REVIEW

Neuropsychiatric symptoms as early indicators of brain tumors

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ABSTRACT

Brain tumors, despite the high mortality and morbidity, they are a rare type of heterogenous tumors that are highly dependent on sex, age, race, level of education, and socioeconomic status. Due to their high mortality rates, it is important to identify as many potential biomarkers for early detection as the earlier the tumor is discovered, the better the prognosis. One such early biomarker we propose in the current paper is the assessment of anxiety, depression, and cognitive changes. In most cancer patients, a certain degree of anxiety and depression is expected upon receiving the diagnosis as it triggers fears regarding the prognosis, possible side effects of the treatment, and even the possibility of the treatment failing. In this paper we analyzed the way anxiety, depression, and cognitive changes present themselves in the case of several types of tumors and whether these could be used as early markers. We have observed that most of the cognitive changes present are due to the location, size, and type of the tumor with some highly connected to anxiety and depression. Moreover, in the case of certain tumors, the removal of the mass has not improved the mood or cognitive function.

KEYWORDS: brain tumors; anxiety; depression; cognitive changes; neuropsychiatric symptoms

INTRODUCTION

Brain tumors are neoplasms developed in the nervous system or the spinal foramen [1]. Brain tumors, generally rare, are a category of heterogenous tumors with varying incidence rates dependent on sex, age, and race with an increasing incidence rate in certain groups possibly due to the improvements and developments in diagnosis and treatment [2]. Amongst them, the most common ones are intracranial metastases, meningiomas, and glioblastomas [3]. In children and adolescents, the two main risk factors for developing brain tumors are exposure to ionizing radiation and genetically inherited disorders. Whereas in adults, they have been linked to a plethora of environmental factors with the new association found between the incidence and electromagnetic fields from power lines, conditions like tuberous sclerosis, and over thirty single nucleotide polymorphisms [4]. Even with the identification of potential underlying genetic markers, there are tumor families that can be determined based on molecular parameters while other tumors are rarely, or never diagnosed through this approach [5].

Precise brain tumors' symptomatology is often lacking or contradictory. However, one aspect that is agreed on is that the manifestation can be either physical (exhibited through increased fatigue, difficulties in focal focusing, and migraines) or behavioral (the symptoms vary from difficulties in the attention span or concentration to depression or anxiety) [6]. All these aspects make it difficult to diagnose brain tumors early.

One of the main neuropsychiatric symptoms is anxiety. The fight or flight response occurs due to a trigger, among which the most common is fear. At the brain level, fear is perceived as an alarm when facing dangerous situations. Anxiety is linked to fear and presents itself on multiple levels, be it cognitive, physiological, or behavioral. Anxiety becomes pathological when the perceived danger is excessive and leads to exaggerated responses [7]. Among the common symptoms that describe anxiety disorders are excessive unjustified worry, public speaking fear, palpitations, difficulties sleeping, fatigue, trembling, and shortness of breath [8]. One accepted cause for anxiety disorders is the involvement of gamma-aminobutyric acid in dysregulating the amygdala – responsible for processing fear and anxiety – creating a chain reaction of affecting thought patterns to feelings to behavior [9].

On the other hand, clinical depression is a debilitating disorder characterized by persistent feelings of sadness, hopelessness, and loss of interest or pleasure in activities that used to be enjoyable [10]. Much like anxiety, depression affects a person on multiple levels by being characterized by sadness, irritability, excessive guilt, difficulty in

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concentrating or the attention span alongside appetite changes, difficulties with sleeping, fatigue, and unexplainable pain eventually leading to social and affective withdrawal, difficulties in performing daily activities, thoughts of self-harming or suicide [11]. Depression disorders have a multifactorial etiology with biological factors (neurotransmitter imbalances, increased amygdala activity, decreased prefrontal cortex activity, hormonal imbalances, genetic predisposition, decreased neuroplasticity, or dysbiosis of the gut-brain axis) [12], psychological factors (negative thought processes, unresolved trauma, chronic stress or anxiety, maladaptive coping mechanisms, interpersonal problems or difficulty processing emotions) [13] or environmental factors (stressful life events, childhood adversities, social isolation, cultural and societal pressures, workplace or academic stress, unstable living conditions, global crisis, discrimination or oppression) [14].

Cognitive changes refer to alterations in the manner a person thinks, processes information, and perceives the world around them [15]. These changes can occur due to numerous factors, including age, mental health conditions, neurological disorders, stress, or trauma [16]. In the context of mental health and depression, cognitive changes are characterized by negative or distorted thinking patterns that affect daily functioning and emotional well-being [17]. Cognitive changes encompass memory deficits (short- and long-term memory even with positive experiences), impaired concentration and attention, difficulties with decision-making, negative thought patterns (catastrophizing, overgeneralization, persistent self-criticism), rumination, and difficulty processing emotions [18]. These cognitive changes are repeatedly linked with anxiety and depression.

LITERATURE SEARCH METHOD

We conducted a systematic search in the PubMed and Scopus databases using the keywords ''neuropsychiatric symptoms in brain tumors,'' ''anxiety in brain tumors,'' ''depression and cognitive function in brain tumors,'' and ''early markers of brain tumors.'' The search included all relevant articles published after 2000 to ensure the inclusion of contemporary studies.

The initial search results yielded 136 articles for ''neuropsychiatric symptoms in brain tumors,'' 633 articles for ''anxiety in brain tumors,'' 160 articles for ''depression and cognitive function in brain tumors,'' and 522 articles for ''early markers of brain tumors.'' After eliminating duplicates and articles published in languages other than English, we reviewed the abstracts of the remaining articles. Following this review, we selected 67 articles that specifically addressed the neuropsychiatric symptoms associated with brain tumors.

The included studies were a combination of retrospective clinical case reports, observational studies, and narrative reviews. No prospective or systematic review studies were identified in the final selection. We focused on data related to the etiopathogenesis of neuropsychiatric symptoms, including their correlation with tumor location, size, and type, as well as their diagnostic value as early markers of brain tumors.

This systematic approach ensured a comprehensive and rigorous review of the existing literature, with the goal of emphasizing findings that could inform the early detection of brain tumors based on neuropsychiatric symptoms.

BRAIN TUMORS AND ANXIETY

Brain tumors and anxiety can be associated in several ways, as the presence of a tumor in the brain can directly and indirectly affect mental status.

Tumors located in regions like the amygdala or prefrontal cortex can lead to heightened anxiety or panic attacks [19], whereas those causing increased intracranial pressure may lead to discomfort or disorientation, indirectly triggering anxiety [20]. Tumors in areas like the pituitary gland or hypothalamus may affect hormone production, leading to mood swings, increased stress, and anxiety [21]. Moreover, brain tumors can disrupt the balance of neurotransmitters (e.g., serotonin, dopamine, GABA), which are critical for mood regulation and anxiety control while seizures can heighten the feelings of fear due to anticipatory anxiety [22].

On the other hand, the diagnosis and treatment of a brain tumor can become emotionally overwhelming and draining, contributing to anxiety about the prognosis, survival, any potential disabilities, or the treatment's side effects, be it surgery, radiation, or chemotherapy [23]. Most brain tumors lead to memory loss or difficulty concentrating as well as emotional disturbances whereas patients who undergo invasive treatments or have a traumatic diagnosis experience may develop post-traumatic stress disorder (PTSD), with anxiety as a prominent symptom [24].

The frontal lobe is mainly responsible for regulating emotions, decision-making, interpretation, and personality [25] which suggests that there is a strong link between the tumors localized in this area and anxiety. A tumor in this region can overstimulate the amygdala leading to increased fear and worry, exaggerate emotional reactions, causing heightened anxiety or panic attacks, reduce resilience to stress, make everyday challenges feel overwhelming, cause overthinking or indecisiveness, irritability, increased sensitivity to stress, difficulty maintaining social interactions, headaches, motor coordination issues, or speech difficulties. On the other hand, when it affects the hippocampus, it can lead to difficulty recalling recent events, and a sense of losing control over cognitive abilities thus leading to emotional and mental distress [21,26].

Pituitary tumors can be associated with anxiety due to their impact on hormone regulation, as the pituitary gland is responsible for controlling many of the body's endocrine functions. The pituitary gland controls the release of hormones that regulate various bodily functions, including stress responses [27]. Tumors that cause an overproduction of cortisol lead to physical symptoms such as weight gain, mood swings, fatigue, irritability, and heightened stress response [28], overproduction of prolactin leads to irregular menstrual cycles, infertility, and sexual dysfunction, as well as emotional symptoms [29]. Pituitary tumors that affect the thyroid-stimulating hormone can lead to fatigue, low energy, and cognitive slowing when it is decreased, and increased heart rate, irritability, and nervousness when it is increased [30]. Moreover, tumors that affect the growth hormone production can lead to acromegaly (in adults) or gigantism (in children), which result in physical changes such as enlarged hands, feet, or facial features alongside emotional symptoms, including anxiety and depression [31].

In some cases, anxiety might be an early symptom of a brain tumor before other neurological signs appear, particularly if the tumor is in areas of the brain that influence emotional regulation, cognition, or sensory processing.

BRAIN TUMORS AND DEPRESSION

Depression can be a common symptom in individuals with brain tumors, and it may occur for assorted reasons depending on the tumor's location, size, and the way it affects brain functions. Depression in patients with brain tumors can be a result of direct physiological effects on the brain, as well as secondary effects from coping with the diagnosis and treatment of the tumor [32].

The frontal lobe and the limbic system are responsible for mood regulation, affective status, and emotions. Tumors that affect these areas can directly alter mood and lead to symptoms of depression [26]. Frontal lobe tumors can lead to apathy, irritability, emotional flatness, and depression [33]. The temporal lobe is involved in memory and emotion processing. Tumors here can disrupt emotional regulation, leading to symptoms of depression, anxiety, or personality change [34]. Tumors affecting the hypothalamus or pituitary gland can disrupt hormonal balances, which can affect mood and contribute to depression. Brain tumors, especially those affecting the frontal lobe or other mood-regulating areas, may alter the production and regulation of neurotransmitters like serotonin [35]. Disruptions in serotonin signaling are strongly linked to depression [36]. Excessive cortisol, often resulting from Cushing's syndrome (caused by a pituitary tumor) is associated with depression and anxiety [29].

As a brain tumor grows, it can lead to increased pressure within the skull. This intracranial pressure can cause a variety of symptoms, including headaches, nausea, and cognitive changes [19]. Tumors in the temporal lobe, which is involved in memory and emotion, can lead to seizures and, in some cases, also contribute to depression [22]. Seizures themselves can be distressing and contribute to feelings of anxiety or depression.

The psychological stress of dealing with a brain tumor diagnosis and undergoing treatments like surgery, radiation, or chemotherapy can contribute significantly to depression [24]. Receiving a diagnosis of cancer comes with its fair share of uncertainties regarding the fear of a poor prognosis, and the challenges of undergoing the treatment which can lead to feelings of sadness, loss of hope, and emotional distress [37]. Moreover, post-surgical or post-treatment depression can still occur during and after the recovery period [38]. For example, the brain' healing process after surgery can affect emotional regulation, perception, and interpretation [39], leading to an increased risk of depression or the exacerbation of the symptoms. Brain tumors can lead to changes in behavior or cognitive function that affect an individual's ability to maintain social relationships or engage in activities they once enjoyed [26]. The symptoms of depression in individuals with brain tumors are similar to those in the general population but may be influenced or exacerbated by the tumor and its treatment [40]. The most common symptoms of depressive disorder are sadness, loss of interest, fatigue, sleep disturbances, feelings of guilt, difficulty concentrating, appetite changes, or thoughts of death and suicide that persist for a period of at least two weeks [41].

As mentioned before, the frontal lobe is heavily involved in personality and behavior therefore if a tumor starts growing in this area, it can cause significant personality changes [42]. For example, a person may become more apathetic, irritable, or emotionally flat, which can be mistaken for depression. They may also lose interest in activities they once enjoyed and show little emotional responses to things around them, which is often seen in depressive disorders [43]. Moreover, tumors in the frontal lobe can cause difficulties in concentration, forgetfulness, or problems making decisions, or they can increase intracranial pressure leading to headaches, nausea, and other neurological symptoms [44].

Temporal lobes, located on the sides of the brain, are involved in processes such as memory, emotion regulation, and language. When a tumor affects the temporal lobes, it can disrupt these functions and lead to mood changes, including depression [20].

Tumors in the amygdala can lead to emotional instability, mood swings, and depressive symptoms, whereas tumors in the hippocampus can result in memory problems, confusion, and disorientation [32]. Tumors in the temporal lobe can impair the ability to form new memories or recall past events and the individuals may experience a decline in their ability to think clearly or make decisions [45].

Pituitary tumors can affect the adrenal glands through the secretion of the adrenocorticotropic hormone (ACTH), which controls cortisol production [27]. Excess cortisol or insufficient cortisol can both contribute to depressive symptoms [28,29]. A large tumor can exert pressure on surrounding structures which may contribute to headaches (chronic headaches that are debilitating and affect overall mood) and vision problems (can compress the optic nerves, leading to visual disturbances – bitemporal hemianopia) [46]. In some cases, pituitary tumors (especially those that affect the growth hormone or sex hormone levels) can lead to changes in physical appearances, such as weight gain, changes in facial features (in acromegaly), or changes in sexual functions. These changes can severely impact self-esteem and lead to depressive symptoms [31].

Depression can sometimes be an early sign of a brain tumor, though it is not always the first or most obvious symptom, but it can appear early, especially if the tumor affects brain regions involved in mood regulation [47].

Early symptoms that might suggest a brain tumor include headaches (often in the morning or with physical exertion), vision problems (blurry vision, double vision, or loss of peripheral vision), cognitive changes (memory problems, difficulty concentrating), nausea, vomiting (often due to increased intracranial pressure), seizures (especially in the case of gliomas and metastatic tumors), personality or behavioral changes (irritability, mood swings, apathy), fatigue or persistent tiredness, dizziness or balance problems [6].

BRAIN TUMORS AND COGNITIVE CHANGES

Brain tumors can lead to a wide range of cognitive changes depending on the location, size, and type of tumor [44]. Cognitive functions, which involve processes like memory, problem-solving, attention, and language, are highly dependent on the proper functioning of the brain [48].

The executive functions are the ones referring to decision-making processes, planning, problem-solving, and emotional regulation and it is a role majorly attributed to the frontal lobe [49]. Therefore, it is not surprising that growing masses in this area can negatively influence these functions, leading to attention and concentration issues, memory deficiencies, questionable judgment, and decision-making, coupled with personality changes [44]. On the other hand, the temporal lobe's main responsibility covers memory, language, and

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Table 1. Anxiety, depression, and cognitive changes in different types of brain tumors.

Tumor type	Study group	Anxiety/Panic attacks	Depression	Cognitive changes	Observations	Source
Glioblastoma	1. 84 patients 2. 565 patients 3. 73 patients	1. 2 patients (moderate anxiety) 2. 124 3. 32 patients	1. 8 patients (moderate depression) 2. 141 3. 36 patients	Balance difficulties, seizures, fatigue, headaches, visual problems, confusion-altered mental state, sleep disturbances	1. Males had significantly lower PHQ-9 scores than females. Males with higher PHQ-9 and GAD-9 scores had shorter overall survival times compared to males with lower scores. Females with higher GAD-7 scores – shorter overall survival times than females with lower scores 2. Younger adults may be more impacted by dramatic changes in function	1. [33] 2. [23] 3. [33] - erratum
Ependymoma	1. 1 child	1. mild anxiety -> almost panic attacks -> social isolation	1. One instance of suicidal ideation -> intermittent depressed mood, suicidal ideation, auditory and visual hallucinations	No cognitive changes at the time of the discovery of the mass	Mood, anxiety, and depression levels kept worsening despite psychotherapy and medication over a three years period. Post-surgical removal of the tumor and treatment, psychological effects disappeared, but the IQ dropped, and the memory function declined	1. [62]
Meningioma	1. 250 patients 2. 176 patients 3. 30 patients 4. 61 patients	1. Anxiety (8.4%) 2. 4 patients 3. Anxiety (40%) 4. 23-30% patients	1. Depression (10%) 2. 11 patients 3. Depression (8%) 4. 27% depression	Global neurocognitive impairment – visual memory, executive function, attention (4)		1. [26] 2. [21] 3. [20] 4. [63]
Chordoma	1. 88 patients 2. 19 patients	1. – 2. 33%	1. 73 patients 2. 11%	1. Headaches, cranial nerve deficit, motor deficit, sensory deficit, bowel disturbance, diplopia	1. Sensory deficit with no other clinical sign or symptom -> higher PHQ-9 score 2. Patients not newly diagnosed were recruited and their progress was followed for years	1. [64] 2. [66]
Neurocytoma	1. 20 patients	1. HAMA (scores between 8.8 and 29.2)	2. HDMA (scores between 13 and 25.7)	High cerebral pressure caused by hydrocephalus	Memory, abstract thinking declined significantly 5-years post-surgery	1. [17]
Craniopharyngioma	1. 109 patients	1. 51 patients	2. 63 patients	Sleep disturbances, visual deterioration, polyuria, amenorrhea, memory disturbances, ophthalmology abnormality	Hypothalamic involvement might result in lethargy -> decreased reactivity -> lower interpersonal relationship, phobia, and paranoia	1. [67]
Glioma	1. 250 patients 2. 176 patients 3. 155 patients	1. Anxiety (8.4%) 2. 9 patients 3. -	1. Depression (10%) 2. 23 patients 3. 32 patients (MDD)		Cancer patients may require even lower threshold for anxiety and depression scales	1. [26] 2. [21] 3. [34]
Schwannoma	1. 176 patients	1. 0 patients	1. 0 patients			1. [21]
Pituitary adenomas	1. 176 patients	1. 2 patients	1. 3 patients			1. [21]
Primary central nervous system lymphoma (PCNSL)	1. 19 patients	1. 2 patients	1. 2 patients	Cognitive deficits and dysfunction, white matter abnormalities, cortical atrophy	Low rate of patients resuming work	1. [51]
Prolactinoma	1. 176 patients	1. 59.1%	1. 28.98%	Sleep disorders, menstrual disorders, galactorrhea, infertility, decreased libido	The patients with sleep disorders had lower PRL levels. PRL levels in prolactinoma patients are associated with education level	1. [29]
Somatotroph adenoma	1. 27 patients	1. Anxiety present	1. Depressive mood present	Specific cognitive deficits, abnormal moods	Surgical intervention has a limited effect on improving the impaired cognitive function and mood	1. [65]

emotion processing, and tumors in this area can cause memory impairments, language difficulties, and emotional changes [50]. The parietal lobe is important for processing sensory information and spatial orientation and when they are impaired it leads to difficulty with spatial awareness, dyscalculia, and agnosia [51]. Symptoms like visual disturbances and visual processing deficits are generally attributed to tumors in the occipital lobe as this area is responsible for processing visual information [52].

Another aspect that is important in determining the type of symptoms that appear as well as possible complications, co-morbidities, and cognitive functioning is the size of the tumor. For example, a larger tumor may cause more significant cognitive deficits by increased pressure on surrounding brain tissue and compression of vital structures [53]. One consequence of a tumor growing is the increase of intracranial pressure (ICP), which in turn can affect the brain's ability to function properly. The most common clinical signs of increased ICP include a variety of manifestations from headaches, nausea, and vomiting to cognitive fog or confusion, and concentration difficulties [54]. Increased ICP can impair cognitive functions like memory, attention, and problem-solving and if it is not treated promptly, it becomes chronic and leads to severe cognitive deficits [55].

The type of brain tumor can also determine the extent and nature of cognitive changes [44]. Tumors like glioblastomas, meningiomas, metastatic brain tumors, and pituitary tumors are more likely to impact cognitive function negatively [56].

Up to 50% of patients with brain tumors experience seizures, which may also impact cognition [57]. In the acute stage, seizures can cause temporary confusion or memory loss during or after the event whereas chronic seizures can lead to long-term cognitive difficulties [58].

A brain has the ability to recover after an injury - neuroplasticity, this function is also involved in maintaining and recovering cognitive functions after the removal or treatment of the tumor by reorganizing itself and compensating for the damage [59]. However, the extent of the repair is dependent on the size, location, type of tumor, and the brain's ability to adapt. In many cases, patients experience cognitive improvement after treatment, though some may have lasting deficits [60].

In terms of memory impairment, tumors commonly cause difficulty remembering new information or events, difficulty recalling important dates, names, or facts as well as short-term memory impairment [18]. These issues are usually accompanied by difficulty focusing on tasks for prolonged periods, inability to maintain concentration on the task at hand, and trouble completing more complex tasks [53]. Besides memory and attention, tumors negatively impact executive function characterized by impaired decision-making, faulty planning and problem-solving, altered speech, and slower thought processes [25]. Moreover, as discussed previously, tumors can also cause motor skill impairments with difficulties in coordinating movement, poor hand-eye coordination, and balance issues alongside visual perception issues (difficulties in recognizing faces and objects, blurred vision) [61].

ANXIETY, DEPRESSION, AND COGNITIVE DEFICITS AS EARLY BIOMARKERS FOR BRAIN TUMORS

It is generally accepted that patients with brain tumors have increased levels of anxiety and depression with some patients being diagnosed with Generalized Anxiety Disorder and Major Depressive Disorder. Whether the affected mental state is due to the diagnosis, treatment, and prognosis, or are an underlying condition present before to the diagnosis, the utility of assessing these parameters as an early biomarker is scarcely studied. The results are summarized in Table 1.

In the case of glioblastoma, one interesting study analyzing 84 patients noted that anxiety and depression scores could be correlated with survival rates. Male patients with higher depression and anxiety scores had a shorter survival time compared to the male patients with lower scores whereas overall, male patients had lower depression scores [33]. Whereas another study including 565 patients with the same type of tumor, has concluded that younger patients might be more negatively affected by the dramatic changes in motor and cognitive function [22].

In the case of a rare tumor, of ependymoma type, in a curious case study of a child that did not need treatment and presented no cognitive changes at the time of the mass discovery, for a period of 3 years, her mood, anxiety, and depression levels kept worsening despite psychotherapy and medication. Moreover, she suffered cognitive changes even after the tumor removal [62].

Regarding meningioma, in multiple studies including 250 [20], 176 [21], 30 [26], and 61 [63] patients, respectively, the percentages identified anxiety-presenting symptoms were 8.4%, 7%, 40%, and up to 30% respectively, whereas the depression scores were significantly lower, but the patients presented with global neurocognitive impairment.

Another category of rare tumors that have illustrated interesting results is chordoma. In a study of 88 patients, 73 of them exhibited depressive symptomatology and what is more interesting is that they identified an association between sensory deficits with a higher PHQ-9 score. The cognitive deficits identified for this type of tumor were headaches, cranial nerve deficits, motor deficits, bowel disturbances, and diplopia [64].

In the case of neurocytoma, in a study of 20 patients, all of them obtained at least twice as high anxiety and depression scores, measured by HAM-A and HAM-D, then healthy controls. Moreover, the authors observed that memory and abstract thinking declined significantly in the 5 years post-surgery [19].

One important observation noted in three studies (with 250 [21], 176 [36], and 155 [34] patients, respectively) is that cancer patients may require an even lower threshold for anxiety and depression scales, suggesting the possibility of decreasing them to a level between 6 and 8.

The highest percentages of anxiety and depression mood, 59.1% and 28.98%, respectively, were observed in a study of 176 patients with prolactinoma who have also reported sleep disorders, galactorrhea, infertility, and decreased libido [29].

Whereas, in the case of somatotroph adenoma, where all 27 patients exhibited anxiety and a depressive mood, has been noted that surgical intervention has a limited effect on improving the impaired cognitive function and mood [65].

CONCLUSIONS

Brain tumors are complex disorders that affect the individual at an emotional, physical, and cognitive level. Often, neuropsychiatric symptoms can be hard to distinguish from certain mental disorders. The present cognitive deficits can be caused by the growing mass, size, and location but

can also be a consequence of anxiety and depression. Overall, anxiety and depression are present in most common types of brain tumors with varying degrees and severity. The utility of analyzing these biomarkers as early signs could prove useful if the scales are introduced as a more common assessment even in the healthy-looking population otherwise it is difficult to distinguish whether these symptoms were already present in the individual or appeared soon after the diagnostic. Further studies are required for a clearer image as brain tumors are dependent on multiple factors, from age, sex, and race/ethnicity to the level of studies, and socio-economic parameters.

Conflict of interest

The authors declare that they have no competing interest.

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