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Impaired neurocognitive function in glioma patients: from pathophysiology to novel intervention strategies

Kyle R. Noll^a, Tobias Walbert^b, and Jeffrey S. Wefel^{a,c}

Purpose of review

This review succinctly summarizes the recent literature regarding etiological contributors to impaired neurocognitive function (NCF) in adult patients with glioma. A brief overview of intervention and prevention strategies is also provided.

Recent findings

A majority of patients with glioma exhibit NCF deficits, most frequently in memory and executive functioning. Impairments are often disabling and associated with reduced quality of life and survival. Cause is multifactorial and includes the tumour itself, treatments received and associated comorbidities. Although modern techniques such as brain mapping, dosing modifications and prophylactic medication aim to improve the NCF outcomes following neurosurgical resection and radiation therapy, a sizeable proportion of patients continue to evidence treatment-related NCF declines related to adverse effects to both local and distributed cerebral networks. Numerous patient and tumour characteristics, including genetic markers and sociodemographic factors, influence the pattern and severity of NCF impairment. Some rehabilitative and pharmacologic approaches show promise in mitigating NCF impairment in this population, though benefits are somewhat modest and larger scale intervention studies are needed.

Summary

Research regarding NCF in patients with glioma has dramatically proliferated, providing insights into the mechanisms underlying impaired NCF and pointing to potential interventions, though further work is needed.

Keywords

brain tumour, glioma, intervention, neurocognitive function, neuropsychology

INTRODUCTION

Primary brain tumours are relatively rare, though they are among the most costly of all cancers due to the treatments required and substantial morbidity and mortality [1]. Glioma comprise about 80% of all malignant brain tumours and are currently classified according to the WHO 2016 integrated diagnostic framework, incorporating both tumour morphology and molecular information [2]. Glioblastoma isocitrate dehydrogenase (IDH)-wild type is the most common (71%) and most malignant glioma in adults. Although rates vary by tumour histology and molecular subtype, most patients with glioma (>90%) will exhibit impairment of neurocognitive function (NCF) [3,4]. Impairment is most frequent and severe in the domains of learning and memory and executive functioning, though the pattern and severity varies according to patient and tumour characteristics. The following section reviews the recent literature examining contributors to

impaired NCF in adult patients with glioma and highlights intervention and prevention strategies.

NEUROCOGNITIVE ASSESSMENT

Impaired NCF in patients with glioma is associated with early disease progression and reduced overall survival [5,6^a,7,8], as well as diminished functional

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KEY POINTS

- The cause of impaired neurocognitive function in patients with glioma is multifactorial, including disruption of local and distal cerebral networks secondary to the lesion and neurosurgical intervention, chemotherapy and radiation therapy, neurologic and psychological comorbidities, and supportive treatments.
- Recent research regarding patient and tumour genetic characteristics indicate that a number of molecular markers may help identify patients at particular risk of neurocognitive deficits.
- Pharmacologic interventions for neurocognitive impairment show modest benefit in patients with glioma, though recent preclinical models have identified some novel targets for therapy warranting further exploration.
- Compensatory strategy training and potentially modification of lifestyle factors such as exercise represent some of the more efficacious intervention strategies for impaired neurocognitive function in glioma, though further study is needed.

independence [9] and quality of life [10]. In addition, Yoshida *et al.* [11] recently reported that preoperative memory functioning predicts return to work at 1-year follow-up. Accordingly, it is unsurprising that assessment and monitoring of NCF in patients with glioma are increasingly recognized as critical aspects of patient care and clinical trials.

Neuropsychological testing represents an objective approach to measuring NCF. Although traditional neuropsychological assessment predominantly involves in-person paper-and-pencil testing, alternative environments (e.g. telehealth) and platforms (e.g. computerized testing) are gaining interest, as some have argued that these may be preferred by patients and increase access to care. To date, little work has examined teleneuropsychology approaches in patients with glioma. A recent study by Cerhan *et al.* [12] indicated that computerized testing was not preferred over traditional paper-and-pencil testing in patients with high-grade glioma. Moreover, correlations between test results obtained from the two methods were low to moderate (0.19–0.39). Despite potential, further work is needed to improve and validate such novel assessment methods before clinical application in neuro-oncology.

CONTRIBUTORS TO NEUROCOGNITIVE IMPAIRMENT

Patient characteristics

Advanced age is associated with poorer NCF in various neurologic populations, including glioma

[13]. In contrast, higher education is associated with better NCF, likely reflecting beneficial impact of cognitive reserve. Numerous patient genetic characteristics are also associated with NCF. A recent study identified a favourable polygenic profile associated with less NCF impairment and greater likelihood of return to work following brain tumour diagnosis, which included genes involved in the survival and growth of neurons (BDNF) and neurotransmitter regulation (DRD2, COMT) [14[■]]. Correa *et al.* [15[■]] reported numerous single nucleotide polymorphisms associated with NCF in patients with brain tumours, such as genes related to LOAD/inflammation/cholesterol transport (PDE7A, IL-6), dopamine regulation (DRD1, COMT), myelin repair (TCF4), DNA repair (RAD51), cell cycle regulation (SESN1) and response to oxidative stress (GSTP1). Accumulating evidence also indicates that patients with brain tumours who harbour the APOE e4 allele exhibit increased risk of impaired NCF [16].

Lesion characteristics

Numerous studies indicate that lesion location plays an important role in the pattern and severity of NCF impairment in patients with glioma [17,18[■]]. Recent investigations have explored more fine-grained associations between specific brain structures and differentially affected NCF domains. Incekara *et al.* [19] described associations between dominant hemisphere white matter abnormalities in the arcuate fasciculus and language repetition, and changes to the inferior frontal-occipital fasciculus with memory and executive functioning. Pisoni *et al.* [20] reported that auditory attention problems are associated with left supramarginal and superior posterior temporal lesions, repetition with more anterior lesions in the parietal, temporal and frontal lobes, and comprehension with cortical and subcortical temporal regions. Liu *et al.* [21] found increased structural connectivity among rich-club nodes and reduced connectivity among peripheral nodes in patients with frontal and temporal lesions. Interestingly, altered local efficiency was associated with memory in temporal lobe tumours and information processing speed in frontal tumours.

Although the literature described above indicates that some NCF deficits may be at least partially localizable and dissociable, studies also suggest diffuse cerebral changes associated with NCF in patients with glioma. Hu *et al.* [22] reported that areas of the temporal lobe contralateral to the lesion show increased grey matter volume pre and postoperatively compared with controls, with increased volume associated with better memory. Da Baene *et al.* [23] noted associations between NCF and

various resting-state functional connectomic properties contralateral to brain tumours. Liu *et al.* [24] reported broad disruption of various resting-state networks underlying NCF impairment in patients with brain tumours following surgery, with increased intra and cross-network interactions. Taken together, accumulating research suggests that even relatively circumscribed tumours can impact both local and distal brain structures and functions, consistent with conceptualizations of the brain as consisting of distributed but integrated networks.

Growth characteristics represent another important contributor to impaired NCF in patients with glioma. van Kessel *et al.* [18²²] reported that larger preoperative lesion volume is associated with worse executive functioning, language and memory in a mixed glioma sample prior to surgery. Evidence also suggests tumour kinetics, as represented by tumour grade and/or molecular characteristics, are important contributors to impaired NCF independent of lesion volume [25,26]. A number of studies recently confirmed that more aggressively proliferating higher grade glioma are associated with more severe NCF impairment than their lower grade counterparts [18²²,23,27]. Other work confirmed that patients with more aggressive IDH-wild type glioma exhibit worse NCF and greater disruption of cerebral networks than those with IDH-mutant lesions [13,18²²,28²⁴]. Jütten *et al.* [29] also reported that IDH-mutant tumours show greater preservation of white matter microstructure than wild-type tumours. These findings suggest that slower growing tumours may allow for greater functional reorganization, mitigating disruption to cerebral networks and better preserving NCF. Other tumour molecular markers may also influence NCF in low-grade tumours, including p53 and GFAP [30].

Neurosurgical intervention

When feasible, tumour resection is an essential aspect of glioma treatment, facilitating diagnosis, treatment planning and reducing neurologic sequelae. Despite use of modern surgical planning and operative techniques to optimize oncofunctional balance, a sizable proportion of glioma patients exhibit NCF decline postoperatively, particularly those harbouring lesions within the language dominant hemisphere near eloquent brain regions [13,31]. Postoperative degradation of NCF may relate to damage to functional tissue, in addition to the impact of oedema and complications such as seizures. A recent study by Loit *et al.* [32²⁵] indicated that perioperative infarcts constitute another important contributor to surgically-acquired NCF impairment. Supratotal resection represents a technique that increases resection margins

to reduce oncologic burden and potentially extend survival. Rossi *et al.* [33²⁶] reported that supratotal resection can be performed safely in patients with low-grade glioma from a quality of life and NCF perspective. However, the NCF test battery utilized was limited and perhaps insensitive to postoperative NCF changes.

Radiotherapy

Most patients with malignant glioma require radiation therapy with or without concurrent chemotherapy. In a recent study involving patients with intracranial tumours 6 months following radiation, Cramer *et al.* [34] reported that nearly 70% of patients exhibited mild cognitive impairment and 10% possible dementia according to criteria adapted from the National Institute on Aging and the Alzheimer's Association. Wong *et al.* [35²⁷] found that 75% of patients with primary or metastatic brain tumours showed impairment on at least one neuropsychological measure 6 months postradiation, with better functioning associated with higher education and not receiving whole brain irradiation. It is well established that white matter structures are sensitive to radiation damage and Tringale *et al.* [36,37] recently noted associations between post-radiation white matter abnormalities in the anterior cingulate and executive function deficits, as well as white matter changes in the medial temporal lobe and temporal pole with memory problems. Although radiation dose to the hippocampus has been reported as a risk factor for memory decline [38], Jaspers *et al.* [39²⁸] failed to replicate this finding in a recent small study involving patients with low-grade glioma, necessitating further work.

Chemotherapy

Considerable evidence indicates that chemotherapy negatively impacts NCF in a substantial proportion of cancer patients, though most research involves noncentral nervous system populations [40]. Some evidence suggests that even relatively well tolerated chemotherapies convey risk of NCF decline in patients with glioma. In a clinical trial for glioblastoma, about 30% of patients showed worsening of NCF following chemotherapy with temozolomide despite disease status remaining radiographically and clinically stable [41]. Late deterioration of NCF has also been found in long-term stable glioma survivors after completion of chemotherapy with procarbazine, lomustine and vincristine, though many of the patients also received radiation [42]. Although little recent work has specifically investigated the impact of chemotherapy upon NCF in

patients with glioma, opportunities are growing, as NCF endpoints are increasingly included in clinical trials.

Other contributors

Numerous additional factors can impact NCF in patients with glioma, including medications for neurologic sequelae, such as steroids, antiepileptics and analgesics [3]. Fatigue and sleep problems are common in glioma patients, which can exacerbate NCF deficits. Affective issues, such as depression and anxiety, frequently occur during the glioma disease course [43]. Recent work indicated that depression and executive dysfunction predict survival, with worst prognosis in patients with cooccurring affective distress and impaired NCF [6^{*}]. Patients may also experience personality or neurobehavioral changes. Aerts *et al.* [44] reported that emotional suppression (e.g. affective blunting) can occur postoperatively in patients with low-grade glioma, which was associated with reduction in aspects of executive functioning such as planning.

PREVENTION AND MANAGEMENT

The high prevalence of impaired NCF in patients with glioma and associated reductions in patient well being underscore the need for effective interventions to better manage and prevent NCF decline. Recent reviews by van Lonkhuizen *et al.* [45] and Coomans *et al.* [3] summarize the literature regarding rehabilitative and pharmacological interventions in patients with brain tumours. In addition to briefly discussing some of these approaches, the following section also describes preventive approaches for preserving NCF in patients with glioma.

Brain mapping

Brain mapping (e.g. functional MRI, diffusion tensor imaging (DTI) tractography, intraoperative direct cortical stimulation) can aid neurosurgeons by delineating boundaries of eloquent cortex and white matter tracts involved in NCF. The focus of most mapping studies remains upon language and motor functioning, though recent work suggests that mapping other domains is feasible [46]. In addition, awake surgery can involve monitoring of complex activities important to individual patients, such as playing violin [47]. However, it should be noted that it remains to be determined whether mapping more diverse functions conveys improved NCF outcomes.

Radiation modality and delivery

Some evidence suggests that hippocampal avoidance may help preserve memory functioning in patients with brain metastases undergoing whole brain radiation [48], with emerging studies indicating potential for the technique in glioma, including glioblastoma [49]. Modifying radiation dose may also impact NCF outcomes; however, a recent clinical trial investigating high versus low-dose radiation therapy for low-grade glioma found no differences between groups in survival or NCF [50]. It should be noted that this study relied upon a brief screening tool (MMSE) for the assessment of NCF and group differences may have been obscured by lack of sensitivity of the MMSE. Proton therapy may also convey a NCF benefit over photon radiation [51], particularly in populations at risk for late effects, though results of large-scale clinical trials directly comparing the modalities in adult patients with glioma are yet to be fully reported.

Pharmacological

A number of studies investigated the potential of nootropic medications for preservation or improvement of NCF in patients with brain tumours, though many studies suffer from small sample sizes and/or lack of control groups. Despite limitations, some evidence suggests that medications used to treat Alzheimer's disease, such as memantine and donepezil, may benefit patients with brain tumours. In a large-scale randomized controlled trial, memantine slowed time to cognitive decline when administered during radiation therapy, though this study involved patients with brain metastases receiving radiation to the whole brain [52]. In another randomized clinical trial, donepezil was administered to a large group of primary and metastatic brain tumour patients following radiation therapy, which resulted in modest improvement in memory and motor speed [53]. A recent follow-up study by Naughton *et al.* [54] analysed self-reported symptom measures from this trial finding that patients with more baseline cognitive symptoms showed greater improvement than controls in social and emotional well being, as well as brain specific concerns at 12 weeks posttreatment, though benefits did not persist at 24-week follow-up.

Although pharmacologic studies have mostly focused on medications typically used to treat neurodegenerative diseases, attentional disorders and fatigue, some recent investigations show preliminary evidence supporting other agents. In a small study involving brain tumour patients with insomnia, Chang and Chun [55] found that hypnotics (zolpidem or trazodone) improved fatigue,

sleep and NCF. Recent preclinical work points to some potential novel interventions. For instance, Li *et al.* [56] reported that antiviral nanoparticle 2 improved object recognition memory in a rat model of glioma, with increased long-term potentiation and dendritic spine density in the CA1 region of the hippocampus. In a mouse model of glioma, Feng *et al.* [57] demonstrated that whole brain radiation resulted in memory deficits, which could be prevented by transient inhibition of the cytokine colony-stimulating factor 1. The antidepressant fluoxetine was found to reduce both anxiety and NCF impairment in mice following chemoradiation with improved long-term potentiation and neurogenesis in the hippocampus [58[□]].

Rehabilitative

Rehabilitative approaches are commonly characterized as either compensatory strategy training or cognitive retraining. Strategy training involves teaching techniques to help compensate for NCF deficits (e.g. mnemonics, clustering), whereas retraining aims to improve the deficient NCF itself. A number of studies suggest that these approaches are beneficial in patients with brain tumours [3,45]. However, most studies suffer from methodological shortcomings and studies regarding NCF retraining approaches, whether therapist-facilitated or computerized, often fail to show transfer of gains from the trained task to important daily life activities. Of the limited more recent work in this area, Richard *et al.* [59[□]] conducted a pilot randomized controlled trial with a small sample of brain tumour patients comparing goal management training for rehabilitation of executive dysfunction versus a brain health programme active control and a wait-list control. The results showed high adherence to the interventions and executive functioning appeared to improve only with goal management training. Regarding computerized approaches, van der Linden *et al.* [60] recently reported a protocol for a randomized controlled trial utilizing a tablet-based application for cognitive rehabilitation in brain tumour patients. The application includes psycho-education, compensation training and retraining, and data collection is underway.

Exercise

Lifestyle interventions, including exercise, have demonstrated some efficacy in the treatment and prevention of NCF impairment in various neurologic populations. Although the related literature involving patients with glioma is limited, Gehring *et al.* [61[□]] reported a recent pilot randomized controlled trial of

exercise intervention, with brain tumour patients showing benefit across numerous NCF domains and self-reported symptoms.

CONCLUSION

Impaired NCF represents an important contributor to the well being and functional independence of patients with glioma. Unfortunately, a majority of patients will exhibit NCF impairment secondary to the tumour itself and/or treatment adversely affecting distributed neural systems. Accumulating evidence suggests that tumour and patient genetics, lesion characteristics and sociodemographic background contribute to individual differences in the pattern and severity of NCF domains affected. Although some evidence suggests that NCF impairment may be mitigated by neurosurgical planning methods, alternative radiation therapy approaches, nootropic medications and rehabilitation, results are mixed, benefits appear somewhat modest and more efficacious interventions and prevention techniques are needed.

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Conflicts of interest

There are no conflicts of interest.

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