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Chapter 10

Neurocognitive Effects of Primary Brain Tumors

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Additional information is available at the end of the chapter

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Abstract

Cognitive impairment, a common finding with the brain tumors, may result from the tumor itself or the treatment used: surgery, chemotherapy, or radiotherapy. Surgery for brain tumors improves the cognitive function due to reduction of compression as in case of removal of noninvasive tumors. Stability of cognitive function also was observed after tumor resection, such as tumors of third ventricle. Postoperative cognitive worsening was observed. Postoperative worsening of executive functions may correlate to volume of the operated area. Cognitive deficits may follow radiotherapy by several months to many years. These deficits may be due to vascular injury, local radionecrosis, and cerebral atrophy. This usually involves multiple domains, including memory, attention, executive function, and intelligence. The irradiated volume of brain tissue has great impact on cognition. Intensity-modulated radiotherapy (IMRT) and proton beam therapy result in greater sparing of healthy brain tissue and allow for a more-targeted delivery of radiation and smaller penetration of tissue beyond the tumor consequently reduce the risk of cognitive deficit after radiotherapy. Chemotherapy treatment in brain tumor seems to have a role in cognitive dysfunction deficits. The toxicity of chemotherapy increased when was given during or after radiotherapy. Chemotherapeutic agents, such as BCNU, CDDP, cytosine arabinoside, and intrathecal or intravenous methotrexate, have toxic effect to the CNS. Glioblastoma patients undergoing radiotherapy with concomitant and adjuvant temozolomide treatment do not develop cognitive deterioration. Patients with brain tumors face the challenge of cognitive impairment due to the tumor itself or treatments. Cognitive deficits in processing speed, memory, attention, and executive functions interfere with patients' daily life activities. Cognitive rehabilitation program has proven to be effective in patients with primary brain tumors. Cognitive impairments have a large impact on self-care, social and professional functioning, and consequently on quality of life. Preventing these late effects is a challenge for the medical team, psychologists, and rehabilitation specialists. Prevention depends in part on being able to predict those at greatest risk. Advances in neurosurgery, chemotherapy, and radiotherapy techniques are helping to a great extent, but may not be totally successful at preventing these late effects.

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Keywords: Cognition, cognitive deficits, brain tumor, cognitive rehabilitation, brain tumor treatment

1. Introduction

1.1. Background

The term intellect designates the totality of the mental or cognitive operations that comprise human thought, and the higher cortical functions that make up the human mind. Memory is a specific cognitive function: the storage and retrieval of information. Other "higher" functions, such as language, calculations, spatial topography and reasoning, music, and creativity, all represent the functions of specific brain systems [1].

Cognitive functioning of brain tumor patients is an increasingly important outcome measure, because cognitive impairments can have a large impact on self-care, social and professional functioning, and consequently on quality of life (QOL) [2]. Patients with brain tumors often experience cognitive dysfunction associated with the disease itself and its treatment, as well, including surgery, radiotherapy (RT), and chemotherapy. Cognitive dysfunction has been recognized as the most frequent complication among long-term survivors. Despite the many advances made in the treatment modalities and surgical techniques, primary malignant brain cancer is a devastating illness, characterized by poor survival rates and significant morbidity as the disease progresses [3]. For many patients, cognitive changes are part of the disease process, but the pattern of impairment can vary markedly in different patients.

Resection of brain tumors may result in improvement of cognitive functions. Teixidor et al. [4] reported long-term improvement of verbal memory, after a transient immediate postoperative worsening, following frontal premotor and anterior temporal area resection, usually after a transient immediate postoperative worsening. Cognitive improvement has also been observed after surgical resection of high-grade gliomas [5], and in some studies stable, cognitive performance was observed after brain tumor resection, for instance, patients with tumors of the third ventricle [6].

Specific cognitive domain deficits after brain tumor removal were observed in some studies. A study conducted by Goldstein et al. [7] reported minimal deterioration in attention after right parenchymal frontal or precentral tumors resection. Another study [8] concluded that right rather than left prefrontal cortex resection was associated with, stroop performance test, selective attentional decline.

Radiation-induced cognitive impairment in some series is reported to occur in up to 50–90% of adult patients with brain tumor who survive >6 months after fractionated partial or whole-brain irradiation [9]. Moreover, because patients with brain tumor are surviving longer because of improved radiation therapy techniques and systemic therapies [10], the patient population experiencing these significant late effects is growing rapidly. Radiation-induced

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cognitive impairment is marked by decreased verbal memory, spatial memory, attention, and novel problem-solving ability [11]. Modern radiation therapy techniques have resulted in decreased acute and early delayed brain injury as well as late demyelination and white matter necrosis with less cognitive functional deficits, including progressive memory impairments, attention, and executive function that finally led to less impact on QOL of most survivors [12].

Neurocognitive sequelae of chemotherapy are less well documented than radiation effects [13]. Chemotherapy-related neurotoxicity to the central nervous system may be increased by intra-arterial administration, especially in combination with osmotic blood–brain barrier disruption, meant to increase the local concentration of chemotherapy in the brain [14]. Neurotoxicity may also be increased by chemotherapy given after, or even during, RT [15]. Primary central nervous system lymphoma is chemoresponsive, such as anaplastic oligodendroglioma (AO) and oligoastrocytoma (OA) tumors, chemotherapeutic agents are often ineffective due to limited ability to cross the BBB. Use of radiation therapy is often associated with significant neurotoxicity [16].

Advances in neurosurgery, chemotherapy, and RT are helping to a great extent in preventing cognitive deficit. Prevention depends in part on being able to predict the risky factors [17].

1.2. Objectives

The chapter examines:

– Cognition and its evaluation

– Brain tumors and cognition

– Brain tumor surgery and cognition

– Effect of adjuvant therapies (radio/chemotherapy) on cognition

– Prevention or reduction of cognitive deficits during the treatment of brain tumors

– Follow-up care and cognitive rehabilitation

2. Cognition and its evaluation

2.1. Cognition

Higher brain function may be subclassified into: (a) distributed functions, which do not localize to a particular brain region but instead require the concerted action of multiple parts on both sides of the brain, for example, attention and concentration, memory, higher-order executive function, social conduct, and personality; (b) localized functions, which are dependent on the normal structure and function of a particular part of one cerebral hemisphere, for example, language and praxis in dominant hemisphere the nondominant hemisphere hemisphere is largely, though not exclusively, responsible for visuospatial skills [18]. Cognitive impair-

ment without crossing the threshold for dementia has been termed "mild cognitive impairment" (MCI) [19]. The MCI syndrome, as an expression of an incipient neurodegenerative disorder that may lead to dementia, is extremely heterogeneous and may coexist with systemic, neurologic, or psychiatric disorders that can cause cognitive deficits [20]. The criteria for MCI encompassed all possible cognitive manifestations of the syndrome and four subgroups have been proposed: deficits only in memory functions; memory deficits plus deficits in another cognitive domain; deficits in a single nonmemory domain; and deficits in more than one nonmemory domain [21].

2.2. Evaluation of cognitive functions

2.2.1. The Montreal cognitive assessment (MoCA)

MOCA was used as test of cognition, measure cognitive function, its cognitive domains: visuospatial/ executive function; naming; memory; language; abstraction; and attention. MoCA is scored out of 30 points. A normal score is 26 or above [22].

2.2.2. Mini Mental State Examination (MMSE)

MMSE is used for global cognitive functioning measurement [23].

2.2.3. Other cognitive domain-specific areas neuropsychological tests: focus on domain-specific areas of cognition:

(1) Hayling Sentence Completion Test, Word Span and Corsi's Test to test working memory [24], verbal and visual memory—Recognition Memory Tests, Words, and Topography [25]. (2) Rey Auditory Verbal Learning Test—RAVLT and logical memory to assess episodic memory, immediate and delayed recall [26], abstract reasoning: nonverbal—Raven's advanced progressive matrices [27, 28], verbal—Proverb Interpretation Test [29]. (3) Attention—Digit Span sub-test from the Wechsler Adult Intelligence Scale-III [30], Elevator Counting with Distraction from the Test of Everyday Attention [31], Trail Making test, part A and part B to test simple speed processing and complex attention, respectively, [32]. (4) Visual perception—Incomplete Letters Test from the Visual Object and Space Perception Battery [33], Rey–Osterrieth Complex Figure recall, to test visuospatial long-term memory, Rey–Osterrieth Complex Figure, copy to test visuoconstructional abilities [34]. (5) Phonemic and semantic fluency [35], language—Graded Naming Test [36], Word Comprehension—Synonyms Test [37]. (6) Executive functions—phonemic word fluency [38]. (7) Frontal Assessment Battery—FAB to assess frontal functionality [39].

For neuropsychological measures, age-, gender-, and education-corrected scores and equivalent scores should be calculated from the raw scores according to normative standards.

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3. Brain tumors and cognition

Cognitive impairment, a common finding with the brain tumors, may result from the tumor itself or the treatment used surgery, chemotherapy, or RT.

3.1. Cognitive impairment due to tumor

More than 90% of patients with brain tumors showed impairments in the cognition at least in one area. The reported impairments of executive function were observed in 78%, while impairments of memory and attention were presented in more than 60% of patients [40].

Zucchella et al. [41] reported cognitive impairment in 54.4% of brain tumor patients, (53.75%) presented with multidomain impairment, while (46.25%) of the patients revealed cognitive deficits 16.25% of them limited to language, 13.75% to memory, 8.75% to attention, 6.25% to logical-executive functions, and 1.25% to visuospatial abilities.

Talacchi et al. [5] reported cognitive impairment in glioma patients 79% of patients have cognitive deficit in at least one test, (24, 3, 31, and 21% in one, two, three, four, or more tests, respectively, and this was correlated with edema, tumor grade, and size. Verbal memory, visuospatial memory, and word fluency were the most frequently affected functions.

3.2. Pathophysiology

Cognitive impairment associated with brain tumors can be induced by direct or indirect compression of normal brain tissue by reactive edema [42].

Tumor tissue can also invade directly into functional brain regions or indirectly disconnect the structures which can further contribute to cognitive deficits [43].

The mechanisms via which brain tumors affect brain function varied, highly malignant tumors grow quickly so they tend to infiltrate and displace the normal brain tissue, while the lower grade tumors tend to grow and infiltrate slowly disrupting brain function causing cognition deficit.

Tumors of ventricular system causes increase in intracranial pressure and hence affect the cognitive function; also large ventricular tumors affect the cognition directly through its compression effect. Functioning brain tumors which secrete hormones may have role in cognitive deficit through endocrine disturbance [44].

The main pathophysiology causes of cognitive dysfunction are not well known, different hypotheses were placed; progression of brain tumors seems to be the predominant one [45], also late treatment effects, for example, surgery, RT, chemotherapy, uses of antiepileptic drugs or corticosteroids), the psychological distress also may contribute in cognitive dysfunction [46].

The cognitive function disturbance in brain tumors may be due to combination of these factors.

4. Brain tumor surgery and cognition

In brain tumors, the first treatment modality is surgery. The aim was to balance the neurological outcomes (minimize the neurological deficits) and oncological outcome [2].

- Does brain surgery improve cognitive deficit?

Surgery for brain tumors improves the cognitive function due to the reduction of compression as after removal of noninvasive tumors, such as meningiomas, improvement of attentional function occur [42]. Patients with high-grade glioma have worse cognitive dysfunction than patients with low-grade glioma (LGG) [47]. The worse cognitive deficits in patients with high-grade gliomas have been attributed to higher incidence of intracranial hypertension, the rapid growth, and the infiltrative nature.

Sweet et al. [48] reported that the localization is associated with cognitive effects. Tumors of the pineal region associated with memory impairment, visuospatial function, attention, visuomotor function, problem-solving, and affective disorders.

Medial temporal lobe epilepsy caused by tumor is associated with cognitive deficit (long-term memory dysfunction, difficulties in learning, attention, naming, visuospatial abilities, executive functions, and intelligence) [49].

Less extensive surgery of the mesiotemporal structures correlates with better memory outcome than in the extensive temporal lobe surgery [50].

Verbal memory decline was observed in dominant temporal lobe resection [51], while visuospatial memory decline associated with nondominant temporal lobe resection [52].

Cognitive improvement has been observed after tumor resection, and improvement of verbal memory has been observed after LGG resections in frontal premotor and anterior temporal areas [4], usually after a transient postoperative worsening. This improvement was related to tumor lateralization [53].

Some studies reported postoperative cognitive worsening in (38%) of patients versus 24% rate of improved patients. Worsening associated with executive functions while improvement was observed with memory function. This worsening may correlate to volume of the operated area (tumor size) rather than the location. The postoperative improvement of memory function, the most frequent preoperative cognitive deficit, occurs due to release of the mass effect [54].

Teixidor et al. [4] reported immediate postoperative worsening for working memory in 96% of cases, and Giovagnoli et al. [55] reported that postoperative scores for cognitive tests were not significantly lower than the preoperative.

Talacchi et al. [5] found unexpected low incidence of additional deficits (38%) immediate postoperative and a considerable rate of early improvement (24%), and this correlated with tumor size and histology. This study reported also that postoperative worsening seems to be due to a generic mechanical effect and to manipulation/removal of tumor periphery rather than to discrete focal injury.

Yoshii et al. [53] reported that the cognitive functions in patients with LGG and meningiomas (MGs) in the right brain were normal preoperative and postoperative whereas it decreased preoperative and did not return to the normal scores postoperative in left brain MGs. Temporal and spatial orientation, similarities, first recall, writing, mental reversal decreased after operation.

The explanation of mild cognitive effects in MGs preoperatively is the ability of normal brain tissue to compensate as the slow growth of tumor provides enough time for this compensation, but after surgical decompression decline in brain function occurs due to remodeling of normal brain tissue [56]. Another explanation is that extracerebral tumor causes compression on brain tissues but local anatomical and functional integrity maintained before surgery.

Stability of cognitive function also was observed after tumor resection, like tumors of third ventricle; the preoperative cognitive impairment in executive function, memory, and fine manual speed did not improve or worsen postoperatively [57].

Postoperative cognitive defects in specific domains were observed, for example, some patients with frontal or precentral tumors showed postoperative minor deterioration in attention [58].

Right prefrontal cortex resection in one study [8] was associated with selective attention impairment (Stroop test performance).

5. Effect of brain RT on cognition

Cognitive deficits following RT are irreversible and progressive complication that may follow RT by several months to many years. These deficits may be due to vascular injury, local radionecrosis, and cerebral atrophy, the severity ranges from mild or moderate to progressive mental slowing, occurring in at least 12% of patients who were treated with radiation therapy [59].

5.1. Hypothesis of radiation-induced cognitive impairment

There are many hypotheses that explain how the cognitive deficits following radiation therapy occur, direct damage and subsequent death of parenchymal cells (oligodendrocytes, neurons, astrocytes, and microglia) or indirect through reactive oxygen species (ROS) production.

Dynamic interactions between the multiple cell types (astrocytes, endothelial cells, microglia, neurons, and oligodendrocytes) within the brain may be the cause of radiation-induced cognitive impairment [60]. Another hypothesis is that the RT can inhibit hippocampal neurogenesis causing the cognitive impairment.

Irradiation of the hippocampus results in loss of neuronal stem cells (NSCs) which are responsible on self-renewal and generating neurons, astrocytes, and oligodendrocytes [61]. The radiation injury to NSCs is dose-dependent [62] and results in decrease in proliferation of NSCs and decrease in its differentiation into neurons [63]. Radiation therapy for brain tumors may lead to a significant reduction in the number of neurogenic cells [64].

Direct damage of parenchymal brain cells due to RT and subsequent death of these leads to cognitive impairment; damage to oligodendrocytes, responsible for myelination, has been thought to play a role [65]. Neuronal irradiation of rodent causes altered expression of the gene activity-regulated cytoskeleton-associated protein, N-methyl-D-aspartate (NMDA) receptors, glutaminergic transmission, and also hippocampal long-term potentiation [66].

Disruption of the blood–brain barrier (BBB) as a result of brain RT has been associated with impaired cognition. This disruption and alteration of the BBB is likely due to imbalance between matrix metalloproteinase-2 and the metalloproteinase-2 tissue inhibitor levels [67], activation of microglial cells plays an important role in phagocytosis of dead cells, sustained activation is thought to contribute to a chronic inflammatory state in the brain [68]. Subsequent inflammation following RT and cell death usually associated with up regulation of cytokines, which are thought to be expressed by microglia, and pro-inflammatory transcription factors in the brain which contribute to endothelial cell dysfunction [69]. Glial and endothelial cells appear to have independent and overlapping roles in the pathogenesis.

Ionizing radiation produces its effect by direct DNA damage or indirect through generating ROS, leading to DNA damage to and activation of early response transcription factors and signal transduction pathways [70]. Activation of these pathways leads to the following: changes in cytokine milieu; the activation/influx of inflammatory cells, particularly microglia; marked increase in expression of the pro-inflammatory genes tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and Cox-2, and the chemokines, Monocyte Chemoattractant Protein-1 (MCP-1), intercellular adhesion molecule (ICAM)-1 and the development of post-irradiation complications [71].

Radiation injury to astrocytes makes them to undergo proliferation, exhibit hypertrophic nuclei/cell bodies, and show increased expression of glial fibrillary acidic protein .These reactive astrocytes secrete a host of pro-inflammatory mediators such as cyclooxygenase (Cox)-2 and the ICAM-1, which may lead to infiltration of leukocytes into the brain via BBB breakdown [72].

RT affects large- and medium-sized blood vessels of the brain. Vascular hypothesis predicts that blood-vessel dilatation, wall thickening with hyalinization, endothelial cell loss and a decrease in vessel density, all these finally lead to white-matter necrosis [73].

The severity of cognitive deficit following radiation therapy appears to be proportional to the dose of radiation therapy received by the hippocampus region [74].

5.2. Predisposing factors

Older ages more than 60 years and in some studies more than 40 years old have increased risk to develop leukoencephalopathy specifically in patients with genetic predisposition to leukoencephalopathy [75] with subsequent cognitive deficit. Also patient with white matter disease such as multiple sclerosis have increased risk, also vascular diseases such as hypertention carry risk [76].

Beside the previous patient-related factors, also there are factors related to treatment include the dose of RT received, dose per fraction and volume of irradiated brain, 5% of patients treated with more than 5000 cGy develop radiation necrosis [77], high radiation dose increases the risk of leukoencephalopathy, daily doses >200 cGy have a significantly increased risk of cognitive damage [75]. The large irradiated volume of brain tissues carries increased risk of cognitive impairment, and whole brain radiation has threefold to fourfold increased risk of encephalopathy [76].

Additional treatments to RT such as chemotherapy have increased risk on cognition than RT alone, systemic and intrathecal treatments have been implicated. Methotrexate chemotherapy when received intravenously or intrathecally after cranial irradiation has an effect on cognition in children and also on adults [78].

5.3. Neuropsychological assessments

Folstein MMSE is brief test that assess delirium or significant dementia. It does not adequately measure all the cognitive areas affected by radiation, and it is not a sensitive tool for detecting cognitive impairment in patients receiving RT [79].

Among the patients who have impaired cognitive function by neuropsychological testing, only 50% were considered abnormal on the MMSE [80].

The National Cancer Institute (NCI) Radiation Oncology Branch adapted the Meyers et al. [45] test battery by adding few measures to assess processing speed, working memory, and attention, which are functions that can be affected by RT [81].

Measurement of quality of life and daily activities of living is an important issue beside the neuropsychological testes, such as the Barthel index to assess the daily living skills and the Functional Assessment of Cancer Therapy-Brain (FACT-Br), to address the quality of life issues concerning brain tumor patients undergoing treatment The Barthel Index assesses daily living skills [82], and the FACT-Br was developed specifically to address the quality of life issues concerning brain tumor patients undergoing treatment [83].

5.4. Cognitive impairment following RT

RT is the leading cause of cognitive deficits involving multiple domains, including memory, attention, executive function, and intelligence.

Patients who received RT performed worse in measures of executive function and information processing speed. Worse cognitive functioning also observed with white-matter hyperintensities and global cortical atrophy [84].

Several studies assed cognitive defects to specific tumor-type and tumor location. Aarsen et al. [85] reported cognitive deficit, with sustained speech and speed of speech in children treated with RT for pilocytic astrocytoma, 60% of patients had difficulty with academics 3 years after treatment.

Cognitive impairment observed in children with medulloblastoma who had treated with RT. These deficits were prominent attention deficits correlated with impaired math and reading performance [86].

Hoppe-Hirsch et al. [87] conducted a study comparing intellectual outcomes of children diagnosed with ependymomas or medulloblastomas, treated with whole-brain radiotherapy (WBRT), and found that only 10% of medulloblastoma patients had an IQ above 90 after 10 years compared to 60% of ependymoma patients, and this result attributed to cerebral hemisphere radiation.

Posteroir fossa irradiation with 35 Gy was associated with lower cognitive scores than that irradiated with a dose 25 Gy, and IQ and verbal comprehension seems to be dose-dependent in posterior fossa tumors [88].

Large-sample controlled clinical trial conducted by Klein et al. [75] assed mid-term and long-term neuropsychological function following the RT in LGG. In the study, 195 patients with LGG compared with 195 healthy controls and 100 patients with hematological malignancies with mean follow-up period of 6 years. The results revealed that patients with LGG had lower scores in all cognitive domains than the controls and hematological patients, and the main cause of cognitive deficits was the tumor, but cognitive deficits of memory domain was observed only in patients who received RT with dose per fraction more than 2 Gy.

Another study was conducted on those patients after 12-year follow-up and found that the attentional deficits deteriorated in patients who received RT. The progressive decline was found even in patients received <2 Gy dose per fraction [89].

Decline in nonverbal memory was observed in patients with LGGs years post-RT, despite the long-term improvements which observed in verbal memory, attention, and executive function [84]. Postoperative RT in LGG was found to have a significant risk of long-term leukoencephalopathy and cognitive impairment [90].

The irradiated volume of brain tissue has great impact on cognition. A study conducted by Jalali et al. [91] reported that patients who treated with stereotactic conformal RT presented with unchanged overall mean full-scale IQ, while one third of patients showed a >10% decline in full-scale IQ as compared to baseline.

Chang et al. [92] found that cognitive deficits after the treatment with sterotactic radiosurgery (SRS) had lower incidence than that in patients treated with whole-brain radiotherapy (WBRT). The cognitive deficit in learning and memory function was (24%) in patients treated with SRS and (52%) in patients treated with WBRT and SRS.

Intensity-modulated radiotherapy (IMRT) is a type RT technique in which more sparing of normal brain tissue can be achieved and precise contouring to the tumor tissue.

Hippocampal sparing with IMRT reduced doses delivered to hippocampus by 87% (0.49 Gy) and 81% (0.73 Gy) [93].

Proton beam therapy results in greater sparing of healthy brain tissue and allows for a more-targeted delivery of radiation and smaller penetration of tissue beyond the tumor [94]. The

mean dose of radiation to the hippocampus could be reduced much more, and it could be half that of IMRT and consequently reduce the risk of cognitive deficit after RT [95].

6. Effect of chemotherapy on cognition

Chemotherapy treatment in brain tumor seems to have a role in cognitive deficits. There is association between chemotherapy used in the treatment of brain tumor and an increased risk for cognitive dysfunction especially, if it is administered with RT.

6.1. Pathogenesis of cognitive impairment

The mechanisms by which chemotherapy-induced cognitive impairment are unclear [96].

Chemotherapy may reduce the number of neural stem/progenitor cells, which have role in memory and learning ability [97], and neural precursor cells are chemo-sensitivity, neural stem, and line age-restricted progenitor cells that form, among other cell types, the myelinating oligodendrocytes in the frontal white matter [98].

Primary pathological lesions including demyelination, inflammation, and microvascular injury [99]. Also mature oligodendrocytes are chemo-sensitive at lower dosage than those required to kill tumor cells [100].

Multiple chemotherapeutic agents affect hippocampal neurogenesis causing decrease in cell proliferation within the germinal region of the hippocampus and development of cognitive deficit [101].

Genetic role in chemotherapy-induced cognitive decline may be impilicated, and there is increased risk of cognitive impairment after RT with the apolipoprotein E4 alleles [102].

6.2. Cognitive impairment of chemotherapeutic agents

Chemotherapy added to slow the tumor progression especially in children to postpone radiation therapy or to reduce the dose of radiation therapy to decrease the neurocognitive sequelae of increasing doses of RT. Neurotoxic side-effects of chemotherapy alone can be difficult, because most patients of brain tumor have been treated with RT and chemotherapy [103].

The evidence that chemotherapy alone causes neurocognitive effects is not consistent. Studies have concluded that chemotherapy effects are negligible and not clinically significant compared to craniospinal irradiation (CSI) [104].

Neurotoxicity of chemotherapy arises during, or shortly after, chemoterapy. RT causes disturbance in BBB, so the toxicity of chemotherapy increased when was given during or after RT. In these cases, the chemotherapeutic drugs reach higher concentrations in brain tissue

because of leakage of the blood–brain barrier due to RT. Intrathecal chemotherapy has higher CNS toxicity compared to systemic chemotherapy [105].

Chemotherapeutic agents, such as BCNU, CDDP, cytosine arabinoside, and intrathecal or intravenous methotrexate, have toxic effect to the CNS. Chemotherapy-related cognitive impairment in primary CNS lymphoma was observed in one or more domains: (attention, executive function, memory, psychomotor speed, and language). Other studies have shown that cognitive stability or cognitive improvement during chemotherapy provided that the tumor was responsive to chemotherapy treatment [106, 107]. Uses of high-dose IV methotrexate or interathecal methotrexate with radiation therapy result in dementia particularly when the radiation is given prior to the methotrexate. Leukoencephalopathy more commonly occurs. MRI shows bilateral periventricular white matter changes. The radiation therapy disrupts the BBB and results in increased permeability of the white matter to the methotrexate [108].

Copeland et al. [109] concluded that chemotherapy had only a slight effect on neurocognitive status and was confined to perceptual motor skills with observed age effect on performance IQ.

Chemotherapeutic agents, such as BCNU, cisplatin, and cytarabine, have proved to be more toxic to neural precursor cells than cancer cells [110]. Carmustine, methotrexate, and cytarabine have been found to induce central neurotoxicity to neural stem cell populations located in the subventricular zone and dentate gyrus [99].

Prabhu et al. [111] conducted a study on LGG patients and concluded that the addition of chemotherapy procarbazine, lomustine, and vincristine (PCV) to RT for LGGs did not result in significant MMSE score decline when compared to RT alone.

Regarding the HRQOL, there is a short-lasting negative impact of PCV chemotherapy on HRQOL during and shortly after treatment, but no long-term effects on HRQOL have been established [112].

Patients with previously untreated anaplastic astrocytoma, OA, or oligodendroglioma were evaluated for the long-term efficacy and safety of accelerated fractionated RT combined with intravenous carboplatin. In a phase II study conducted by Levin et al. [113], they found that after RT, patients received procarbazine, lomustine (CCNU), and vincristine (PCV) for 1 year or until tumor progression, 10% of those patients developed serious clinical neurologic deterioration and/or dementia requiring full-time caregiver attention.

Hilverda et al. [114] reported that glioblastoma patients undergoing RT with concomitant and adjuvant temozolomide treatment did not develop cognitive deterioration.

In LGG patients, temozolomide is not only successful in terms of extending the survival duration but also has been proven to maintain or even improve HRQOL while patients are on treatment [115].

Patients with recurrent high-grade glioma (HGG), successfully treated with temozolomide, achieved significant improvement in the HRQOL domains, whereas patients with disease progression had significant deterioration in most HRQOL domains [116].

7. Prevention or reduction of cognitive deficits during treatment of brain tumors

Reduction in treatment-related brain tissue toxicity has occurred with advances in neurosurgical techniques, advances in radiation therapy techniques, and use of neuroprotective agents.

7.1. Pharmacological prevention of neurocognitive impairment

Neuroprotective agents may be used to protect healthy tissue against neuronal cell death or degeneration caused by the treatment of brain tumor.

Lithium can be used to protect progenitor cells in the hippocampus through inhibition of radiation-induced apoptosis and induction of the DNA repair, and the tumor cells not included in this protection process. A study conducted by Yang et al. [117] found that neurocognitive performance in mice was improved after receiving lithium concomitant with RT, anthor neuroprotective drug; fenofibrate which prevents activation of microglia. Administration of fenofibrate during whole-brain RT prevents effects on hippocampal neurogenesis in mice, as it enhances survival of newborn neurons in the dentate gyrus [118].

7.2. New treatment techniques

The use of image-guided surgery such as the intraoperative magnetic resonance imaging resulted in improvement in tumor resection and reduction of residual [119]. The use of endoscopic biopsy is a minimally invasive method can be performed safely in conjunction with diversion of cerebrospinal fluid in cases of obstructive hydrocephalus and decrease neurocognitive decline [120].

New radiation techniques such as IMRT are able to minimize the radiation to healthy brain structures. With using IMRT, hippocampus can be localized and hence the dentate gyrus can be spared, resulting in prevention or decrease neurocognitive decline to some extent [121]. Lin et al. [122] reported significantly lower rates of memory loss posttreatment and with no treatment-related decline in quality of life with IMRT RT.

Insignificant neurocognitive decline was found in a study conducted by Wahba et al. [123] after use of reduced CSI followed by adjuvant chemotherapy in patients with average-risk medulloblastoma.

With proton beam RT, there is less radiation to surrounding normal brain tissues and decrease the area at risk for radiation injury, therefore, sparing of neurocognitive functioning [124].

7.3. Stem cell implantation

Mesenchymal stem cell implantation may reduce the cognitive impairment by two mechanisms: First, reversal of inflammatory process, as implanted mesenchymal stem cells can migrate to the site of damaged brain tissue and then release growth factors, [125]. Second, human mesenchymal stem cells can differentiate into neurons in the hippemocampal area and prevent radiation-induced late cognitive impairment [126].

8. Rehabilitation

Patients with brain tumors face the challenge of cognitive impairment due to the tumor itself or treatments. Cognitive deficits in processing speed, memory, attention, and executive functions interfere with patients' relationships, occupational activities and daily life activities.

8.1. Pharmacologic treatment of neurocognitive impairment

Methylphenidate (MPH) is a CNS stimulant that increases synaptic concentration of dopamine and noradrenaline in the brain [127]. De-Long et al. [128] conducted a pilot study on children with ALL or brain tumor, they found that approximately 75% of those patients had response to treatment with MPH regarding neuropsychological dysfunction.

Meyers et al. [129] reported significant improvements in processing speed, memory, mental flexibility, and even mood, in adult patients with brain tumors and receiving MPH. Conklin et al. showed encouraging results in the use of psychostimulant medication. On 122 survivors of childhood brain tumors or ALL who were enrolled in a double-blinded, cross-over trial comparing the acute efficacy and adverse effects of MPH and placebo.

Donepezil is acetylcholinesterase inhibitor and has efficacy in the treatment of cognitive functions impairment; uses of donepezil in adult patients with brain tumors treated with RT demonstrate improvements in cognition impairment such as attention, concentration, and verbal memory [130].

However, stimulant medication is short-acting and is not expected to result in long-term improvement in academic achievement and neurocognitive functioning once it is discontinued; on the other hand, newer pscyhostimulant medications have been widely used in children with attention-deficit hyperactivity disorder (ADHD) and have proven to have fewer side effects and a longer half-life than MPH, for these reasons further studies are needed [131].

8.2. Cognition rehabilitation program

Cognitive rehabilitation program has proven to be effective in in-patients with primary brain tumors. The program consists of psychoeducation, teaching of strategies to compensate for problems in attention, memory, and executive functioning in daily life.

Cognitive remediation program (CRP) highly structured and individualized regimen, included traditional massed practice rehabilitation, instruction in metacognitive strategies, and cognitive-behavioral psychotherapy focused primarily on improving resistance to distraction. Butler and Copeland tested the effectiveness of CRP. Thirty-one subjects who had been treated from CNS tumors included in the study, and they were suffering from cognitive impairment such as attention deficits documented by continuous performance test (CPT). Cognitive behavioral psychotherapy was used. Significant improvement in focused attention and attention/concentration was observed in those who underwent the CRP, but no significant benefit was measured with regard to arithmetic computation. The authors concluded that the intervention produced improved neurocognitive functioning on meas-

ures of attention, but that it was too early to expect a downstream effect on the desired end result of improved academic achievement [132].

A study conducted by Butler et al. all patients was offered the CRP treatment, improvement neurocognitive variables were observed but this was not statistically significant. The study results demonstrated highly significant improvement in academic achievement for those who completed the CRP, and significant gains in their child's or adolescent's attention/concentration in activities of daily living [133].

The majority of the participants of cognitive rehabilitation program found the program to be useful. However, older participants found the program more burdensome than younger participants [134].

Richard et al. [135] conduct a study to compare two cognitive rehabilitation program, goal management training (GMT) which is a neuroscience-based integration of mindfulness and strategy training and the Brain Health Workshop (BHW) which offers supportive psychoeducation about living with a brain tumor. They found that significant improvement in executive functions and greater attainment of pre-training functional goals in the GMT group while The BHW group showed in significant improvement in mood and behavioral regulation.

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