Neurocognitive Dysfunction in Brain Tumor Patients following Radiation Therapy: A Review of Biological Hypotheses, Current Treatment Outcomes, and Novel Therapeutic Strategies

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ABSTRACT

Given the difficulty of surgical resection of brain neoplasms located adjacent to vital structures of the brain as well as the challenges posed by the blood-brain-barrier for the efficacy of chemotherapeutic agents, whole brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS) are often turned to for patients with brain metastases as well as primary brain neoplasms. Though radiation therapy may be successful in local control of these tumors, many patients experience treatment-related neurocognitive issues, later in life. In this review, we examine cognitive dysfunction in brain tumor patients following radiation therapy, with an emphasis on the pediatric population. Articles were found using NCBI's PubMed and relevant search terms. We first review the hypotheses regarding the biological mechanisms underlying these neurologic manifestations such as neuroinflammation, extracellular matrix disruption, and inhibition of angiogenesis. Cognitive defects and related effects on health-related quality of life in brain tumor patients treated with radiotherapy are then discussed. We also address novel treatment strategies aimed at minimizing neurocognitive delays such as hippocampal-sparing radiotherapy planning, intensive chemotherapy regimens, and the growing field of proton therapy. Possible molecular therapeutic targets are discussed as well as preclinical studies examining human embryonic and neural stem cell transplantations. Finally, we examine the role of aerobic exercise, multidisciplinary rehabilitation, and other interventions that may help to curb the negative effects of radiotherapy on cognitive development and function.

KEYWORDS: brain tumor, WBRT, SRS, IMRT, cognitive decline, radiotherapy, pediatrics, memory impairment, hippocampus, neural stem cells

Introduction

Approximately 210,000 cases of primary and metastatic brain tumors are estimated to be diagnosed each year in the United States. Notably, primary brain tumors are the most common type of solid tumors in children (4,600 primary brain neoplasms are estimated to be diagnosed this year) and are the leading cause of cancer-related deaths in children under the age of 20. (1)

Generally, surgery is the first method of treatment for brain tumor patients. However, tumors deeply-seated within the brain or located near critical structures that control important functions are difficult to remove due to possible iatrogenic neurologic damage. (2) Also, chemotherapy may be utilized for treatment, though the clinical applications of chemotherapy may be limited as a result of both significant side effects and insufficient delivery due to the blood-brain-barrier. (3)

Thus, radiation therapy is often turned to for the treatment of both primary and metastatic brain neoplasms. (4,5) Roughly 200,000 brain tumor patients in the US are treated with some form of radiation each year. (6) Specifically for brain cancers, stereotactic radiosurgery (SRS) and whole brain radiation therapy (WBRT) are often used. SRS delivers a high dose of radiation in one session, whereas WBRT administers ionizing radiation to the entire brain. However, the use of radiation therapy for the treatment of brain tumors is limited by the risk of radiation-induced damage and subsequent functional deficits. This review aims to summarize the neurocognitive effects following radiation therapy in patients with brain tumors with an emphasis on the pediatric population, novel methods of treatment aimed at minimizing cognitive dysfunction, as well as interventions that may be attempted should cognitive delays present.

Methods

We utilized NCBI's PubMed to identify relevant articles using combinations of search terms such as: brain tumor, cognition, cognitive deficits, radiation therapy, proton therapy, stereotactic radiosurgery, whole brain radiation therapy, intervention, exercise, and pediatric. A total of 94 papers were chosen for inclusion in this review.

Hypotheses Explaining Radiation-Induced Cognitive Dysfunction

There are many hypotheses that aim to explain the mechanisms underlying cognitive declines following radiation therapy. Most intuitive is the assumption that direct damage and subsequent death of parenchymal cells (oligodendrocytes, neurons, astrocytes, and microglia) contributes to cognitive decline. Damage to oligodendrocytes, which are responsible for myelination of the CNS, has been thought to play a role. Though studies examining rats undergoing fractionated WBRT did find a decrease in the number of oligodendrocytes, no change in the number of myelinated axons or the thickness of myelin sheaths were noted 12 months following treatment. (7,8) Neurons in irradiated rodent brains are found to have altered expression of the immediate-early gene activity-regulated cytoskeleton-associated protein, N-methyl-D-aspartate (NMDA) receptors, glutaminergic transmission, and hippocampal long-term potentiation, all of which are essential to synaptic plasticity and thus cognition. (9) The response of both astrocytes and

microglia to radiation is thought to contribute to changes in the cellular microenvironment which will be discussed below.

With regards to cognitive decline, radiation damage of the temporal lobe (specifically the hippocampus) likely plays a role. Both memory and learning are influenced by the proliferation of neural stem cells in the hippocampal granule cell layer, which allows for neuron renewal and synapse restructuring. In mature rats, the proliferative potential of this layer has been observed to be greatly reduced following radiation at doses lower than those typically required to injure dysplastic glial cells. (10) However, *in vivo* studies have demonstrated that older rats experienced cognitive declines following WBRT without impaired hippocampal neurogenesis or demyelination seen in younger rats, suggesting that other mechanisms in non-hippocampal regions are likely to also contribute to neurocognitive issues. (9)

As such, much of the literature has addressed disruption of the integrity of the blood-brain-barrier (BBB) following radiotherapy as a possible explanation for impaired cognition. Increased inflammation following radiation therapy has been implicated. The up regulation of cytokines, which are thought to be expressed by microglia following radiation, and pro-inflammatory transcription factors in the brain are thought to contribute to endothelial cell dysfunction and consequent disruption of the BBB. (11,12) The disruption of the extracellular matrix of the BBB may also be involved as WBRT has been previously documented as altering the expression of matrix metalloproteinases (MMP), leading to collagen IV degradation in both *in vitro* and *in vivo* studies. (13) Also, radiation inhibits physiologic angiogenesis in the brain, as evidenced by increased vascular permeability and impaired endothelial cell proliferation in irradiated tissues. (14) Studies have demonstrated that brain samples of rats exhibiting cognitive decline following fractionated WBRT had decreases in vessel density, cerebral blood flow, the number of endothelial cells, and angiogenic factors such as vascular endothelial growth factor (VEGF). (15,16)

In addition to disruption of the BBB, the changes mentioned above may also play a role in stem cell lineage. Notably, a study by Monje et al. found that the changes outlined above were observed in the neural microenvironment of radiation-treated mice and resulted in hippocampal progenitor cells differentiating into glial rather than neural cells.[17] In spite of these findings, there is still a poor understanding of the cellular or molecular mechanisms leading to cognitive dysfunction following radiotherapy. Elucidation of the hypotheses above has led to studies exploring them as potential therapeutic targets that will be discussed shortly.

Cognitive Dysfunction and Related Effects on Quality of Life

Retrospective studies estimate that neurologic handicaps and impaired cognition are observed in 65% and 85%, respectively, of patients who were under 3 years of age when they underwent radiotherapy. (18) Many studies have aimed at particular cognitive defects to specific tumor type and location. For example, in children previously treated for pilocytic astrocytoma with normal intelligence prior to diagnosis, all children were noted to have deficits with sustained speech and speed of speech; radiotherapy in these patients further contributed to lower cognitive functioning. Notably, 60% of patients in this study had difficulty with academics 3 years after treatment. (19) Pediatric patients treated for medulloblastoma were not noted to have visual

memory deficits as have been noted in other studies, though attention deficits were quite prominent and were correlated with impaired math and reading performance. (20) In comparing intellectual outcomes of children diagnosed with either ependymomas or medulloblastomas and subsequently treated with WBRT, only 10% of medulloblastoma patients had an IQ above 90 after 10 years as compared to 60% of ependymoma patients and was hypothesized to be due to cerebral hemisphere radiation (given that this was the only significant difference between the two groups). (21) Notably, declines in both IQ as well as verbal comprehension seems to be dose-dependent, as children with posterior fossa tumors having received 35 Gy of radiation had lower average scores in both categories as compared to those receiving 0 and 25 Gy. (22) Similar studies have found that compared to age-matched controls, brain tumor patients treated with radiotherapy have significantly lower verbal IQ, processing speed, visual and verbal immediate memory, learning deficits, and selective attention. (23-26) Interestingly, children with brain tumors have also been demonstrated to have significantly poorer working and verbal memory as well as attention deficits even prior to treatment, suggesting that interventions are necessary to mitigate the effects of both the disease process as well as radiotherapy on cognition. (27)

Also of note is the strong correlation between cognitive dysfunction stemming from radiotherapy and a lower quality of life. (28,29) Adults that had been previously diagnosed and treated for brain tumors in childhood have been found to have a 10%-23% lower likelihood of attaining a basic education, and this effect was even more marked for female survivors at a 45% lower probability compared to age-matched controls. A younger age of diagnosis was also significantly associated with a lower likelihood of completing basic education. (30,31) Also, patients that had been previously diagnosed with CNS neoplasms and treated with WBRT had a roughly 10% lower likelihood of ever being married in their lifetime (this effect is even more pronounced at an estimated 29-38% lower likelihood for male CNS survivors older than 30 years of age). (32) Similar studies have found that CNS neoplasms survivors often have lower rates of educational attainment, employment, and marriage and consequently a significantly lower quality of life. (33) Survivors' outlook on life is also impaired, as brain tumor survivors that underwent WBRT exhibit low present and expected future life satisfaction as well as higher rates of psychological distress as compared to survivors of other solid tumors.(34) The impaired psychosocial development of brain tumor survivors is also apparent as patients have been shown to be 50% more likely to experience depression or anxiety and 70% more likely to exhibit antisocial behaviors, with cranial irradiation being noted as a specific risk factor for both. (35)

Alternative Radiotherapy Treatment Planning and the Promise of Proton Therapy

Clinical studies have demonstrated that patients receiving higher doses of radiation (and subsequently larger volumes of the brain being treated) have worse prognosis regarding cognitive outcomes. (36,37) Dose-dependent effects in pediatric brain tumor patients have been demonstrated with regard to motor skills/dexterity (hippocampus and temporal lobe), verbal learning (cerebrum), and visual perception (temporal lobe). Though declines relative to age-matched controls were noted in a variety of other areas, no association was found between the neurologic structure radiated and the cognitive defect experienced for others tested (such as visuospatial working memory or vocabulary). (38)

As such, many studies have examined alternative treatment strategies, such as utilizing SRS alone as opposed to WBRT and SRS to minimize the exposure of the brain to radiation. Patients with brain metastases treated with SRS alone experienced declines in Mini Mental Status Examination (MMSE) scores 9 months earlier than those assigned to WBRT and SRS, which suggests that control of tumor growth should be the primary concern for maintaining cognitive function. (39) However, other studies have found that patients treated with SRS alone had a lower incidence of experiencing decline in learning and memory function (24%) 4 months after treatment than those with WBRT and SRS (52%); consequently, the authors recommended initial SRS with close clinical monitoring before moving to use of WBRT. (40) Similarly, recent findings from a phase III randomized clinical trial of 213 patients with brain metastases (median follow-up: 7.3 months) found a significantly greater incidence of cognitive decline in patients treated with WBRT + SRS (91.7%) as compared to those receiving SRS alone (63.5%), with lower immediate recall, memory, verbal fluency and subsequently quality of life. (41)

The advent of intensity-modulated radiotherapy (IMRT) has also allowed for treatment planning and contouring to avoid radiating hippocampal neural stem cells with WBRT. Previous retrospective studies have demonstrated that WBRT with hippocampal sparing via IMRT reduced doses delivered on a per-fraction basis to the hippocampus by 87% (0.49 Gy) and 81% (0.73 Gy) via helical tomotherapy and linear accelerator-based treatments, respectively, with median doses of 5.5 Gy and 7.8 Gy delivered via the same methodologies. (42) Similar studies adopting this approach for adult patients with brain metastases have reported significantly lower rates of memory loss 4 months post-treatment and with no treatment-related decline in quality of life.(43) A prospective phase II trial utilizing hippocampal sparing WBRT reported no significant declines in immediate verbal and nonverbal, executive functioning, or psychomotor speed following treatment, with delayed memory recall being the only neurocognitive function significantly affected. (44)

Another approach is utilizing a lower dose of radiation with adjuvant chemotherapy. Early findings indicate that such an approach for lower to medium risk brain neoplasms can be curative and may be associated with declines in verbal, nonverbal, and full-scale IQ scores but less than those observed with higher doses of radiation alone.(45-48) Other studies examining the role of postoperative chemotherapy to allow for a delay in radiotherapy for a variety of brain neoplasms had similar progression-free survival as compared to standard treatment plans including radiation with minimal observed cognitive dysfunction. (49,50)

Most prominent among these trials are the “Head Start” trials, which attempt to use chemotherapy in place of radiotherapy for malignant brain neoplasms. Patients are placed on multiple cycles of chemotherapy for 5 months to reduce the size of the tumor and are then given a single large myeloablatic dose of chemotherapy followed by rescue with autologous hematopoietic stem cells. If no disease is seen on MRI following treatment, then radiotherapy is not used. Studies examining the effectiveness of this approach for supratentorial primitive neuroectodermal tumors (sPNETs), which typically have a poor prognosis, found a survival advantage as well as a significant decline in patients requiring radiation for local control. (51) Similarly, a majority of patients under the age of 3 years old with non-metastatic medulloblastoma treated under this regimen did not require radiation and consequently had both intelligence and quality of life scores within normal ranges, though there was a high toxicity-

related mortality rate (4/21). (52) Venkatramani et al. also reported the ability to defer radiation for supretentorial ependymomas, though for infratentorial ependymomas such an approach appears to be ineffective. (53) However, studies have previously demonstrated that 40% of cancer survivors of other sites experienced significant cognitive dysfunction after high dose chemotherapy followed by hematopoietic cell transplantation rescue 1 and 5 years post-treatment; as such, monitoring patients on similar treatment protocols over a long time frame is needed. (54,55)

Another novel treatment method that holds promise is proton-beam radiotherapy. Proton therapy is believed to result in greater sparing of healthy tissue and better outcomes due to narrower beams that may allow for a more-targeted delivery of radiation as well as a smaller penetration of tissue beyond the tumor. (56) Given the new nature of this technology, relatively few clinical studies have been completed examining the theoretical advantages of proton therapy for brain neoplasms. Studies that have been done to estimate the clinical benefit of proton therapy based on simulated proton therapy for pediatric medulloblastoma cases found that the mean dose of radiation to the hippocampus could be limited to almost half that of IMRT and consequently lower the risk of cognitive issues later in life.(57) Notably, initial studies have demonstrated that the quality of life of 142 pediatric brain tumor patients 3 years after proton therapy improved to levels similar to healthy age-matched peers, though a comparison was not done comparing such patients to those treated with conventional radiotherapy and thus merits further study.(58)

Results of Potential Therapeutic Targets and Stem Cell Therapies in Preclinical Trials

Given the various radiation-induced mechanisms previously covered that are hypothesized to interfere with the integrity of the BBB and subsequently lead to cognitive dysfunction, a variety of molecular targets implicated in these mechanisms have been studied. For example, known anti-inflammatory agents such as NSAIDs, peroxisome proliferator-activated receptors (PPARδ) agonists, atorvastatin, and ramipril have been tested following WBRT in mice and rats to reduce microglial activation and subsequent inhibition of hippocampal neurogenesis. However, preclinical studies with the goal of minimizing neuroinflammation have yielded mixed results in preventing cognitive declines.(59-64) Though the possible role that MMPs may have in ECM degradation were previously discussed, presently no work has been done to examine whether this may provide benefit in pre-clinical irradiated brain studies. With regards to angiogenesis, systemic hypoxia following WBRT restored cerebrovascular density and reversed learning and memory impairments. As such, radio-protective drugs have been evaluated in preclinical trials and have been shown to be effective at protection of brain vasculature via preventing loss of endothelial cells and also lowering the proportion of rats brains demonstrating white matter necrosis.(15,65,66) However, studies utilizing any of these approaches have not been attempted in the clinic.

Another field of study that have begun to draw interest are stem cell therapies, given prior studies in mouse models of Alzheimer's disease that have demonstrated improved cognitive functioning following neural stem cell transplantation. A variety of mechanisms such as restoration of brain-derived neutrophic factor (BDNF) levels (involved in neuronal

differentiation, neurogenesis, and synaptic plasticity necessary for long-term memory) as well as attenuation of inflammation via reduced cytokine expression has been proposed. (67-73)

With regards to brain tumors and radiotherapy, it is believed that transplantation of stem cells can alleviate radiation-induced cognitive dysfunction by increasing the number of neurons via differentiation. Stem cells may also alter the neural microenvironment in the hippocampus to promote synaptic plasticity necessary for memory formation and information processing. Preclinical studies have found that athymic rats that had been both irradiated and had intrahippocampal transplantation of human neural stem cells (hNSCs) expressed activity-regulated cytoskeleton-associated protein (Arc, an established marker for detecting active neurons) at similar levels to control levels. Rats undergoing transplantation were found to have consequently improved hippocampal spatial memory and a significantly lower decline in cognitive dysfunction. (74,75) Intrahippocampal nHSCs transplantation has also been demonstrated to provide cognitive benefit lasting 8 months post-radiation (which was not observed following human embryonic stem cell transplantation) and may also attenuate radiation-induced neuroinflammation. (76,77) Notably, transplantations were found to result in the greatest cognitive outcomes if given 4 weeks following radiation as opposed to 2 days or 1 week after radiotherapy, with nearly 40% of surviving stem cells following a neuronal lineage in the CA1 and CA3 subfields of the hippocampus.(77) Also, human embryonic stem cell-derived oligodendrocytes in irradiated rats have been found to successfully migrate throughout major white matter tracts to participate in functional repair, which resulted in complete recovery of cognitive function to baseline levels. Motor deficits were also found to improve following transplantation of stem cell-derived oligodendrocytes into the cerebellum. (78) However, no significant clinical studies have been documented to our knowledge to date assessing the effectiveness of neural or embryonic stem cell intrahippocampal transplantations in either the pediatric or adult brain tumor populations.

Aerobic Exercise, Multidisciplinary Rehabilitation, and Other Interventions

In addition to the treatment options discussed earlier, many other interventions such as cardiovascular exercise may be helpful in improving cognitive functioning. Preclinical models have aimed at better elucidating whether exercise does attenuate radiation-induced cognitive dysfunction and the molecular mechanisms by which it may do so. Studies in mice have demonstrated that voluntary running starting 1 month following WBRT prevented marked declines in spacial memory, with possible mechanisms including partial neuron regeneration in the dentate gyrus and increased hippocampal expression of VEGF and IGF-1.(79) Similar studies in irradiated rats have demonstrated that 3 weeks of forced running attenuated radiation-induced declines in hippocampal neurons and expression of BDNF and was correlated with improved behavioral performance.(80) Declines in BDNF have been implicated in playing a large role in radiation-induced cognitive dysfunction, as other studies in rats subject to 30 Gy of WBRT have demonstrated significant declines in BDNF gene transcription via an epigenetic mechanism. Notably, a decrease in histone-deacetylase 1 (HDAC1) - dependent H3 acetylation was noted at BDNF gene promoters, which was reversed following administration of an HDAC inhibitor with consequent improved hippocampal neurogenesis.(81) As discussed earlier, BDNF plays a key role in memory formation via promotion of neuronal differentiation and neurogenesis, and attenuation of declines of BDNF in Alzheimer's disease models and other

neurocognitive disorders have been associated with improved learning and memory in preclinical models.

Surprisingly, there have been a limited number of studies examining the effectiveness of exercise and other cognitive rehabilitations for both pediatric and adult brain tumor populations. Studies utilizing fMRIs for pediatric posterior fossa cancer survivors have demonstrated that declines in executive function, notably working memory, can be improved via cardiorespiratory exercise. (82) However, levels of exercise among pediatric brain tumor survivors are reported to be greater than one standard deviation below age-matched peers, and as such interventions may be necessary to promote activity among such patients to realize potential cognitive benefits from exercise. (83-85) Furthermore, cognitive rehabilitation in glioma patients has been demonstrated to lead to improved verbal memory and attention with less mental fatigue 6 months after intervention as compared to control subjects.(86) Four-week conventional rehabilitation programs (including physical and neuromuscular electrical stimulation as well as aerobic exercise) for brain tumor patients have noted similar success with significant rises in MMSE scores as well as visual attention, selective, and auditory attention.(87) Similarly, Gehring et al. reported significantly higher attention and visual memory scores among 140 adult survivors of low-grade and anaplastic astrocytoma patients 6-months following cognitive rehabilitation with less mental fatigue reported by patients undergoing rehabilitation. (88) Also, a cohort of 11 adult patients diagnosed with higher-grade gliomas (i.e. glioblastoma multiforme) with Karnofsky performance scores of 80% or higher participating in weekly neurocognitive rehabilitation sessions for 3 months exhibited higher mean attention, verbal, and memory scores, though only verbal scores exhibited significant increases from baseline.(89) A larger controlled clinical trial of over 100 adult glioma survivors participating in a multidisciplinary rehabilitation program found significant increases in self-care, locomotion, mobility, communication, and psychosocial scores at 3 month follow-up among the patients participating in the program compared to control, though only gains in cognition and communication were noted at 6 month follow-up.(90)

However, it is important to note that systemic reviews of multidisciplinary rehabilitation in brain tumor patients have found a “low-level” quality of evidence supporting rehabilitation for long-term cognitive improvement. Also, no studies thus far have clearly demonstrated significant improvements in health-related quality of life following such interventions. As such, studies examining the effect of exercise and cognitive rehabilitation on longer-term cognitive performance are warranted to better define the optimal setting, type, intensity, and duration of neurocognitive interventions, especially given the paucity of literature in the pediatric brain tumor population. (91)

A variety of other alternative interventions have been attempted to prevent cognitive declines. Notably, Meyers et al. found that half of brain tumor patients who took the CNS stimulant methylphenidate before and during radiotherapy experienced cognitive function increases despite neurologic injury demonstrated on MRI. (92) However, more recent studies have found prophylactic methylphenidate does not result in a significant rise in MMSE scores or increases in quality of life. (93) Memantine, an NMDA antagonist commonly used in Alzheimer’s, and Ginkgo biloba (also used in Alzheimer’s to disease to improve cognitive deterioration) has been found to significantly prolong the time until onset of declining executive function and processing

speed for patients with brain metastases treated with WBRT of up to 24 weeks with some improvements in quality of life. (94,95)

Conclusion

While great advances have been made in the treatment of cancer, cognitive disabilities may persist in patients (particularly children) with brain tumors for which radiotherapy remains a mainstay of treatment. Current research efforts aim to reduce neurotoxicity and associated cognitive dysfunction of treatment by alternative treatment planning such as larger doses of chemotherapy or avoiding vital structures such as the hippocampus during radiation planning via IMRT. It is a worthwhile endeavor to further elucidate the mechanisms by which radiation impairs cognitive abilities to allow for cellular and molecular pathways to be targeted in the future. Other innovative treatment modalities, namely proton therapy and intrahippocampal stem cell transplantations, may also have a large role to play in times to come given promising early findings with the objective of improving quality of life for cancer survivors.

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