MEDICAL SCIENCES

ASSOCIATION OF GLIOBLASTOMA WITH MENTAL STRESS

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https://doi.org/10.5281/zenodo.13326841

Abstract

Gliomas tend to have a poor prognosis and are the most common primary malignant tumors of the central nervous system. Compared with patients with other cancers, glioma patients often suffer from increased levels of psychological stress, such as anxiety and fear. Chronic stress is thought to impact glioma profoundly.

However, because of the complex mechanisms underlying CS and variability in individual tolerance, the role of CS in glioma remains unclear [2]. This review suggests to study deeper potential role of chronic mental stress in gliomas, particularly glioblastoma, etiology, pathogenesis. Mental stress management among population may lead to better results in gliomas prevention and treatment. After diagnosis, glioblastoma [GBM] patients undertake tremendous psychological problems such as anxiety and depression, which may contribute to GBM progression. However, systematic study about the relationship between depression and GBM progression is still lacking [1]. Given the negative impact of maladaptive psychosocial and biobehavioral factors on normal immune system functions, the question remains as to how psychological conditions potentially affect the brain tumor patient anti-tumor immune response [3]. Since immunotherapy has yet to show efficacy at increasing malignant glioma patient survival in all randomized, phase III clinical trials to-date, this review provides new insights into the potential negative effects of chronic distress on brain tumor patient immune functions and outcomes [3]. Central nervous system [CNS] tumors account for 1.6% of all newly diagnosed cancers worldwide according to Global Cancer Statistics 2020 [4], with gliomas being the most common primary CNS tumors, accounting for approximately 75%. from all detected [5]. In this article we will talk about gliomas and what them belong to chronic stress. How to decrease risk factors of initiation of brain oncology.

Keywords: gliomas, glioblastomas, chronic stress, brain tumors.

Mental stress in patients with a brain tumor

Stress is a normal and fairly common human reaction that helps overcome difficulties in critical periods. The reaction to stress can have different manifestations and is called acute stress. However, long-term effects of stressful factors, especially in people with an irrational diet or sleep disorders, can lead to the transition of acute stress to the stage of exhaustion, when cells lose the ability to maintain their functional properties: chronic stress develops [6]. Cohort studies show that mood disorders such as depression and anxiety [7] are observed significantly more often in patients after diagnosis and increase during treatment and operations [8]. Numerous studies have shown that the relationship between chronic stress and glioblastomas is direct and bidirectional. However, the primary question remains open: chronic causes glioma or chronic stress causes glioma [9]. However, sudden onset depression and anxiety can also be early symptoms of glioma. While neuropsychiatric symptoms are the first clinical sign of a brain tumor in 18% of reported cases [10]. In this paper, we will try to reveal the connection between chronic stress and glioblastomas. Let's consider how certain mechanisms affect the progression of these tumors and how it can be combated. Depression and anxiety are common in patients with a terminal illness. Meta-analyses have found that cancer patients in the palliative care setting have a rate of mood disorders, including depression, anxiety, and adjustment disorder, of 29%. Notably, this rate of psychological conditions is likely underappreciated and/or underreported, as cancer patients experience chronic distress and demoralization without the presence of a psychiatric diagnosis [11].

Molecular mechanisms of Mental stress in patients with a brain tumor

The effect of chronic stress on both humans and laboratory rats is realized by a rather complex pattern of interactions. Thus, the system can be divided into receptors that directly determine stressors, processing and reaction centers [12]**.** With the help of long-term neural connections, information enters the processing center - the Limbic system. The adreno-cortisol apparatus, controlled by the Pituitary-hypothalamus-adrenal axis, serves as the body's response to one or another stress factor. The sympathetic nervous system also assumes its role in regulation [13]**.** During the action of the stressor, the sense organs collect information about it and transmit impulses to the primary cortex of their area, respectively. Then,

through a complex system of interactions, the impulses are transmitted to the thalamus for cortico-thalamic integration. The thalamus plays a key role in the development of the stress response, acting as a processing relay station. Here, information is processed and transmitted to areas involved in stress processing. In our case, it is the prefrontal cortex, the amygdala and the hippocampus. The prefrontal cortex is responsible for the complex behavioral responses associated with the stress response, while the hippocampus is responsible for the creation of long-term memories associated with chronic stress. The amygdala activates the ways of integration of the nervous system with the neuroendocrine system, initiating the pituitary-hypothalamus-adrenal axis [14 15 16 17]. It is clear that the processing of stress involves huge arrays of neural interactions and cannot fail to affect the functions of whole parts of the brain. Chronic stress can cause an imbalance between excitatory and inhibitory neurotransmission, which leads to a change in the strength and stability of synapses. Research on rats revealed that under the influence of chronic stress, the activity of such parts of the brain as the lateral and basolateral gyrus, the lateral habenula, significantly increased.[18] At the same time, the synaptic plasticity of neurons was disturbed in the hippocampus and prefrontal cortex. These changes are also characteristic of patients with mood disorders. Pathomorphologically confirmed reduction in the mass of neurons of the prefrontal cortex, reversible damage to the hippocampus and hypertrophy of the amygdala. However, damage is relative, because different individuals have different resistance to stress [19 20 21]**.** Signals evoked in response to chronic stress converge in the paraventricular nuclei, the control nucleus of neuroendocrine pathways [22]**.** Activation of the pituitary-hypothalamus-adrenal axis is triggered by the release of corticotropin-releasing hormone and arginine-vasopressin. Hormones bind to corticotropin-releasing hormone receptor 1 [CRHR1] on corticotropic cells of the anterior pituitary, leading to the synthesis and secretion of adrenocorticotropic hormone [ACTH]. ACTH then acts on the adrenal cortex to stimulate the synthesis and release of glucocorticoids [GC] [23 24], characterized by cortisol in humans and corticosterone in rodents [25]**.** This neurological transmission also activates the sympathetic nervous system, which stimulates the release of catecholamines. Arasympathetic regulation is represented by the vagus nerve. In addition, the vagus nerve is an important hub of the microbiota-gut-brain axis [25]**.** Chronic stress creates a powerful effect on the body. It acts through the central nervous system, disrupting the balance between the sympathetic and parasympathetic nervous systems. As a result, excessively synthesized stress signaling molecules constantly circulate in the blood and cerebrospinal fluid, as a result of constant activation of the adrenal and cortisol systems [26]**.** High levels of these factors affect the immune response and can cause inflammation. At the same time, a violation of vagal inhibition can have a negative effect on the gut microbiota, increasing conductivity, which only leads to an exacerbation of the process [27]**.** Inactivation of tumor protein 53 [p53] is a critical event in the malignant transformation of most tumor cells [28]**.** In vivo studies in rats have confirmed that chronic stress stimulates NE to initiate G-protein-protein kinase A [Gs-PKA] signaling through β2 - adrenoceptors [β2 - AR]. As a result, reactive oxygen species are formed that damage cellular deoxyribonucleic acid, with the accumulation of metabolites of the latter in the cytosol if the repair is damaged. In addition, cytosolic β-arrestin1 [ARRB1] mediated NE-induced protein kinase B [AKT] and murine two-minute activation 2 [MDM2], while nuclear ARRB1 acted as a catalyst for MDM2-dependent p53 ubiquitination, promoting p53 degradation and DNA damage in the frontal parts of the cerebral cortex [29]**.** Meanwhile, high levels of GCs during chronic stress mediate the effects of chronic stress on p53 through the induction of serum and glucocorticoid-regulated kinase 1 [SGK1], which in turn increases MDM2 activity and decreases p53 function [30]**.** Clinical data also suggest that loss of p53 function is a key initiating event in glioma development [31]**.** It is also important to clarify that p53 protein damage alone is not sufficient for tumorigenesis. As far as we know, mutations must accumulate and be passed on to subsequent generations of cells to initiate progression [32]**.** Gliomas are common in the frontal and temporal lobes of the human brain, but there is still insufficient evidence that DNA damage in these regions specifically initiates glioma formation [33]**.** Prolonged proliferation is the most important characteristic of glioma cells. Serum levels of the stress hormones GC and NE have been shown to increase significantly under chronic stress. NE and GC promoted uncontrolled proliferation of gliomas in vivo, and in vitro experiments using human glioma cell lines showed that GC and NE promoted glioma cell growth by activating phosphoinositide 3-kinase**,** protein kinase B. The signal is transmitted through glucocorticoid receptors and β- adrenoreceptors [β-AR] [34]**.** At the same time, β-ARs initiate extracellular phosphorylation of signal-regulated kinase [ERK], enabling them to exert a direct influence on the proliferation of glioma cells [35]**.** AKT pathways are non-alternative intracellular signaling pathways involved in cell growth, division and apoptosis. In addition, the ERK phosphorylation cascade is a central regulator of intracellular signaling. NE also directly promoted proliferation by regulating cyclin D1/cyclin-dependent kinase 4/6 [CDK4/6] expression in glioma cells [36]**.** The data show that glutamatergic synapses form between neurons and cells, and this trend is observed in both rats and humans. Neuronal activity mediated by the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA] receptor has also been shown to induce glioma invasion and growth. During this growth, neurons also released neuroligin-3 to activate the mammalian phosphoinositide 3-kinase target of rapamycin pathway in glioma cells and promote glioma cell proliferation [37]. At this time, there are no visual studies that would confidently demonstrate a correlation between chronic stress and the formation of excitatory synapses. However,

researchers [38] found that gamma-aminobutyric acid [GABAergic] interneuron activity is reduced in rats after chronic visual deprivation, a form of chronic stress. This condition leads to increased proliferation of glioma in the primary visual cortex. Unlike glutamatergic synapses, which transmit excitatory signals, GABAergic neurons are the main inhibitory neurons of the CNS. Thus, chronic stress disrupts the balance between excitatory and inhibitory signals in the brain. In such conditions, the sensitivity of cells to excitatory influences increases, which in turn can contribute to the establishment of excitatory synapses between neurons and gliomas [39]**.** Chronic stress has recently been implicated as a cause of vision loss in patients with glioma [40]**.** While it was possible to prove interrelated factors of chronic stress and complications of glioma in mouse models, it is still quite problematic to do this in human lines in vitro. Although clinical observations indicate this, stress hormones synergize this process and stimulate the proliferation of glioma cells. Chinese scientists in 2023 used further method to study molecular mechanisms Chronic stress accelerates glioblastoma progression via DRD2/ERK/β-catenin axis and Dopamine/ERK/TH positive feedback loop: Chronic unpredictable mild stress and chronic restrain stress were used to mimic human depression in mice. Human GBM cells and intracranial GBM model were used to assess the effects of chronic stress on GBM growth. Targeted neurotransmitter sequencing, RNA-seq, immunoblotting and immunohistochemistry were used to detect the related molecular mechanism. The results were further: Chronic stress promoted GBM progression and up-regulated the level of dopamine [DA] and its receptor type 2 [DRD2] in tumor tissues. Down-regulation or inhibition of DRD2 abolished the promoting effect of chronic stress on GBM progression. Mechanistically, the elevated DA and DRD2 activated ERK1/2 and consequently inhibited GSK3β activity, leading to β-catenin activation. Meanwhile, the activated ERK1/2 up-regulated tyrosine hydroxylase [TH] level in GBM cells and then promoted DA secretion, forming an autocrine positive feedback loop. Remarkably, patients with high-depression exhibited high DRD2 and β-catenin levels, which showed poor prognosis. Additionally, DRD2 specific inhibitor pimozide combined with temozolomide synergistically inhibited GBM growth. The conclusion of this study was: The study revealed that chronic stress accelerates GBM progression via DRD2/ERK/β-catenin axis and Dopamine/ERK/TH positive feedback loop. DRD2 together with β-catenin may serve as a potential predictive biomarker for worse prognosis as well as therapeutic target of GBM patients with depression [1].

Interactions among distress, immunosuppression, and cancer

Untreated distress may affect brain tumor patient outcomes through the interactions between psychosocial distress and the immune system. The relationship between excess adrenergic signaling and immune dysregulation, inflammation, and tumor growth is well-established. Increased distress promotes the release of stress hormones, primarily in the form of catecholamines including epinephrine and norepinephrine via the sympathetic nervous system [SNS], as well as glucocorticoids via adrenal cortex [3].

Conclusions

The effect of chronic stress on the initiation, proliferation, and progression of gliomas is a controversial topic. A growing number of recent preclinical studies have shown that chronic stress does promote tumorigenesis. However, some meta-analyses of cohort studies still refute the effect of long-term work stress, as well as the disruption of circadian rhythms due to night shifts do not have an effect on the risk of cancer [41]. Many subsequent studies have shown that mood disorder and chronic stress have an important impact on the prognosis of patients with glioma. Recently, there is increasing evidence that chronic stress as a concomitant risk factor may contribute to the development and progression of glioma. The related molecular and systemic mechanisms mentioned above have been discovered in animal studies, and most of them have been clinically confirmed in patients with various types of cancer. Individual responses to stress may vary, so the effect of stress on glioma risk may vary from person to person. Some patients can take steps to prevent stress, such as walking, spending time with loved ones, pets, etc., potentially reducing the risk of developing cancer. Others may use negative coping strategies, such as overeating, drinking, or smoking, which can increase the risk of developing cancer. But despite such a large sample, more detailed studies still show a link between chronic stress and the development of gliomas. [41] It is summarized that chronic stress is associated with glioma by affecting eight hallmarks of cancer, namely genomic instability and mutation, unlocking phenotypic plasticity, maintaining proliferative signaling, reprogramming cellular metabolism, resistance to apoptosis, activation of invasion and metastasis, inflammation, tumor-promoting and polymorphic microbiomes. In turn, gliomas contribute to mood deterioration and the emergence of chronic stress as such, worsening the prognosis. Malignant brain tumors are a profoundly devastating disease associated with significant increases in depression, anxiety, and distress among patients. We propose a direct biological link between psychosocial stressors and poor outcomes in malignant glioma patients. High adrenergic signaling and endogenous steroid activity may impair immune system functions, resulting in the uncontrolled proliferation of tumor cells, as observed in non-CNS cancer patients. The influence of chronic mental stress [CMS] on gliomas is a controversial topic. An increasing number of recent preclinical studies have shown that CMS promotes tumorigenesis. However, some meta-analyses of cohort studies suggest that long-term work stress and chronic jetlag caused by night shift work do not increase the risk of cancer. Many follow-up studies have shown that CMS and CMS-induced mood disorders were important prognostic factors for glioma. There is also increasing evidence that CS as an environmental risk factor can promote the development and progression of glioma. Associated molecular and systemic mechanisms have been identified in animal studies and most have been

demonstrated in cancer patients. However, association of gliomas, particularly glioblastoma – the most spread and high mortality glioma, with mental stress has to be studied further. New knowledges about this association may lead to better results in gliomas prevention and treatment through effective chronic mental stress management strategies [42].

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