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Treatment of cognitive deficits in brain tumour patients: current status and future directions

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Purpose of review

Increased life expectancy in brain tumour patients had led to the need for strategies that preserve and improve cognitive functioning, as many patients suffer from cognitive deficits. The tumour itself, as well as antitumour treatment including surgery, radiotherapy and chemotherapy, supportive treatment and individual patient factors are associated with cognitive problems. Here, we review the recent literature on approaches that preserve and improve cognitive functioning, including pharmacological agents and rehabilitation programs.

Recent findings

Minimizing cognitive dysfunction and improving cognitive functioning in brain tumour patients may be achieved both by preserving cognitive functioning during antitumour treatment, including techniques such as awake brain surgery, less invasive radiation therapies such as stereotactic radiotherapy and proton therapy, as well as with interventions including cognitive rehabilitation programmes. Novel rehabilitation programs including computer-based cognitive rehabilitation therapy (CRT) programmes that can be adjusted to the specific patient needs and can be administered at home are promising. Furthermore, personalized/precision medicine approaches to identify patients who are at risk for cognitive decline may facilitate effective treatment strategies in the future.

Summary

Cognitive functioning has gained greater awareness in the neuro-oncological community, and methods to preserve and improve cognitive functioning have been explored. Rehabilitation programmes for brain tumour patients should be further developed and referred to in clinical practice.

Keywords

brain tumour, cognitive deficits, rehabilitation, treatment

INTRODUCTION

Cognitive functioning refers to mental processes such as attention, perception, thinking, reasoning and remembering, the so-called 'higher' cerebral functions. Intact cognitive functioning is important, as it enables to function autonomously within society. In patients with a brain tumour, the presence of the tumour directly threatens cognitive functioning. This is the case in patients with primary brain tumours such as meningiomas and malignant gliomas, as well as in patients with brain metastases, the most prevalent brain tumours. As even mild cognitive deficits can have functional and psychosocial consequences, preserving and improving cognitive functioning in these patients is important to maintain functioning and wellbeing through the disease course.

Many brain tumour patients exhibit cognitive impairment at some point during the disease course, and cognitive deficits are already present in over 90% of the patients with a primary brain tumour

and brain metastases before treatment [1,2]. Tumour characteristics such as location, size, histology and growth rate as well as patients characteristics, including age, cardiovascular risk and cognitive

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KEY POINTS

- In clinical trials, cognitive outcomes should be implemented to gain information on the positive and negative effects of novel (cognition-sparing) treatment strategies on cognition on the short and long term.
- In clinical practice, cognitive impairment should be screened for, and eligible patients should be informed about and informed on/referred to interventional programmes.
- Computer-based cognitive rehabilitation programmes provide access to large patient populations and enable patients to follow rehabilitation in their own environment and at their own pace.
- Future studies should further unravel the association between genetic and cognitive factors to clinically screen for patients who are most vulnerable to cognitive decline.

reserve are associated with the severity of cognitive impairment [3]. In addition, advances in molecular profiling suggest that germline and tumour genetic factors are also associated with cognitive functioning in brain tumour patients, both before and in response to treatment [4,5]. Apart from the local damage, brain tumours also cause global cognitive dysfunction by disruption of cognitive networks, with attention, memory and executive functioning being the most frequently affected domains [4].

Depending on the tumour type, location and growth rate, treatment with surgery, radiotherapy or chemotherapy decreases tumour burden, improves (cognitive) functioning and prolongs survival in most brain tumour patients, but may also cause cognitive deficits. In addition, other factors such as supportive treatment with antiepileptic drugs and corticosteroids, as well as concomitant symptoms such as fatigue and mood disorders are also associated with cognitive deficits [6]. Hence, the tumour itself, antitumour and supportive treatment, clinical, psychosocial and genetic factors as well as cognitive reserve [5] can have an impact on cognitive functioning. Preservation of cognitive functioning by minimalizing the negative impact of antitumour and supportive treatment is therefore important. Furthermore, amelioration of cognitive impairment may be achieved by offering interventions such as pharmacological treatment and cognitive rehabilitation.

In this review, we first aim to evaluate antitumour treatment strategies that aim to prevent or minimize cognitive deficits, thereafter we discuss intervention approaches that aim to improve cognitive functioning, covering the recent literature on pharmacological treatment and cognitive rehabilitation.

TEXT OF REVIEW

Preservation of cognitive functioning

Treatment options for tumour patients often include a combination of surgery, radiotherapy, chemotherapy and supportive treatment.

Surgery

Extensive surgical resection has shown to confer survival benefit in primary brain tumours including gliomas [7], and in general, brain tumour patients experience less seizures, headache and signs of intracranial pressure after surgery. Maximal well tolerated resection while avoiding severe disabling neurological and cognitive deficits is the main challenge in brain tumour patients. Identifying acquired cognitive problems after surgery may be difficult, as presurgery cognitive testing is not always embedded in clinical care, complicating prepost comparison, and deficits are often subtle and may be overshadowed by pronounced and mostly transient speech and motor deficits [8^a]. In glioma patients, studies showed that patients experienced cognitive deficits after surgery [9,10]; however, these were partly transient, and at the individual patient level, postoperative improvement was seen as well [11]. In patients with meningioma, cognitive functioning frequently improves after surgery, but remains significantly lower than in healthy controls [12,13]. Postoperatively, the most affected cognitive domains are memory and executive function [13].

Awake surgery with intraoperative electrical stimulation and real-time monitoring aims to identify brain circuits crucial for cognitive functioning. It allows for more precise resection of the tumour without damaging surrounding tissue, and is thereby assumed to preserve cognitive functioning in glioma patients [14–16]. However, most studies only included follow-up of a few months, and studies on long-term cognitive outcomes after awake surgery are lacking. Also, nowadays, testing during awake tumour resection is mainly focused on the domains of language and motor function in patients with left-hemispheric tumours. More recently, a few explorative studies in brain tumour patients evaluated the feasibility and effects of monitoring other cognitive functions during awake surgery, for example executive functioning (that is inhibition) and working memory [17,18].

Radiation therapy

Radiation may lead to significant, but mostly transient, cognitive disability in 50–90% of the patients, occurring in the acute phase (during radiation),

early-delayed (in the first months after radiation) and late-delayed (up to years after radiation) [19[¶]]. Acute side effects include inflammation and injury to neuronal structures, causing oedema that leads to symptoms such as headache, nausea and dizziness and cognitive deficits. Early-delayed effects are associated with demyelination and oedema, which may affect cognitive functioning as well [20]. Although acute and early-delayed side effects are thought to be transient, late-delayed damage is of the greatest concern, because the related cognitive impairments can be irreversible and progressive. Late-delayed complications may lead to focal deficits (radiation necrosis), and more importantly, to chronic diffuse encephalopathy, which may even result in dementia [21]. In severe cases of late-delayed radiation injury, imaging studies demonstrated diffuse leukoencephalopathy and progressive atrophy [22], while histopathology may show small vessel necrosis in the white matter and depletion of stem cells in the hippocampal area and subventricular zone. However, a larger subgroup of patients experience mild-to-moderate, though persistent cognitive impairment following radiation therapy [22].

Less invasive radiation techniques such as limited fraction dose, stereotactic radiotherapy instead of whole brain radiotherapy [23–25], and sparing the hippocampus during radiation may possibly result in less cognitive problems in patients with primary brain tumours and brain metastases [24]. In addition, proton radiation therapy, which reduces entrance dose and eliminates exit dose, is also expected to contribute to preservation of cognitive functioning by sparing normal tissue to a larger extent [26].

Chemotherapy

Compared with radiation therapy, the adverse effects of chemotherapy on cognitive functioning in brain tumour patients have gained less attention. Distinguishing cognitive deficits caused by chemotherapy is challenging in primary brain tumour patients, as most patients who underwent chemotherapy also underwent surgical resection and radiotherapy. However, late cognitive deficits have been demonstrated in glioma patients, years after radiation and Procarbazine, lomustine and vincristine chemotherapy [27]. In contrast, a systematic review in patients with primary central nervous system (CNS) lymphoma without previous surgery or radiotherapy suggested that cognition improved after induction chemotherapy compared with baseline, presumably also partly due to corticosteroids [28]. For patients with systemic cancer, even without CNS metastases, there is an emerging body of research demonstrating that

chemotherapeutic agents may cause cognitive deficits both on the short and long term [29]. Common cognitive domains affected by systemic chemotherapy include learning, memory, information processing speed and executive functioning [30], which has been described as the ‘chemo brain’ [22] or ‘cancer-related cognitive impairment’ (CRCI) [31]. With regard to long-term deficits in these patients, imaging studies have demonstrated structural changes in the brain, including volume reduction and altered white matter integrity [32], which are associated with long-term cognitive problems [29].

There has been little evidence on neuroprotective strategies to prevent chemotherapy-related cognitive impairment in brain tumour patients. Animal studies suggested the possibility of preserving cognitive decline by administration of preventing agents while undergoing chemotherapy [33–36], or exercise to assist in preventing cognitive dysfunction during or after chemotherapy by increasing neurogenesis [36–38], but there are no clinical data.

Targeted therapy and immunotherapy

Angiogenesis inhibitors, such as bevacizumab, have been successful in the treatment of various systemic cancers. However, in glioma patients, there is no evidence for overall survival benefit, nor for decline in (cognitive) functioning [39,40]. Results of trials investigating immunotherapy and their impact on cognitive functioning in patients with glioma [41], CNS lymphoma [42] and meningioma [43] are still to be expected.

Supportive treatment

Factors such as epilepsy, antiepileptic drugs (AEDs) and corticosteroids may affect cognition and behaviour as well. AEDs have a significant negative effect on attention and information processing speed [44], though second-generation AEDs such as levetiracetam and oxcarbazepine seem to minimize the negative impact of seizures on health-related quality of life (HRQoL) and cognition [45,46]. Perioperative corticosteroids improve cognition because of diminishing oedema, but there is otherwise evidence of detrimental (cognitive) effects of long-term corticosteroid use [6].

Interventions to preserve and improve cognitive functioning

Two approaches are often distinguished when looking at interventions that aim to improve cognitive functioning: pharmacological treatment and cognitive rehabilitation therapy (CRT).

Table 1. Pharmacological agents for the management of cognitive impairment in brain tumour patients

Ref.	Pharmacological agent	Study design	Population (n)	Timing	Relevant results
Boele <i>et al.</i> [51]	Modafinil	Double-blind, placebo controlled cross-over trial	Primary brain tumour (n = 37)	At baseline, after 6 weeks of modafinil/placebo and 6 weeks after opposite treatment	Modafinil did not exceed the effects of placebo
Brown <i>et al.</i> [47]	Memantine	Double-blind, placebo controlled RCT	Brain metastases (n = 508)	At baseline, and at 8, 16, 24 and 52 weeks after the start of WBRT	Memantine delayed time to cognitive decline and reduced the rate of decline in memory, executive function and processing speed
Butler <i>et al.</i> [52]	Methylphenidate HCl	Double-blind, placebo controlled RCT	Primary and metastatic brain tumours (n = 68)	At baseline, during and 4, 8 and 12 weeks after RT	No difference in MMSE score between the groups
Correa <i>et al.</i> [48]	Donepezil	Pilot	Primary brain tumour (n = 15)	After treatment with RT + CT or CT	A significant postbaseline improvement in attention, motor speed, visual memory
Gehring <i>et al.</i> [53]	Methylphenidate and modafinil	Open-label, randomized pilot trial	Primary brain tumour (n = 24)	At baseline and 4 weeks thereafter	Improvement in processing speed and executive functioning
Meyers <i>et al.</i> [54]	Methylphenidate	Open-label without control group	High-grade gliomas (n = 30)	At baseline, week 4, 8, 12 thereafter	Improvement in various tests, mood, subjective improvement in 20/26 patients after 4 weeks
Rapp <i>et al.</i> [50]	Donepezil	RCT	Primary and metastatic brain tumours (n = 198)	After partial RT or WHBT	Modest improvement in memory and motor speed
Page <i>et al.</i> [55]	Armodafinil	Double-blind, placebo-controlled RCT	Meningioma and glioma (n = 54)	At the end of RT and 4 weeks after RT	No difference between the treatment arms on any of the cognitive tests
Shaw <i>et al.</i> [49]	Donepezil	Open-label without control group	Primary brain tumours, one metastatic (n = 35)	6 months post RT	Improvement in various cognitive tests after 24 weeks

CT, chemotherapy; RCT, randomized controlled trial; RT, radiotherapy; WBRT, whole-brain radiation therapy.

Pharmacological treatment

Pharmacological agents that have been studied in brain tumour patients include amongst others donepezil, armodafinil and modafinil. Table 1 includes trials on pharmacological agents in brain tumour patients, including more than 10 patients [47–55]. In a large randomized controlled trial, the efficacy of memantine, a NMDA receptor antagonist also used in Alzheimer's disease, was found to delay cognitive decline in patients with brain metastases during whole-brain radiotherapy [47], although the trial lacked statistical significance due to patient loss. There has also been interest in donepezil, an

acetylcholinesterase inhibitor also used in patients with Alzheimer's disease, and results of three studies in brain tumour patients suggested that donepezil improved some aspects of cognitive functioning, including attention, memory and motor speed [48–50]. Other trials that aimed to investigate methylphenidate [56] and combined levothyroxine/liothyronine supplementation [57] were terminated because of accrual issues. Thus, although some studies reported small successes of pharmacological treatment, limitations including limited sample size, recruitment issues and the lack of a control group to account for practice effects hamper conclusions.

Cognitive rehabilitation

CRT refers to neuropsychological interventions aimed at preventing or treating cognitive deficits, and is based on the principles of neuroplasticity (i.e. learning) and designed to improve cognitive abilities through compensation or retraining. Retraining includes repeated practice of tasks that aim to strengthen impaired cognitive functions. Compensation training focuses on learning new strategies and alternative means to improve daily functioning and achieve goals, for example pacing, breaking down complex task into smaller steps and using mnemonics. The two are often studied in combination. CRT can be provided to individual patients or in groups, at home or in rehabilitation centres and with traditional face-to-face approaches as well as through computerized programs. In other patient populations, such as stroke patients and traumatic brain injury patients, CRT has shown to be effective and is often incorporated in the standard of care [58,59]. In brain tumour patients, a number of cognitive intervention

programmes have been developed (see Table 2) [60–67]. Although often hampered by methodological issues, for example not all studies included a control group to rule out effects of practice and natural recovery [60], most programmes reported some improvements in cognitive test-performance [61–65] and also with regard to subjective cognitive functioning [66]. Similar to the pharmaceutical trials, problems with accrual have been reported in several trials, especially when CRT was offered in the early disease stage. There is no consensus on the optimal timing for CRT. If the aim is to minimize or prevent cognitive problems due to adjuvant treatment and to make the most use of still intact skills, CRT should start as early as possible [6,64,68]. An early cognitive training programme for early post-surgery primary brain tumour patients showed that cognitive functioning already improved after a few weeks [64]. Conversely, as patients with newly diagnosed brain tumours often undergo multiple time-consuming and intensive treatment regimens that may also cause cognitive problems, offering

Table 2. Cognitive rehabilitation interventions targeting cognitive impairment in brain tumour patients

Ref.	Intervention outline	Study design	Population (n)	Timing	Effect on cognition
Gehring <i>et al.</i> [66]	Weekly individual supervised compensation training and computerized retraining	RCT	Low-grade and anaplastic gliomas (n = 140)	At least 6 months postsurgery	Improvement in short-term cognitive complaints, long-term cognitive functioning and mental fatigue
Hassler <i>et al.</i> [65]	Compensatory training. Weekly group training sessions for attention, verbal and memory skills	RCT	Grade III and IV glioma patients (n = 11)	Postsurgery, RT and CT	Modest improvement in memory and attention
Maschio <i>et al.</i> [63]	Cognitive rehabilitation training (RehabTR). Weekly sessions using computerized retraining	Pilot study	Patients with brain tumour related epilepsy (n = 16)	Postsurgery	Improvements in short-term verbal memory, episodic memory, fluency and long-term visuospatial memory improved immediately and at 6-month follow-up
Sacks-Zimmerman <i>et al.</i> [67]	CogMed: Computer-based cognitive remediation therapy (CRT)	Prospective pilot study	Low-grade glioma patients (n = 3)	Postsurgery	Results of only three patients have been published
Richard <i>et al.</i> [61]	Goal Management Training (GMT): Behavioural intervention combining mindfulness and strategy training	Pilot randomized trial (three groups)	Primary brain tumour patients (n = 26)	Postsurgery and >3 months post possible RT and/or CT	Executive functioning improved at 4-month follow-up
Van der Linden <i>et al.</i> [60]	ReMind: iPad-based psycho-education, strategy training and retraining	Feasibility study	Low-grade glioma and meningioma (n = 15)	Before surgery or other treatment	Intervention was found to be feasible, results of the RCT are expected
Yang <i>et al.</i> [62]	Virtual reality: Computer-based cognitive rehabilitation program	Trial comparing VR and computerized retraining with computerized retraining	Primary brain tumour patients (n = 38)	After surgery, and further treatment with RT/CT	Improvement in visual and auditory attention, short-term visual spatial memory
Zucchella <i>et al.</i> [64]	Compensation training and computerized training	RCT	Primary brain tumour patients [62]	Postsurgery	Improvement of visual attention and verbal memory

CT, chemotherapy; RCT, randomized controlled trial; RT, radiotherapy; VR, virtual reality.

rehabilitation after antitumour treatment may be fit best for patients with a longer prognosis both in terms of timing and in terms of effectiveness. At this time, patients also attempt to resume their normal daily activities and return to work and then start to experience cognitive problems. Consequently, flexible computer-based CRT programmes that can be adjusted to the specific patient needs and can be administered at home may especially be suitable.

Other interventions

Given the overlapping impact of both cognitive and emotional problems, intervention programmes that address outcomes as HRQoL, fatigue, mood or a combination of these may have indirect positive effects on cognitive functioning as well. Several uncontrolled studies that investigated psychological/psychosocial interventions [69,70] and yoga [71] in brain tumour patients showed to be feasible, reported some successes with regard to various HRQoL outcomes and were highly appreciated by patients. In addition, several exercise programmes in glioma patients similarly showed to be feasible, improved functional outcome [72,73] and suggested to have positive outcomes with respect to HRQoL outcomes [74,75,76]. In meningioma patients, uncontrolled studies on exercise programmes found decreased symptoms of depression and insomnia [77], and improved functional outcome [78].

CONCLUSION AND FUTURE OPPORTUNITIES

During the past years, cognitive functioning has gained greater awareness in the neurooncological community. More clinical trials have included cognitive performance as an endpoint, and methods to preserve and improve cognitive functioning have been explored. Important long-term data with regard to novel cognition-sparing treatment strategies such as awake surgery, hippocampal sparing and proton therapy are awaited.

The implementation of the so-called personalized or precision medicine into clinical practice allows optimization of therapy based on the patients' individual (genetic) profile, in order to maximize the therapeutic effect and minimize side effects. More specifically, patients vulnerable to cognitive decline might be identified at an early stage, which allows for personalized and timely intervention. Recent studies have highlighted the importance of molecular markers in neurooncology, and their link with cognitive functioning. Glioma patients with isocitrate dehydrogenase 1 (*IDH1*)

mutant gene may exhibit less cognitive impairment than their wild-type counterparts [5,79]. With regard to germline genetic characteristics, studies have suggested that the APOE $\epsilon 4$ allele, a known risk factor for Alzheimer's disease [80], single nucleotide polymorphisms in the catechol-O-methyl transferase (*COMT*), brain-derived neurotrophic factor (*BDNF*) and dystrobrevin-binding protein one (*DTNBP1*) genes are associated with (impaired) cognitive functioning in brain tumour patients as well [81]. The evidence so far is, however, insufficient to implement formally testing of these genetic polymorphisms in clinical practice.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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