateral ventricles	Colloid cyst	
Avery[74], 1971	Euphoria, drowsiness, and apathy	Tuberculum sellae	Meningioma	Some residual psychiatric disturbance following resection
Avery[74], 1971	Depression, apathy	Right cribriform plate	Meningioma	Post-op manic episode before resolution of symptoms
Avery[74], 1971	Depression, apathy	Right cribriform plate	Meningioma	Improvement after surgery
Avery[74], 1971	Apathy, change in work behavior	Cribriform plate	Meningioma	Improvement after surgery

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

Manic symptoms (Table 3)

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

Table 3 Brain tumors and manic symptoms[41]

Ref.	Psychiatric symptoms	Tumor location	Tumor type	Remarks
Bhatia *et al*[76], 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*[77], 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*[31], 1999	Depressed mood, mania, suicidal ideation, irritability, guilt, grandiosity, early insomnia, olfactory hallucinations	Brainstem (ponto-mesencephalic)	Astrocytoma	Improvement with ECT
Mazure *et al*[78], 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*[8], 1995	New-onset manic symptoms	Bitemporal	Glioblastoma multiforme	
Mark *et al*[79], 1991	Treatment-resistant bipolar disorder	Acoustic nerve	Neurinoma	Symptoms resolved completely after tumor resection
Greenberg *et al*[29], 1988	Manic symptoms	Brainstem	Metastases, origin unknown	
Jamieson *et al*[17], 1979	Mania	Right occipital, temporal and parietal lobes	Metastatic tumors-unknown primary source	
Scherrer *et al*[72], 1974	Recurrent manic episodes	Frontal	Unknown	
Avery[74], 1971	Mania, euphoria	Olfactory nerve	Meningioma	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.

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[17-19].

Psychosis (Table 4)

Another common psychiatric presentation of brain tumors is hallucinations and psychosis. Madhusoodanan *et al*[4] 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[8].

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*[4] on associations between tumor locations and psychiatric symptoms concluded that while anorexic 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 aside from the anomic aphasia. A brain computed tomography (CT) and magnetic resonance imaging (MRI) showed a large tumor in the left temporal lobe, compressing the left lateral ventricle and causing a midline shift. She underwent surgical resection of the tumor and radiotherapy. Pathology reports showed that the tumor was a glioblastoma multiforme. In this case, surgery and radiotherapy did not result in resolution of the anomic aphasia.

Among other less common and atypical psychiatric manifestations of brain tumor is a case of pathological laughter reported by Tsutsumi *et al*[21]. A 60-year-old female presented with abnormal laughter and left-hemiparesis. Her laughter was induced by non-specific stimuli and lasted for a few minutes. The MRI showed a ring-enhanced lesion in the subcortical area of the

Table 4 Brain tumors and psychotic symptoms[41]

Ref.	Psychiatric symptoms	Tumor location	Tumor type	Remarks
Krayem *et al*[27], 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*[80], 2013	Visual and auditory hallucinations, spasmodic laughter, minimal spontaneous speech	Cerebellum	Glioneuronal	Partial improvement of symptoms with surgery
Arasappa *et al*[81], 2013	Lethargy, anhedonia, persecutory delusions, and third person auditory hallucinations	Fourth ventricle	Choroid plexus papilloma	Improvement with surgery
Canuet *et al*[26], 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*[46], 2008	Schizophrenia	Left temporal lobe	Anaplastic oligodendroglioma	Improvement with surgery
Bunevicius *et al*[46], 2008	Depression, psychosis	Left temporal lobe	Intra-cerebral cyst	Refractory symptoms
Bunevicius *et al*[46], 2008	Schizophrenia	Left temporal lobe	Glioblastoma multiforme	
Parisis *et al*[82], 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*[83], 2003	Delusions, hallucinations	Pituitary	Hormone producing adenoma	
Maiuri *et al*[84], 2002	Hallucinations	Posterior thalamus	Glioblastoma multiforme	Partial improvement of symptoms with surgical treatment and antidepressants
Miyazawa *et al*[85], 2001	Headaches and psychotic symptoms	Pineal	Pineal meningioma	Improvement with surgery
Miyazawa *et al*[85], 2001	Headaches and psychotic symptoms	Pituitary	Unknown	Improvement with steroid/hormone treatment
Craven[86], 2001	Acute psychotic episode	Pineal	Germinoma	
Vardar *et al*[87], 2000	Psychotic symptoms and cognitive deterioration	Right temporo-parietal	Arachnoid cyst	
Mordecai *et al*[88], 2000	Psychotic and obsessive-compulsive symptoms, left-sided weakness, diabetes insipidus, decline in academic functioning	Bilateral basal ganglia	Germinoma	
Werring *et al*[89], 1999	Visual hallucinations, palinopsia, posterior headache	Occipital	Tuberculoma	
Carson *et al*[90], 1997	Pediatric psychosis - hallucinations, aggression, violence	Third ventricle	Choroid plexus papilloma	Symptoms improved after surgical removal
Ball[91], 1996	Persecutory delusions, auditory and visual hallucinations, fluctuating levels of consciousness followed by grand-mal seizures	Cerebellopontine angle	Meningioma	
Filley *et al*[8], 1995	Psychotic symptoms (perceptual disturbances)	Temporal	Low-grade oligoastrocytoma	
Okada *et al*[92], 1992	Positive and negative psychotic symptoms	Left basal ganglia	Unknown	Positive symptoms resolved after surgical resection, but negative symptoms persisted
Trabert *et al*[93], 1990	Symptoms of anorexia followed by seizures and psychosis	Temporo-basal	Angioma	
Nagaratnam *et al*[94], 1990	Paranoid delusions	Left frontal lobe	Venous angioma	
Ko *et al*[57], 1989	Paranoid ideation, irritability, short-term memory difficulties	Left parieto-occipital metastatic lesion	Origin in right kidney	No surgical intervention due to advanced stage
Dyck[95], 1985	Auditory hallucinations	Sylvian fissure	Lipoma	
Binder[96], 1983	Sudden behavioral changes followed by paranoid delusions; no focal neurologic signs	Right lateral ventricle	Meningioma	Complete resolution of symptoms after surgical intervention
Binder[96], 1983	New-onset rage attacks on background of chronic schizophrenia	Bilateral occipital	Meningioma	Resolution of rage attacks after surgical removal
Dunn *et al*[97], 1983	Peduncular hallucinations	Midbrain compression	Cystic craniopharyngioma	Prompt resolution after drainage of cyst
Soulairac *et al*[98], 1979	Peduncular hallucinosis	Right temporal	Astrocytoma	
Buchanan *et al*[99], 1975	Pressured speech, hypomania, persecutory delusions	Lateral ventricle	Meningioma	
Blustein *et al*[73], 1972	Thought disorder, auditory hallucinations	Left parieto-occipital	Porencephalic cyst	

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

Table 5 Brain tumors and personality changes[41]

Ref.	Psychiatric symptoms	Tumor location	Tumor type	Remarks
Lajara-Nanson[100], 2000	Personality changes and hypersexual behavior	Ventricular	Ventricular cyst	Improvement with surgery
Paul *et al*[101], 2000	Personality changes, memory impairment, poor concentration	Extramedullary with infiltration of the cerebral dura	Plasmacytoma	
Fahy *et al*[102], 1995	Frontal lobe symptoms in absence of neurological signs	Frontal	Meningioma	
Jones[103], 1993	Personality changes, aggressive behavior, and emotional lability	Ventricular	Ventricular cysts	Improvement with surgery
Fulton *et al*[55], 1992	Personality changes, walking difficulties, incontinence, neurologic signs	Frontal lobe	Multiple metastases	Poor response to steroid treatment
Fulton *et al*[55], 1992	Bizarre, disinhibited behavior, neurologic signs	Multiple left orbito-frontal and right thalamus	Astrocytoma	Poor response to steroid treatment
Fulton *et al*[55], 1992	Withdrawn, inappropriate behavior, neurologic signs	Bifrontal	Unknown	Poor response to steroid treatment
Lobosky[104], 1984	Personality changes and emotional lability	Ventricular	Ventricular cysts	Improvement with surgery
Barbizet *et al*[66], 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 Brain tumors and eating disorders[41]

Ref.	Psychiatric symptoms	Tumor location	Tumor type	Remarks
Vad Winkler *et al*[105], 2009	Eating disorder	Pituitary gland	Craniopharyngioma	Improvement with surgery
Vad Winkler *et al*[105], 2009	Eating disorder	Third ventricle	Craniopharyngioma	Developed pituitary deficiency after surgery
Houy *et al*[106], 2007	Anorexia nervosa	Frontal side of the right sylvian valley	Cavernous hemangioma	Improvement with surgery
Lin *et al*[107], 2003	Anorexia nervosa	Hypothalamic region, third ventricle, pineal region, lateral ventricle, corpus callosum	Unknown	
Wolańczyk *et al*[108], 1997	Anorexia nervosa, delusions, catatonia	Right parietal lobe	Arachnoid cyst	
Chipkevitch *et al*[54], 1993	Atypical anorexia nervosa, depressive symptoms	Hypothalamus	Teratoma	
Berek *et al*[109], 1991	Anorexia nervosa	Third ventricle	Teratoma	
Trabert *et al*[93], 1990	Symptoms of anorexia followed by seizures and psychosis	Temporo-basal	Angioma	
Climo[110], 1982	Anorexia nervosa	Hypothalamus	Craniopharyngioma	
Weller *et al*[111], 1982	Anorexia nervosa	Pineal gland	Pinealoma	
Goldney[112], 1978	Anorexia nervosa	Hypothalamus	Craniopharyngioma	
Swann[113], 1977	Anorexia nervosa	Hypothalamus	Pinealoma	
White *et al*[114], 1977	Anorexia nervosa	Hypothalamus	Glioma	
Heron *et al*[115], 1976	Anorexia nervosa	Hypothalamus	Unknown	
Daly *et al*[116], 1973	Anorexia nervosa	Hypothalamus	Ectopic pinealoma	

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

right frontal lobe along with extensive perifocal brain edema. Upon total resection of the tumor, glioblastoma multiforme 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[1].

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 7 Brain tumors and miscellaneous symptoms[41]

Ref.	Psychiatric symptoms	Tumor location	Tumor type	Remarks
Feng *et al*[20], 2013	Anomic aphasia	Left temporal lobe	Glioblastoma multiforme	No resolution of aphasia after surgical treatment
Hoffmann *et al*[117], 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*[118], 2012	Attacks of sensory overload and unusual familiarity	Left temporal lobe	Epidermoid tumor	
Rosenzweig *et al*[119], 2010	Epilepsy, paroxysmal ictal phonemes	Left superior temporal gyrus	Angiocentric glioma grade I	Resolution of symptoms after surgery
Tsutsumi *et al*[21], 2008	Abnormal laughter, left-hemiparesis	Right frontal lobe	Glioblastoma multiforme	Resolution of psychiatric symptoms after surgical treatment
Sokolski *et al*[120], 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*[121], 2003	New-onset pedophilia	Right orbito-frontal	Unknown	
Daigneault *et al*[122], 1999	Aggression, precocious puberty and worsening seizures	Hypothalamic	Hamartoma	
Konovalov *et al*[123], 1998	Korsakoff's syndrome	Third ventricle	Colloid cyst	Complete resolution after surgical removal
Caplan *et al*[124], 1992	Intractable seizures followed by coprolalia, compulsive behaviors, aphasia	Left anterior temporal	Ganglionoma	Symptoms subsided after surgical resection
Ko *et al*[57], 1989	Expressive aphasia, short-term memory difficulties, no focal neurologic signs	Multiple metastatic left fronto-parietal lesions	Origin in right lung	
Ko *et al*[57], 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 refused- no autopsy report given	
Ribeiro *et al*[125], 1989	Bonnet syndrome, blindness	Posterior parasagittal	Meningioma	
Durst *et al*[126], 1988	Koro	Corpus callosum	Lipoma or dermoid tumor	
Binder[96], 1983	Behavioral changes, confusion with neurological signs developing after 24 h	Left thalamic	Glioblastoma multiforme	
de Bures *et al*[127], 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[22].

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[2].

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[2].

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[2].

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[23]. 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[24].

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[2]. 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[25].

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 benztropine 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[28].

Other treatment modalities include electro-convulsive 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[29-32] 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[33].

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[34]. 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].

Various studies describe the impact of tumor location and the variety of symptoms. Dorsolateral tumors lead to difficulties with organization and planning. Orbitofrontal 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 hypersomnic 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[37] 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[38]. 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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