NEUROCOGNITIVE IMPAIRMENTS IN BRAIN TUMOR PATIENTS

Ivo J. Kehayov, Borislav D. Kitov, Christo B. Zhelyazkov, Stefan D. Raykov, Atanas N. Davarski
Department of Neurosurgery, Medical University, Plovdiv, Bulgaria

ABSTRACT
There is an increased scientific interest in cognitive impairments caused by brain tumors during the last decade. It has lead to the introduction and routine clinical usage of neuropsychological test batteries in brain tumor patients, thus making them an important clinical measure for the assessment of the efficacy of the different treatment regimens such as surgery, radiotherapy and chemotherapy. The effect of cognitive deficit on patients’ quality of life and survival has been unequivocally proven. These are among the most common neurological symptoms associated with brain tumors. The improvement in cognitive function and delay in neurocognitive decline are acceptable endpoints in clinical trials. Cognition has been demonstrated to be an independent predictor of survival in patients with cerebral neoplasms.

Key words: cognitive deficit, brain tumor, glioma, neurotoxicity, surgery

INTRODUCTION
Cognitive function (from Latin “cognoscere” – to know, to learn) is the process by which sensory input is elaborated, transformed, reduced, stored, recovered, and used.1 Cognition is considered to be a complex multifaceted system, composed of several interwoven mental domains: attention/concentration, visuospatial and constructional skills, sensory and perceptive function, language, memory, executive functions, and intellectual functioning.2,3 Those are regarded to be determined by either localized or distributed substrate in the central nervous system.4,5 The clinical psychopathological correlates of brain tumors have been thoroughly discussed over the past decades.6 However, cognition is relatively underestimated in current literature. Therefore, this review aims to cast light on the latest achievements in the diagnosis and prognosis of cognitive dysfunction before and after neurosurgical interventions.

ETIOLOGY OF THE COGNITIVE DEFICIT IN BRAIN TUMOR PATIENTS
Patients with brain tumors often experience cognitive dysfunction associated with the disease and its treatment, including surgery, radiotherapy (RT), and chemotherapy. As more effective therapies have prolonged survival for many patients, cognitive dysfunction has been recognized as the most frequent complication among long-term survivors.7 Visuconstruction, processing speed, and verbal memory measures may be the most important domains to assess when evaluating cognitive change in brain tumor clinical trials.8 Executive functions, which are also commonly affected in the brain tumor population, influence the patient’s safety and abilities of daily living.9 Cognitive difficulties often have an impact on quality of life and interfere with the patient’s ability to function at premorbid levels.10,11 Cognitive deterioration, which may eventually progress to dementia, worsens patient’s quality of life and well-being.12,13

Neurocognitive impairments in brain tumor patients are among the most common neurological symptoms which precede the time of diagnosis. Cognitive dysfunction results from the neoplastic process itself, secondarily from shift or compression of intracranial structures, and associated brain edema.14,15 Although tumor type or volume has not been found to predict cognitive performance, cognitive dysfunction is seen more frequently at diagnosis in rapid-growing tumors such as glioblastomas than in slow-growing ones such as low-grade gliomas.16 Cognitive deficit can result from brain cortical lesions but due to the vast cortico-subcortical pathways, it may also occur after white matter injury, or even following damage to the cerebellar structures.17

Correspondence and reprint request to: I. Kehayov, Department of Neurosurgery, Medical University, Sofia.
E-mail: dr.kehayov@gmail.com; Mob.: +359 899 105 352
15A Vassil Aprilov St., Plovdiv 4002, Bulgaria
Received 24 September 2012; Accepted for publication 10 October 2012
Radiation-induced cognitive impairment, including dementia, is reported to occur in up to 50–90% of adult brain tumor patients who survive more than 6 months post-irradiation. This cognitive impairment is marked by decreased verbal memory, spatial memory, attention, and novel problem-solving ability. Radiation-induced dementia is a rare occurrence with fraction sizes less than 3Gy. However, patients who survive more than 2 years after focused whole-brain irradiation have a continually increasing risk of developing dementia over time. Importantly, all of these late sequelae can be seen in the absence of radiographic or clinical evidence of demyelination or white matter necrosis. In spite of the relative rarity of progressing to frank dementia, radiation-induced cognitive impairment has significant effects on quality of life. The majority of more than 6 month survivors of partial or whole-brain irradiation have a symptom cluster consisting of fatigue, changes in mood, and cognitive dysfunction. Furthermore, brain tumor patients are surviving longer due to improved radiation therapy techniques and systemic therapies, so the patient population experiencing radiation-induced cognitive impairment is growing rapidly. Consequently, the search for biomarkers to identify patients who will/will not develop cognitive impairment after fractionated whole brain radiotherapy and therapeutic strategies to prevent/ameliorate radiation-induced cognitive impairment have become very important.18,19

Neuroinflammation is viewed as playing a major role in radiation-induced cognitive impairment. During the past 5 years, several preclinical studies have demonstrated that interventional therapies aimed at modulating neuroinflammation can prevent/ameliorate radiation-induced cognitive impairment independent of changes in neurogenesis. Translating these exciting preclinical findings to the clinic offers the promise of improving the quality of life in patients with brain tumors who receive radiation therapy.20

Radiation encephalopathy has been classified in three phases - acute, early delayed, and late delayed - according to the length of time between the administration of RT and the onset of the injury.21

Acute encephalopathy develops within days of RT. Disruption of the blood–brain barrier (BBB) by endothelial apoptosis and increased cerebral edema and intracranial pressure have been reported as underlying mechanisms. Early-delayed effects occur weeks to 6 months following RT and are reversible in most cases. A transient decline in cognitive functioning may occur but it is not predictive of any cognitive problems that may develop later. The delayed effects of RT become apparent a few months to many years after treatment, and often produce irreversible and progressive damage to the central nervous system through vascular injury causing ischemia, demyelination of the white matter, and necrosis. Risk factors for developing delayed RT-induced brain injury include a greater volume of radiated tissue, a higher total dose of radiation, concomitant administration of chemotherapy, age greater than 60 years, and the presence of comorbid vascular risk factors.7,21 Magnetic resonance imaging (MRI) typically shows hyperintensity in the periventricular and subcortical white matter, and these changes often are more severe in the elderly.22 Whole-brain irradiation may lead to brain atrophy and leukoencephalopathy associated with severe cognitive decline, especially, when fraction sizes exceed 2Gy.23

The acute and sub-acute changes in normal appearing white matter fibers indicate radiation-induced demyelination and mild structural degradation of axonal fibers. The structural changes after RT are progressive, with early dose-dependent demyelination and subsequent diffuse dose-independent demyelination and mild axonal degradation. Diffusion-tensor MRI is potentially a marker for assessment of radiation-induced white matter injury.24 CA Hahn et al., using positron-emission tomography (PET) scanning, report on a dose-dependent decrease in glucose metabolism at three weeks and sixth months after conventional RT in patients with central nervous system tumors correlated with decreased performance on neuropsychological tests for problem solving, cognitive flexibility, and global measures of psychopathology.25

EL Chang et al. conducted a randomized controlled study including 58 patients with newly diagnosed 1 to 3 brain metastases divided into 2 groups – patients treated with stereotactic radiosurgery (SRS) alone (n=30) and a second group treated with SRS plus whole-brain RT (WBRT) (n=28). The primary endpoint was neurocognitive function: objectively measured as a significant deterioration (5-point drop compared with baseline) in Hopkins Verbal Learning Test-Revised (HVLT-R) total recall at 4 months. Patients treated with SRS plus WBRT were at a greater risk of a significant decline in learning and memory function by 4 months compared with the group that received SRS alone. Initial treatment with a combination of SRS and close clinical monitoring is recommended as...
the preferred treatment strategy to better preserve learning and memory in patients with newly diagnosed brain metastases.\textsuperscript{26} AE Kayl et al., after reviewing the literature, point out that despite the frequency of subjective patient complaints, studies evaluating the cognitive abilities of patients have inconsistently reported chemotherapy-related declines. Discrepant findings across studies (some documenting chemotherapy-related cognitive declines and others failing to detect such changes) may be attributed to differences in methodology. Most studies have been retrospective in design, omit pretreatment assessment of function, use small or heterogeneous samples, use inappropriate measures to assess cognition, and fail to incorporate control subjects. Though rare to date, prospective, randomized, longitudinal studies that incorporate pretreatment comprehensive neuropsychological assessment are necessary to define the severity and pattern of treatment-related change. Building on a foundation of solid science, future studies may identify subgroups of patients susceptible to significant chemotherapy-related cognitive decline. Once these groups are identified and the mechanisms underlying the decline are elucidated, attention may be turned to the development of treatments that may optimize cognitive function and improve patient quality of life.\textsuperscript{27} DD Correa confirms that it is hard to establish the side effects of chemotherapy on cognition because most of the patients with brain tumors receive parallel radiotherapy. Whole-brain RT alone or in combination with chemotherapy results in a more pronounced cognitive dysfunction than either partial RT or chemotherapy alone. Antiepileptics and corticosteroids, often used in the treatment of these patients, may further disrupt cognitive functioning. The pattern of cognitive difficulties is consistent with frontal subcortical dysfunction, and domains suggested to be particularly sensitive to treatment-induced cognitive dysfunction include several aspects of attention and executive functions, learning and retrieval of new information, and graphomotor speed.\textsuperscript{22}

Epileptic seizures are the first symptom of an intracranial tumour in 30-90\% of patients. The older generation of antiepileptic drugs are known to decrease cognitive functioning. These drugs may result in impairments of attention and cognitive slowing, which can have secondary effects on memory by reducing the efficiency of encoding and retrieval. Data on cognitive side-effects of the newer drugs are still scarce. Apart from antiepileptic drugs, cognitive function may be negatively affected by the seizures themselves.\textsuperscript{28}

**ASSESSMENT OF COGNITIVE DEFICIT IN BRAIN TUMOR PATIENTS**

Neuropsychological tests are increasingly being used as outcome measures in clinical trials of brain tumor therapies.\textsuperscript{8} Cognitive deterioration is indicated to be an early predictor of tumor progression in recurrent malignant gliomas and can precede MRI evidence of progression by 6 weeks.\textsuperscript{13} Neurocognitive assessment will also likely impact future treatment decisions by providing critical risk-versus-benefit assessments of different treatment regimens. Tumor control, short- and long-term neurotoxicity, and rates of neurocognitive decline are all outcomes that may vary among different treatment regimens and subsequently inform treatment decisions.\textsuperscript{29}

Evidence-based cognitive screening tools in brain tumor patients are: Mini-Mental State Examination (MMSE), Modified Mini-Mental State Examination (Modified MMSE) and Neurobehavioral Cognitive Status Examination (NCSE).\textsuperscript{14,30,31} The major disadvantage of the MMSE is the lack of sensitivity to cognitive dysfunction in higher scores. Performance in the supposedly normal range (score 27 of 30 possible points) does not mean that the individual is free of significant cognitive problems, nor does stability of the MMSE score over time mean that the person has not experienced significant changes, either for better or for worse.\textsuperscript{32} This fact necessitates the usage of more sensitive and selective tests to assess cognitive decline in brain tumor patients.

The choice of cognitive test depends on the goal of the assessment (i.e., in the context of patient care, treatment outcome analysis, or cognitive rehabilitation). If cognitive function is the outcome measure in clinical trials, the use of comprehensive series of tests, in contrast to the use of individualised testing, has advantages in that it allows for the collection of vast amounts of information on cognitive status in a highly standardised manner. These series cover the different cognitive domains such as memory, attention, orientation, language abilities, and executive function, which represent functions of both the dominant and the non-dominant hemisphere.\textsuperscript{28} Table 1 demonstrates an exemplary approach of MJ Taphoorn et al. for cognitive assessment of patients with primary malignant brain tumors.
COMMONLY USED NEUROPSYCHOLOGICAL TESTS IN BRAIN TUMOR TRIALS

MODIFIED MINI-MENTAL STATE EXAMINATION (3MS)
The mini-mental state examination (MMSE) was developed as a screening tool for dementia and is insensitive to mild cognitive impairments or focal lesions. The 3MS examination incorporates 4 added test items, more graded scoring, and some other minor changes of the MMS examination. These modifications are designed to sample a broader variety of cognitive functions, cover a wider range of difficulty levels, and enhance the reliability and the validity of the scores. The 3MS examination generates more information to assess brain dysfunction with little additional test time and effort.33

STROOP COLOUR AND WORD TEST
The Stroop test is one of the most extensively studied measures of selective attention.34 The test
often consists of three sets of stimuli: (a) colour words printed in black ink; (b) colour patches or coloured X’s; and (c) colour words printed in ink of different colour (e.g., the word “RED” printed in blue ink). The participant must read the colour words on the first sheet, the colours on the second sheet, and the colour of the ink (i.e., not the words) on the third sheet. In the latter task, the normal tendency to read the words rather than the colour of the ink in which the words are printed, elicits a significant slowing in reaction time called the “Stroop effect” or the “interference effect”.35 The Stroop Colour and Word test is a method for evaluating interference, a measure of effective executive control as part of the executive functions, and one of the neuropsychological methods for detecting early brain dysfunction.36

**Verbal Fluency Test**

Verbal fluency is one of the most frequently used measures of executive functioning.37 The two types of verbal fluency tasks are phonemic and semantic. Phonemic fluency tasks require participants to say (or write) as many words as possible beginning with a specific letter (e.g., A, F or S). Semantic fluency tasks require participants to say (or write) as many words as possible within a certain category (e.g., animals). In general, persons with frontal lobe damage demonstrate impaired phonemic fluency, while their semantic fluency remains relatively intact. Verbal fluency obviously depends on language proficiency and the size and integrity of one’s semantic store. However, task analysis indicates that verbal fluency also reflects executive function, in that performance will be impaired if one cannot sustain attention to the task, devise an efficient strategy for production, search the lexicon, and monitor responses to prevent errors, including repetitions/perseverations. In general, both letter and category fluency are more likely to be impaired by left- than right hemisphere damage, and both can be impaired by frontal lesions.35,38,39

**Trail-Making Test A&B**

On this test, participants use a pen or pencil to connect a series of circles that are scattered on the page. In Part A, all the circles contain numbers, which must be connected in ascending order (i.e., 1 to 2 to 3 and so on). In Part B, however, some circles contain numbers, and others contain letters, and participants must alternate between the two (i.e., 1 to A to 2 to B and so on). Both parts require visual search and motor planning, but Part B is thought to place an especially heavy load on executive function. People must inhibit the previously established number-to-number rule and alternate between two stimulus domains, while keeping the new rule in working memory for the duration of the task.39,40

**Wisconsin Card Sorting Test (WCST)**

In the most common version of the WCST, participants are presented with a deck of cards and are asked to sort them into piles under four sample cards. The cards can be sorted according to various rules, but the only feedback given is whether a response is correct or not, and thus one must infer the rule. Further, the sorting rule changes during the test, requiring the participant to inhibit the prepotent response, infer a new rule, and switch to it. The two most common scores derived from the task are the number of categories achieved and the number of perseverative errors (in which the participant makes a response that continues to follow the no-longer-valid rule). The WCST’s demands on abstraction and flexibility in the face of changing contingencies make it a canonical test of executive function.35,39

**Digit-Symbol Test**

Substitution tests are widely used as clinical and research tools in neuropsychology, the best known of which is the Digit-Symbol Substitution Test, one of the subtests from the Wechsler Intelligence Scales. Several adaptations of the test now exist. Substitution tests are essentially speed dependent tasks that require the participant to match particular signs-symbols, digits, or letters to other signs within a specified time period. Substitution tests are sensitive to brain dysfunction in a nonspecific way because their performance draws on many different processes: the simple responses generated in substitution tests depend on the integration of complex neuropsychological processes, including visual scanning, mental flexibility, sustained attention, psychomotor speed, and speed of information processing. This nonspecific sensitivity to brain dysfunction, combined with the possibility of group administration and the short test time, make substitution tests highly suitable as screening instruments.41

**Digit Span Test**

This test consists of two parts. In the digit span forward and digit span backward tasks, a series of digits are read to the subject, who is required to repeat the digits either in the given order or in the reverse order. These tests measure short-term memory and working memory, respectively, for verbal stimuli.28,42
HOPKINS VERBAL LEARNING TEST-REVISED (HVLT-R)
This test comprises six alternate forms, each consisting of a list of 12 nouns with four words drawn from each of the three semantic categories (e.g., four-legged animals, precious stones, human dwellings). The semantic categories differ across the six forms. The HVLT-R includes three learning trials, a delayed recall trial (given without forewarning after a delay of 20-25 minutes), and a randomized list of 12 target and 12 nontarget words, 6 of which are drawn from the same semantic categories as the targets. The examiner reads the word list and asks the patient to verbally repeat the list of words (immediately and after a delay) in any order, and to identify the words from a list that is presented orally. Recall performance is recorded verbatim on a scoring sheet for each of the immediate recall trials and for the delayed recall and recognition trials. Subjects are not warned that the delayed recall will be tested later. The HVLT-R is used to provide a brief assessment of verbal learning and memory.43

CLOCK DRAWING TEST (CDT)
The Clock Drawing test is a simple and quick test to administer. The subject is given a sheet and a pencil. He/she is asked to draw a clock, mark in the hours, and then draw the hands to indicate a specified time, commonly, 10 after 11. The result is scored from 1 to 10. This test can reflect a wide range of brain dysfunctions. For example, inability to place the hands on a clock suggests visual-spatial disorder which may occur in the posterior area of either hemisphere, although the deficit is thought to be more specific to the right hemisphere. In some cases, the subject may perseverate, drawing more than two hands or numbering beyond 12. These observations are strongly suggestive of anterior lesions. Frontal planning skills may be evident in the drawing of the clock. It should be noted whether the subject begins by spacing the 12, 3, 6, and 9, and then proceeds to fill in the gaps with the remaining numbers, or if the subject begins numbering at 12 and continues consecutively and in a clockwise fashion. Inability to recognize or reproduce numbers suggested a form of acalculia that is most often seen in left posterior dysfunction. The presence of neglect will cause the client to ignore the left side of the clock and is usually associated with right parietal lesions.44

Depending on the aim of assessment, separate neuropsychological tests can be grouped in batteries to cover wider range of cognitive functions which can be affected by brain tumors and their treatments. Since a combination of cortical and subcortical lesions, epilepsy, surgery, radiotherapy, anti-epileptic drugs, corticosteroids, and psychological distress is likely to contribute to neurocognitive dysfunctioning in an individually unpredictable way, it would be most pragmatic to choose a core testing battery that gauges a broad range of neurocognitive functions. Additionally, the neuropsychological measures have to meet the following criteria: (1) assess several domains found to be most sensitive to tumor and treatment effects; (2) have standardized materials and administration procedures; (3) have published normative data; (4) have moderate to high test-retest reliability; (5) have alternate forms or are relatively insensitive to practice effects, and are therefore suitable to monitor changes in neurocognitive function over time; (6) include tests that have been translated into several languages or require translation primarily of test directions; and (7) total administration time is 30–40 min. The neurocognitive domains deemed essential to be evaluated include attention, executive functions, verbal memory, and motor speed.45

Thus, the evaluation of treatment regimens for brain tumors patients should not only focus on progression-free survival, but also examine functional outcomes and adverse treatment effects on the normal brain.46

CONCLUSIONS
The analysis of the review shows that further efforts are needed in using standardized and sensitive cognitive tests within multicentre, prospective clinical trials in the field of neuro-oncology. Data obtained from these studies would improve the awareness of the neurotoxicity of the different treatment regimens. Furthermore, physicians and their patients would make decisions based not only on survival and time to disease progression but also on the quality of life which is largely affected by the patient’s cognitive status.

REFERENCES
4. Stoyanov D. Relationships between brain and mentality in psychoorganic syndromogenesis. In: Neuroscience and challenges of psychological medi-


34. Stuss DT, Floden D, Alexander MP, Levine B, et al. Stroop performance in focal lesion patients: Disso-
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