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REVIEW

Psychiatric symptoms in glioma patients: from diagnosis to management

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Abstract: Patients with primary intrinsic brain tumors can experience neurological, cognitive, and psychiatric symptoms that greatly affect daily life. In this review, we focus on changes in personality and behavior, mood issues, hallucinations, and psychosis, because these are either difficult to recognize, to treat, or are understudied in scientific literature. Neurobehavioral symptoms are common, often multiple, and causation can be multifactorial. Although different symptoms sometimes require a different treatment approach, we advise a comprehensive treatment approach, including pharmacological treatment and/or psychotherapy where appropriate. Further research is needed to obtain a better estimate of the prevalence of psychiatric symptoms in glioma patients, and the extent to which these affect everyday functioning and family life.

Keywords: glioma, psychiatry, personality, mood, hallucinations, psychosis

Background

Gliomas (World Health Organization [WHO] grade II, III, or IV) are the most common primary malignant brain tumors, with an incidence of six per 100,000.[1] Despite efforts in improving the treatment of gliomas, these tumors cannot be cured. Patients suffering from a low-grade glioma (WHO grade II) have a median survival of 5–15 years,[2] while this is 2–3 years for patients with a WHO grade III tumor.[3,4] For patients with WHO grade IV tumors, the median survival does not exceed 12–14 months.[5] While survival is traditionally stratified by tumor grade, genetic markers including IDH mutation, 1p/19q codeletion, and MGMT methylation have more recently been established as important prognostic markers in glioma patients.[6] The antitumor treatment usually consists of a combination of surgery, radiotherapy, and chemotherapy. In addition, drugs for symptom management, such as corticosteroids and anticonvulsants are often prescribed for a prolonged period of time.[7,8]

As the tumor progresses, various symptoms resulting from the disease often become more pronounced. As both the disease and its treatment have a direct effect on brain functioning, patients commonly experience neurological, cognitive, and psychiatric symptoms.[9] Neurobehavioral symptoms may affect the patient's ability to engage with clinical decision-making and ultimately may affect survival. Moreover, these symptoms can negatively affect patients' direct social environment, such as spouses, family members, and close friends.[10] With the patients' increasing demand for mental and physical support, these significant others often become informal caregivers. Because of the substantial impact of the disease and its treatment on the everyday lives of patients and their loved ones, it is important to pay attention to symptom management and quality of life. Changes in personality and behavior, mood issues, hallucinations, and psychosis are either difficult to recognize, to treat, or are understudied in scientific literature. In this review, we will therefore focus on these neurobehavioral

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symptoms. Different treatment options are summarized and presented in Table 1.

Changes in personality and behavior

Most studies focusing on changes in personality and behavior in brain tumor patients use a qualitative study approach, or are case reports. An estimation of the real frequency of behavioral problems experienced by glioma patients and their informal caregivers is uncertain, but these qualitative studies allow for a detailed description of commonly experienced issues.

Symptoms of anger, loss of emotional control, indifference, and change in behavior are commonly reported.[11–15] Changes in personality can lead to difficulties recognizing and interpreting social behavior. Such difficulties in social cognition can interfere severely with family life and social relationships. For other brain tumor patients, personality changes can manifest as exhaustion and anxiety, leading to withdrawal from social situations, and feelings of sadness and grief.[14] These changes may, as in any cancer patient faced with a dismal prognosis or uncertainty concerning the future, in part be explained or compounded by processes of grief or an adjustment disorder. However, personality changes can also result directly from the presence of the tumor or its treatment. The precise extent to which tumor location impacts on psychopathology is not well understood.

Classically, three "frontal lobe syndromes" have been proposed to arise in patients with brain tumors located in specific prefrontal areas.[16] In this model, damage to dorsolateral prefrontal areas is associated with impaired executive functioning, orbitofrontal damage may cause disinhibition and impulsiveness, and lesions in the medial frontal areas may result in apathy or abulia.[17,18] It is worth acknowledging that this broad model is underpinned by relatively little recent, high-quality evidence that is specific to brain tumor patients. Brain tumor-specific studies may be important, given the considerable uncertainty over how tumor-related metabolic changes, diaschisis, and cerebral edema or mass effect may interact with location to mediate the behavioral phenotype.

A few quantitative studies do indicate that behavioral problems are more evident in patients with frontal tumors than in controls without neurological compromise.[19] Patients with frontal tumors report more executive dysfunction, apathy, and disinhibition than patients with nonfrontal tumors.[20] However, clinically significant levels of apathy and executive dysfunction are reported by many patients with tumors located outside the frontal lobes too, and the relationship is not straightforward.[20] Indeed, it is likely that highly complex interactions between cortical and subcortical damage adds to behavioral problems. For example, patients with heteromodal frontal or parietal tumors often experience negative mood states. When paralimbic structures are involved, mood problems become more aggravated. However, damage to motor and somatosensory cortex is associated with positive mood and seems to ameliorate negative mood states.[21] It therefore seems unlikely that behavioral problems are a direct result of frontal or nonfrontal damage. One recent study using voxel-based lesion−symptom mapping (VLSM) provides some interesting evidence for more subtle neuropsychological effects of tumor location. The ability to discern the emotions and intentions of others was

Table 1 Treatment options for changes in personality and behavior, mood issues, and hallucinations and psychosis in patients with glioma

Treatment options		
Changes in personality and behavior	**Mood issues**	**Hallucinations and psychosis**
Psychological treatment: psychoeducation; cognitive behavioral therapy; coping enhancement	Pharmacological treatment: antidepressants; anxiolytics	Reduction or cessation of medications that may cause the hallucinations and/or psychosis
Neurorehabilitation	High-intensity psychological treatment: cognitive behavioral therapy; interpersonal therapy	Pharmacological treatment: antipsychotics
	Alternative approach: problem-solving therapy; mindfulness; exercise intervention; nurse-delivered supportive intervention	Supportive care: familiar nursing; regular reassurance; de-escalation and reorientation
		Psychological treatment: cognitive behavioral therapy; coping enhancement
		Alternative approach: acceptance and commitment therapy; mindfulness

impaired in patients with tumors in the temporal lobe. More complex components of personality and behavior (such as the ability to conceptualize and describe internal emotions and the facets of one's character) were adversely affected by tumors in prefrontal regions.[22] The advent of more sensitive neuroimaging and analysis techniques such as VLSM brings the opportunity to explore the relationship between tumor location and psychopathology in greater detail than was previously possible.

Many patients have only limited awareness of their symptoms. Impaired emotion recognition and behavioral problems are associated with a lack of self-awareness, which can lead to perspective-taking difficulties. After surgery, brain tumor patients are more likely to underestimate their psychological problems and the negative impact of changes to their emotional functioning, interpersonal relationships, neurocognitive functioning, and coping skills.[23] This can be distressing for partners and others who are closely involved.[23] Moreover, lack of awareness of deficits can have a major impact on the outcome of rehabilitation after treatment.[24] As social and behavioral problems are often very difficult to detect in clinical neuro-oncological practice, but can affect the lives of patients and their partners in a very profound way, these issues are of special concern.

Managing changes in personality and behavior

Recently, Chambers et al published a comprehensive overview of guidelines for psychosocial care in neuro-oncology.[25] In terms of management of changes in personality and behavior, the authors advise patient education, early detection of symptoms, and referral to neuropsychology, neuropsychiatry, or neurorehabilitation services if needed.[25]

To encourage early detection of symptoms, health care professionals should enquire after behavioral problems in routine consultation. While patients may not be aware of problems in everyday life, the informal caregivers can usually indicate if behavioral changes cause issues. Although to our knowledge, there are no brain tumor-specific, validated paper-and-pencil screening instruments available to assess changes in behavior, a question such as the personality change item of the Functional Assessment of Cancer Therapy-Brain[26] ("I am bothered by the change in my personality", with answer options ranging from "not at all" to "very much") may suffice in determining whether patients should be referred for extensive psychological assessment. Neuropsychological testing is then warranted to assess different aspects of the patients' social cognition. However, development of screening instruments and validation of existing, more comprehensive questionnaires such as the Neuropsychology Behavior and Affect Profile[27] and the Katz Adjustment Scale-Revised[28] in the brain tumor patient population would be worthwhile.

To help patients and their informal caregivers cope with changes in personality and behavior, it is important to provide education. Improved education can reduce uncertainty and distress, and increase empowerment.[29,30] In a recent systematic review, Langbecker and Janda investigated the available interventions to improve information provision for brain tumor patients and their informal caregivers.[31] They conclude that although satisfaction rates of patients and their informal caregivers improve when an intervention is offered, more research is needed to determine the most effective intervention components and the most appropriate timing for the delivery of the intervention.

In usual practice, the focus is mostly on the physical recovery of the patient,[32] but improvements in neurocognitive functioning are sometimes evaluated as well through brief screening measures such as the functional independence measure (FIM).[33–37] Some evaluation studies show modest improvement in brain tumor patients' social cognition (assessed with the FIM as social interaction, problem-solving, and memory[38]), which does not appear to be related to the tumor type.[35,36,39] However, it remains unclear whether the very brief FIM cognitive scores adequately reflect more subtle behavioral and personality changes and difficulties in social functioning in everyday life. Moreover, only inpatient groups were studied, which hinders the generalization of findings – especially with respect to patients with less malignant tumor such as low-grade gliomas. More prospective studies and randomized controlled trials (RCTs) to evaluate the role of neurorehabilitation in improving social functioning are therefore warranted.

Psychologists can support patients and informal caregivers to employ more effective coping strategies to deal with changes in personality and behavior.[40] Alternatively, an adapted cognitive behavioral approach could be used. Defining the changed personality as the end behavior, an assessment can formulate an understanding of the patient's thoughts and emotions, and where these might interact to cause the problematic behavior. With this approach, it may become possible to identify possible targets for therapeutic intervention. However, there are, to our knowledge, no intervention programs available aimed specifically at glioma patients' difficulties with changes in behavior and personality. Although (neuro) psychologists aware of the

disease-specific symptoms of brain tumors may effectively apply the principles of cognitive behavioral therapy (CBT), further studies are also warranted here.

Mood issues

Following the diagnosis of glioma, many patients experience psychological distress and mood issues. Mania, feelings of anxiety, depression, and even suicidal ideation can occur. Furthermore, shock and disbelief, anger and despair, dysphoria and anxiety, or intrusive thoughts about the disease may be prominent.[41] Often, these emotional reactions are transient in nature, but sometimes their severity and/or persistence suggests an adjustment disorder or a major depressive disorder.[42] Moreover, mania and other mood disorders may in rare cases occur secondary to the brain lesion itself,[43] although the underlying mechanisms are not well understood.[44,45] Therefore, a biopsychosocial framework, taking into account the dynamic interactions between neurocognitive factors, psychological processes, and the social environment has been suggested as useful to conceptualizing these disorders.[46] For example, patients with a personal or family history in psychiatric disease are more susceptible to psychological maladjustment after brain tumor.[47,48] Moreover, mood issues can be attributed variously to side effects of treatment (eg, antiepileptics[49]), biochemical changes in the brain,[45] changes in cytokine levels,[50] elevated intracranial pressure, or the location of the tumor.[51] Frontal cortex lesions and lesions in the parietal association cortex and paralimbic structures have been associated with mood changes, specifically.[21] Demographic variables such as sex, age, marital status, ethnicity, and education level are not consistently associated with anxiety and depression in glioma patients, but increased physical disability and cognitive impairment often co-occur with mood issues.[52]

Systematic reviews and longitudinal studies suggest that approximately 15%–20% of glioma patients will develop clinical major depressive symptoms during the first 8 months after diagnosis.[52,53] In this, no clear distinction between low- and high-grade gliomas can be made based on the available literature.[52] The increased risk for depression may be maintained up to a year after surgical intervention.[54] This makes depression considerably more likely than in the general population (where the point prevalence is approximately 5%).[55] However, there is no consistent evidence that brain tumor patients are at a higher risk of depression than patients with cancer not involving the central nervous system.[48,56]

To date, very little research has been performed to examine the prevalence of suicidal ideation among brain tumor patients. In a large retrospective study among adult survivors of a childhood brain tumor, approximately 12% of patients experienced suicidal ideation.[57] In this study, depression, psychoactive medication use, history of seizures, and observation or surgical treatment were associated with suicidal ideation. With regard to successful suicide, there are indications that brain tumor patients are at an increased risk for death by suicide.[58,59] However, others have reported that patients with brain tumors are less likely to commit suicide than other patients with cancer,[60] and are more likely to die an accidental death instead.[61] Nevertheless, the use of glucocorticoids such as dexamethasone, which is often prescribed in glioma patients, increases the risk for suicide or suicide attempt, depression, and panic disorder considerably.[62] From the epilepsy literature, we know that suicidal thoughts can co-occur after temporal lobe surgery.[63]

It is a commonly acknowledged problem that mood issues, when understandable given the disease stage or process, can be difficult to discuss for health care professionals.[64] In neuro-oncology, this likely not only pertains to understandable psychological reactions, but also to what can be expected based on the tumor type, location, and treatment side effects.[65] Mood issues that are potentially treatable may then be overlooked and undertreated.[66] This can have serious negative consequences for glioma patients' quality of life,[67] and even their morbidity and survival.[47,68]

Managing mood issues

As mentioned above, recognizing mood issues may be difficult in the glioma patient population. When it is suspected, either from the patient's perspective or the informal caregiver's point of view, that mood issues interfere with everyday functioning, clinical assessment is needed to diagnose or exclude mood disorders. While it remains necessary to conduct a thorough psychiatric assessment to assess the degree of mood issues, there are screening measures that could be useful in the clinic. Recently, efforts have been made to validate three of these instruments in the glioma patient population.[69] The Hospital Anxiety and Depression Scale[70] and the Patient Health Questionnaire-9[71] can be useful to screen for mood issues. The Beck Depression Inventory-II[72] is also often used in clinical practice but has not yet been validated in glioma patients. However, the utility of any screening scale for mood issues in glioma patients with significant cognitive impairment, or in patients in the palliative phase, is currently unknown.

National and international guidelines suggest that depression in patients with a chronic physical condition should,

where possible, be treated with a combination of medication (eg, selective serotonin reuptake inhibitors [SSRIs], serotonin norepinephrine reuptake inhibitors, anxiolytics), and a high-intensity psychological treatment such as CBT or interpersonal therapy.[73,74] Generally, pharmacological treatment and psychotherapeutic treatment are thought to contribute equally to beneficial effects.[75]

A lack of RCTs in glioma patients makes it difficult to gauge whether the same treatment strategies should be pursued in patients with brain tumor.[76] Glioma patients are at a high risk of cognitive deficit and fatigue and may struggle to fully benefit from CBT. Antidepressant treatment brings the possibility of adverse drug interactions, for example, an increased risk of antiepileptic drug (AED) toxicity secondary to inhibition of metabolizing liver enzymes. Although antidepressants generally do not trigger epilepsy in healthy individuals, their risk of precipitating seizures in patients with a tumor growing in their brain is unknown. Regardless, both physicians and patients may at times be reluctant to initiate new pharmaceutical treatment.[77] RCTs are therefore warranted to investigate the effectiveness of the standard treatment for mood disorders. Some retrospective evidence suggests that SSRIs may be well tolerated by patients with glioblastoma but more research is clearly required.[78]

Other initiatives should not be overlooked. Presently, we are conducting an RCT to evaluate the effects of an internet-based guided self-help course on depressive symptoms in glioma patients.[79] Other interventions that are already evidence-based in other patient populations include problem-solving therapy[80] and mindfulness.[81,82] Moreover, interventions based on exercise programs appear to have a positive impact on both mood and the quality of life,[83] and nurse-delivered interventions based on information provision and supportive attention show beneficial effects on mood in newly diagnosed cancer patients.[84] Adapting existing and effective interventions to the glioma patient situation, by taking their disease-specific symptoms into account, could lead to improved evidence-based care for mood issues in glioma patients.

Hallucinations and psychosis

Although rare, some brain tumors present themselves through neurobehavioral or psychiatric symptoms only.[85] Hallucinations[16] and even psychosis[86] have been reported in brain tumor patients. These symptoms can be very unsettling to patients and their informal caregivers. Currently, there is no evidence of a causative relationship between classical paranoid schizophrenia and brain tumors. Although large studies are lacking, there are indications that idiosyncratic psychoses can occur after resection of the (mesial) temporal lobes. Case studies describe acute psychosis, agitation, and suicidal/homicidal ideations with paranoia following surgery.[86]

Indeed, most studies of hallucinations and psychosis in glioma patients are case reports. As case reports often feature highly complex cases, with glioma patients who are suffering not only from the tumor, but also from epilepsy that is difficult to treat, psychosis, behavioral problems, and/or suicidal ideation,[63,87,88] it is very difficult to make general statements about the prevalence of these symptoms in glioma patients per se. A review of case studies found that 22% of 148 cases experienced psychotic symptoms (here defined as delusions or hallucinations).[89]

Psychiatric symptoms seldom occur in isolation from other (psychiatric) symptoms in patients with brain tumors, eg, as shown in a study by Sokolski and Denson.[90] Hallucinations in any sensory modality may occur as an epileptic phenomenon. In such cases, the hallucinations may subside after effective AED treatment, or surgical removal of the tumor.[91] In addition, associations have been found between epilepsy and mood disorders. For example, manic or hypomanic states have been reported in patients undergoing temporal lobectomy for epilepsy, and postoperative mood disorders seem to be associated with preoperative postictal psychosis.[92] Although psychosis appears to be more common in patients with temporal lobe epilepsy (~5%–15% of patients)[93] than in brain tumor patients, it can occur and can have a major impact on people's lives.

Managing hallucinations and psychosis

It is important to obtain a clear view of the patients' hallucinations, and/or psychotic symptoms. In general, patients are able to describe their hallucinations if prompted. Hallucinations suggestive of an organic cause, such as brain tumor, are often visual, and auditory hallucinations tend to be nonpersecutory in nature.

Treatment of hallucinations usually consists of pharmacological treatment (eg, antipsychotics).[94] Olanzapine or risperidone for example have been shown to counteract hallucinations.[95] However, it is unclear how well these drugs work to reduce unimodal hallucinations not accompanied by other psychiatric symptoms, but mainly resulting directly from the lesion. On the other hand, hallucinations and psychosis often co-occur with other psychiatric symptoms.[90] This is important to note, as the treatment used for the management of other symptoms can have an adverse effect on hallucinations and psychosis, and vice versa. For example, the use of steroids

or AEDs can induce psychosis in brain tumor patients.[96] Steroid psychosis generally arises at or shortly after the onset of corticosteroid treatment, and a higher dose increases the risk. The psychosis is characteristically, but not inevitably, affective and may fluctuate. Furthermore, although rare, antidepressants (SSRIs) may evoke hallucinations, which generally subside after cessation of medication.[97] In close collaboration with the treating neuro-oncology team, reduction or cessation of medications that may cause the hallucinations and/or psychosis can be indicated. Alternatively, a regular low-dose antipsychotic such as haloperidol can be useful.

As hallucinations and psychotic symptoms can be very unsettling for both patients and their significant others, a nonpharmacological approach can prove beneficial as well. To reduce anxiety and disorientation, nursing provided by a familiar face, regular reassurance, de-escalation, and reorientation can provide relief. Other options include CBT for psychosis,[98] or a combination with coping enhancement such as hallucination-focused integrative therapy, which has been shown to improve the quality of life.[99] Mindfulness-based interventions[100] and acceptance and commitment therapy[101] for treating the emotional problems that may follow a psychotic episode have also been investigated, and show promising results. For auditory hallucinations specifically, Thomas et al recently provided a rather complete overview of the recent developments in treatment, including RCTs focusing on different types of CBT, and avatar therapy.[102] Here, computer-generated avatars allow the patient to role-play with different responses to their auditory hallucination.

Conclusion

Neurobehavioral symptoms are common in brain tumor patients, often occur concurrently, and are difficult to tell apart. For example, affective disorders can co-occur with or mirror alexithymia,[103] fatigue, and apathy, whereas a different approach in treatment may be necessary. Symptoms should preferably not be treated separately, but comprehensively. Depending on the severity of symptoms, pharmacological treatment and/or psychotherapy may be advisable. Therapists supporting brain tumor patients should always have thorough knowledge of the disease-specific symptoms of brain tumors to adequately address patients' and informal caregivers' needs. More research is needed to obtain a better estimate of the prevalence of the different psychiatric symptoms in glioma patients, and the extent to which these affect everyday functioning and family life.

Disclosure

The authors report no conflicts of interest in this work.

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