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Depression- the first symptom of a brain tumor or a consequence of the process neoplastic process - a review of the literature

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Abstract:**Introduction and objective**

CNS malignancies account for about 1.6% of all diseases today. In people diagnosed with a brain tumor with a poor prognosis, we often see disorders from the psychiatric spectrum, most often depressive disorders. In this paper, we want to focus on whether depression occurs as a sequel to cancer or perhaps is the first of the symptoms of a CNS tumor.

Review methods

For the analysis, the PubMed medical database was searched, and articles containing studies and case reports of people with CNS tumor and depressive disorders that occurred either before diagnosis or at any time during the course of the disease were selected

Abbreviated description of the state of knowledge

CNS tumors produce symptoms such as epilepsy, visual disturbances, paresis, but also behavioral disorders. This is determined by the location of the tumor. Depression is a mental disorder manifested mainly by lowered mood. This disorder can coexist with tumors occurring in the frontal lobe or be present regardless of the location of the tumor, in people diagnosed with a tumor with a poor prognosis.

Summary

Analyzing the selected articles, we see that in people who were diagnosed with a tumor located in the frontal lobe, often the first symptom was depressive disorders, which even preceded neurological symptoms. When depression is diagnosed, appearing suddenly and refractory to treatment, one should consider whether there is an underlying pathological lesion in the CNS. Unfortunately, there are no specific guidelines for imaging studies in depressive disorders. People who suffer from malignant tumors with a poor prognosis should be cared for by a psychologist, because as the disease progresses, the symptoms worsen, affecting the prognosis.

Keywords: brain tumor; glioblastoma multiforme; depression; cognitive impairment; cancer.

Introduction and purpose

CNS tumors are some of the rarer cancers that occur in adults. It is estimated that they account for 1.6% of tumors [1]. In children, brain tumors are the most common solid tumors. We can classify these lesions on the basis of location into tumors that develop below the tentorium of the cerebellum, or subthalamic tumors. These are located in the posterior part of the cranial cavity involving the cerebellum and brainstem. Tumors such as cerebellar

medulloblastomas and gliomas mainly occur in this location. The second example is supranuclear foci, which localize above the tentorium of the cerebellum. Tumors that arise in this location are classified histologically as hemangioendotheliomas, gliomas. Craniopharyngiomas are also found here. Glioblastoma multiforme (GBM) is one of the tumors with a poor prognosis. The cells of this tumor have the ability to rapidly proliferate, occupy more brain structures and metastasize. Depending on the location, patients sometimes present subtle signs of the process forming in the brain tissue. Even histopathologically benign lesions can cause dysfunction and neuropsychiatric disorders in a person, including psychiatric disorders, epileptic seizures, aphasias, headaches and seizures [2].

One of the main psychopathological disorders accompanying CNS tumors is depression, which in most cases is resistant to treatment with antidepressant drugs. By mapping the brain, identifying the areas involved, we can surmise that this is sometimes an important symptom of the disease preceding neurological disorders. [3]. Above that, depression can accompany cancer regardless of the location of the tumor, Cancer patients undergo a number of therapies that worsen their psychophysical condition leading to anxiety and depressive disorders. Depression is one of the most common disorders in the world according to the WHO. Its main symptoms are abulia, apathy, anhedonia and a sense of emptiness, tearfulness. Often these symptoms are accompanied by a reduction in life activities and an excessive sense of anxiety. Patients over and above report sleep disturbances. Currently, there are many ways to diagnose depression in such individuals and a wide range of treatments.

The purpose of this paper is to review the literature including studies conducted and case reports and to determine the correlation between the occurrence of depression and brain tumor, and to draw attention to greater vigilance in performing imaging studies in diagnosing depressive disorders.

Materials and Methods:

An electronic database of PubMed was searched using keywords and keywords: "brain tumor", "glioblastoma multiforme", "depression", "cognitive impairment", "cancer". Articles were analyzed and evaluated for suitability for inclusion in the review. Case reports that characterized any age group with a diagnosed brain tumor, in which symptoms related to depressive disorders occurred at any time, were included and qualified. In addition, studies that were published in either Polish or English were included, free access to the article was

present. Articles that were published above 2015 were searched. In the absence of an abstract, the article was retrieved and analyzed. Tumors were classified according to the WHO classification. Articles that could not be downloaded in their entirety and articles mentioning depression without a connection to CNS cancer were excluded .

Current knowledge:

The main neurological symptoms occurring in the presence of brain tumors include headache, first epileptic seizure episode, speech and cognitive dysfunction [2,3]. In addition, nausea and vomiting associated with increased intracranial pressure According to studies, up to 50-78% of brain tumors can manifest psychiatric disorders without presenting neurological disorders at the beginning [4]. Moreover, it is estimated that depression in people diagnosed with malignant brain tumors is much more common than in other types of cancer. In people with GBM, depressive disorders occur with a frequency of up to 87.5% [5]. Symptoms related to psychiatric symptoms occur when the tumor is located in the frontal cortex area. Depressive symptoms and lowered mood occur when the tumor localizes to the left orbitofrontal region [6]. Fatigue, which accompanies patients and is one of the symptoms of depression, is closely associated with the female gender both before and after treatment . [7]

Currently, imaging studies including MR, CT are used to diagnose brain tumors, which allow us to determine the location of the lesion, the extent of necrosis and the presence of contrast enhancement. We can augment this diagnosis with a PET scan that gives us data on the metabolism and physiology of the tumor. [8].

An important test that gives us accurate information about the mutations present and the aberrations, methylations that allow us to determine the benefit of a given tumor therapy is molecular testing. This test gives us the opportunity to determine the exact genome of the tumor and evaluate the effectiveness of treatment, or the possibility of including the patient in a particular type of clinical trial [5].

Depression these days as one of the more common psychiatric disorders is diagnosed on the basis of an interview with the patient. The patient's psychophysical state, his drive, willingness to act are carefully analyzed. The main scale that helps make the diagnosis is the Beka scale, which determines the severity of depressive symptoms. Unfortunately, often in

people with cancer, symptoms suggesting the presence of depression are overlooked. It is much more difficult in such people to determine their emotional state and make an accurate diagnosis. Nowadays, many forms of treatment for mental disorders are available, such as antidepressant medications, psychotherapy and shock, which are also counted as a form of treatment in people suffering from depressive disorders. [9]

Effect of depression and its treatment on survival of patients with glioblastoma multiforme

A link has been sought between the effects of antidepressants and the development of glioma. Based on a cohort study conducted between 2005 and 2014 in the canton of Zurich, Switzerland, which at the time included 404 patients over the age of 18, it was shown that antidepressants have no effect on slowing the proliferation of tumor cells. The results of a study conducted in the canton of Zurich, Switzerland, contradicted that antidepressants that interact with voltage-dependent potassium channels (citalopram, escitalopram) or mediate the PIK3K/Akt.mTor pathway have an impact on the survival of a patient with glioblastoma multiforme with or without present MGMT promoter methylation [10].

There was also a study showing the impact of depressive disorders on prognosis in glioma. They studied 84 patients with the tumor type who suffered from depression. The study consisted of assessing these individuals against the PHQ-9 and GAD-7 scales, both genders, and ages 40-60 were included. The results of the study were compared with MRI results. It turns out that patients who scored higher on the PHQ-9 and GAD-7 scales on MRI showed significantly larger areas of necrosis than those with lower scores, which qualified these individuals for a worse prognosis [11].

In addition, a study in 2022 proved that both depressive disorders, but also gender, WHO classification, prognosis and being married, partnered also affected the worsening of survival in glioma patients. [12]

Patients with such disorders should be put on special protocols that include antidepressant treatments, psychotherapy. Unfortunately, we do not have such standards in the world, and the diagnosis of psychopathological disorders in people with CNS tumors is often overlooked due to the focus of attention and treatment directed at the underlying disease.

Relationship between brain tumor and depression - literature review

In 2020, a 29-year-old woman presented to her doctor for depressive symptoms such as depressed mood, tearfulness, and anhedonia. The only neurological symptom was impaired speech fluency. The woman had no family history of mental illness and showed no risk characteristics for this disease. Based on the history, a diagnosis of major depressive disorder was made. Due to persistent speech disorders, an MR was performed, which showed a tumor in the right frontal lobe area. The patient was operated on. A diagnosis of second-degree glioma was made. The patient underwent radiation therapy after surgery. After this treatment, the symptoms of depression disappeared. The woman did not show psychopathological disorders [6].

In 2019, an article was published that described a 69-year-old woman with a long-standing history of depression associated with a suicide attempt, who had recently stopped responding to medication. Above that, neurological symptoms such as speech and cognitive impairment appeared, imaging studies were performed, which revealed a grade IV malignant Glioma. The lesion was surgically removed. After surgery, neurological symptoms regressed, while depressive symptoms persisted despite treatment [13].

Another example is a case report of a man described in 2020. A 46-year-old patient with depressive symptoms and adaptation problems who did not respond to antidepressant treatment. Of the neurological symptoms at this point, headache was predominant. In addition, he complained of irritability, lack of interest and motivation. The man showed no interest in hygiene and his own appearance. After some time, the patient's symptoms of catatonia began to intensify. On physical examination, muscle weakness of the right side was noted. An MRI imaging study was performed, which showed a left tumor located in the frontal lobe. Surgical treatment was applied; unfortunately, the patient died within days of surgery [2].

An example of the occurrence of depression prior to the diagnosis of a brain tumor is also described in the description of a 28-year-old woman, published by who, after giving birth, began to show depressive disorders, lack of interest in the child, and unwillingness to care for him. She felt emptiness and an urge to cry, but did not report sadness. In addition, she complained of a headache diagnosed as a migraine. She denied nausea and vomiting. On examination, it was noted that the patient had problems with memory focusing and speech disorders. MR imaging was performed, revealing a tumor undergoing contrast enhancement in the left frontal lobe area. Surgical treatment and radiochemotherapy were applied,

achieving complete removal of the lesion. At the last follow-up 3 years after surgery, the patient showed no psychopathological disorders [14].

A study conducted on 61 patients in the age group from 18 to 80 years with a diagnosis of benign or malignant tumor with brain metastasis was published in 2023, in addition to which a group of people -61 who were diagnosed with GMB between the ages of 22-78 were singled out. For the final evaluation, 32 patients who completed the study were included. Both genders participated in this study. Data were collected between 2016 and 2018, and the study included people who had tumor locations in different lobes of the brain. In-depth interviews were conducted with the patients and they were assessed on the CES-D scale for the severity of their depression. Their psychophysical state was assessed both before and after surgery. The last interview was conducted 8 weeks after surgery. Based on the information obtained from the patient for the study, a proprietary SSQ questionnaire was also created to help diagnose the patient's mental state. The results showed that the presence of depression in brain tumors is as common in men as in women. Before removal of the tumor lesion, 36% of patients scored above 16 on the CES-D scale, which was classified as major depression. In patients after GBM surgery, the score of this scale was above 16 in as many as 78.5% of patients, while only 22% of those with benign tumors had such a score. It has been proven that patients with GBM feel sadness, helplessness much more often and to a higher degree. This study showed that patients especially with GBM are prone to depressive disorders. It turns out that the highest severity of symptoms and the best time to detect it is 3 weeks after surgery [10].

The study, published in 2022 and conducted in 2021-2022, included 176 adult patients with a newly diagnosed brain tumor. It found that depressive symptoms were significantly more common in those with a GBM diagnosis. The SCAN schedule was used to conduct the study, and interviews and examinations were conducted by qualified physicians in the field. Above that, their findings were correlated with the location of the tumor thanks to radiological results obtained via magnetic resonance imaging. Patients were divided according to the location of the tumor, lateralization, its size and the extent of the swelling. Their psychophysical state before surgery was assessed. As many as 24% had depressive symptoms present. In these patients, the diameter of the tumor was more than 4 cm. In addition, the presence of peri-tumor edema had a significant impact on the presence of depression, it was diagnosed in as many as 33.3%. Mental disorders were present much more often, in 43% of the subjects, in tumors with poor prognosis especially in gliomas. In addition, it turned out

that those whose tumors were supratentorial suffered from depressive disorders with higher frequency. As many as 30.6% of patients, including 24.7%, showed depressive symptoms. Among the subjects whose tumors were located sub-amyotome, only 4% represented psychopathological disorders. Above that, it was shown that these symptoms appeared with significantly higher frequency in subjects whose tumor was located on the left side [15].

In 2016, a study was published showing the effect of brain tumor surgery on the occurrence of psychopathological symptoms. The study included 57 patients in which as many as 22 had a tumor in the frontal region, and it was those with this location who showed depressive symptoms. Moreover, it was shown that tumors with a volume of $> 35\text{cm}^3$ were characterized by more severe psychopathological symptoms than smaller foci. It was shown that after removal of the surgical lesion, the majority of patients experienced partial regression of depressive symptoms - in 40%, as many as 45% of the subjects had their depressive disorders completely disappeared after surgery, while only 15% showed no change. This study involved brain meningiomas [16].

Evidence of the cessation of depression after neurosurgery is also provided by the case of a 54-year-old woman published in 2015, who presented to her doctor for progressive depressive symptoms. She was treated with duloxetine, which was later changed to venlafaxine. No improvement in treatment. It was reported by her family that the patient was beginning to have memory problems and was exhibiting aberrant behavior. A neurological examination performed showed no abnormalities. It was decided to perform imaging studies, which showed a tumor in the frontal lobe on the left side. After histopathological examination, a meningioma was diagnosed. The woman underwent a neurosurgical procedure. In follow-up psychiatric examinations conducted after the patient's surgery, she did not show any psychopathological disorders. This condition also persisted in the last follow-up the patient underwent 2 years after the meningioma was removed [17].

Multidisciplinary approach in the evaluation of depression in patients with cancer

Cancer is associated with many discomforts, both physical and psychological. The incidence of cancer progresses with every turn. There are many guidelines indicating treatment choices and enabling improved prognosis and prolonged life. Unfortunately, the constant struggle with the disease significantly affects mental health due to the deterioration of quality of life. People with the disease fall as much as 4 times more often into depression mainly diagnosed

with MDD than people without cancer. The link between depression and MDD is found in pathophysiology. The problem involves changes in the nervous system as well as other organs. A large role is attributed to hormones including cortisol, which are secreted as a result of situations accompanied by chronic anxiety. Another point worth noting is dysbiosis and inflammatory bowel disease, which can lead to nerve inflammation, increased inflammation and lowered immunity, which can eventually lead to cancer progression. Other aspects showing a link between depression and cancer are lifestyle, smoking and abnormal habits [18]. In order to fight depression, it is necessary to implement many changes in a person's life that will affect both his mental and physical zones . A study that was conducted in 2017 showed that the use of chemotherapy and surgical treatment does not impair the quality of life and functioning, and even slightly improves the physical and mental state of people with a brain tumor [19]. A huge support for these individuals is the family. Unfortunately, both anxiety and depressive disorders affect not only the patient but also those around him. Those close to the person are much less able to cope with their emotions and are more likely to shut down, exhibiting depressive symptoms [20].

Results

Analyzing the above case reports and test results, we are unable to say unequivocally when depressive symptoms herald the presence of a brain tumor. Often, people who were diagnosed with depression as the first symptom of cancer reported many symptoms indicative of mental disorders. Interestingly, the most frequently denied feeling was that of sadness. Subjects reported that they experienced increased weeping and a sense of emptiness, but did not understand for what reason. Unfortunately, there are no guidelines that clearly define in which patients with psychopathological disorders should undergo imaging studies to rule out neurological disease. Often such patients are treated with antidepressants until neurological disorders appear that prompt imaging diagnosis. However, based on the above data, we can see a huge correlation between depressive disorders and the occurrence of brain tumors. The studies presented here focused specifically on meningiomas and gliomas of various degrees of malignancy. It turns out that these disorders appear with greater frequency when the lesion is located in the left frontal lobe. Symptoms also correlate with the subnuclear or supranuclear presence of a CNS tumor. Removal of the tumor mass results in a high percentage of cases in a complete return to normal psychological status, as evidenced by the case reports and studies described above. Nonetheless, we are not able to determine unequivocally which individuals exhibiting depressive behavior should undergo imaging

studies such as CT scans or more accurate MRI followed by PET- MRI to rule out the presence of a tumor-lesioned brain area, edema or necrosis. Lack of standardization in this case may result in a later diagnosis of the disease and the development of cancer. This may contribute to the inability to perform neurosurgery due to localization or infiltration preventing treatment with a chance of full recovery. In all of the descriptions presented, neurological disorders, particularly speech or memory disorders, appeared later or shortly after the onset of depressive symptoms or behavioral disorders. Patients with a better prognosis and more differentiated cells on histopathological examination, i.e. meningiomas, low-grade gliomas, were followed by regression of depressive disorders in most cases after neurosurgery. Patients fully recovered psychophysically. Present was the percentage of patients who, despite complete removal of the lesion, continued to exhibit depressive disorders related to their diagnosis and the treatment process. Unfortunately, surgical treatment cannot be considered the norm as a treatment for depression. Studies conducted on individuals who were diagnosed by imaging, histopathology and molecular studies with glioblastoma multiforme characterized by high aggressiveness and being highly malignant lesions showed that depressive disorders progressed as the disease progressed. Despite optimization of antidepressant treatment and the use of drugs from different groups, the intended effect was not achieved. These individuals, regardless of the location of the tumor, show sadness, resentment, anxiety, apathy and lack of interest. It has also been proven that people who have these symptoms severely have a shorter survival time. Depression in them usually began at the time of diagnosis and became increasingly severe as it progressed, regardless of the treatment used. Antidepressant treatment had no effect, which has been linked to the existence of brain networks responsible for lowering mood in cancer.

Conclusions

Based on the work presented here, we can conclude that depression can be both the first symptom of cancer and a consequence of the suffering of patients. As the first symptom, it appears at the onset of lesions in the left frontal lobe in particular. Typically, after removal of the lesion, patients fully recovered mentally in the case of tumors with a good prognosis. Unfortunately, in those who were diagnosed with tumors of high malignancy and poor prognosis, depressive symptoms were exacerbated despite neurosurgery. This was associated with quality of life, physical pain and psychological pain. Depression in these individuals

developed and intensified regardless of the primary location of the tumor. Above that, in these patients, these symptoms were associated with a worse prognosis.

In conclusion, imaging studies should be considered in patients whose depressive symptoms appear suddenly, with no family history of burden and refractory to antidepressant treatment, in order to exclude neurosurgical pathologies. Above all, those diagnosed with a brain tumor should be included in protocols for early detection and escalation of psychopathological disorders, especially those who have heard the diagnosis with a poor prognosis.

Author's contribution

Conceptualization K.A.; Writing, review and editing, K.A., U.Ž., K.D., A.Š., Z.K., H.C.K., D.M., K.S., I.T. All authors have read and agreed with the Publisher version of the manuscript.

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