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Correlations between histological subtypes and neurocognitive assessment of language area tumors. Our 43 case series and review of the literature

MIHAELA COŞMAN[1)], IONUŢ MIHAIL PANŢIRU[2)], ROXANA ŞERBAN[3)], LUCIA INDREI[4)], NICOLETA DUMITRESCU[5)], IRINA RĂILEANU[6)], MIRELA IULIA ALDEA[2)], ANA MARIA DUMITRESCU[7)], ION POEATĂ[1,2)]

[1)]*Department of Neurosurgery, "Grigore T. Popa" University of Medicine and Pharmacy, Iaşi, Romania*

[2)]*Department of Neurosurgery, "Prof. Dr. Nicolae Oblu" Emergency Clinical Hospital, Iaşi, Romania*

[3)]*Department of Pathophysiology, "Grigore T. Popa" University of Medicine and Pharmacy, Iaşi, Romania*

[4)]*5th Year Student, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

[5)]*6th Year Student, "Grigore T. Popa" University of Medicine and Pharmacy, Iaşi, Romania*

[6)]*Department of Neurology, "Arcadia" Policlinic, Iaşi, Romania*

[7)]*PhD Student, "Grigore T. Popa" University of Medicine and Pharmacy, Iaşi, Romania*

Abstract

Background: Brain tumor location is related with specific, focal neurological impairment, but also with more diffuse, generalized and subtitle neurocognitive dysfunctions. For a better evaluation of these cases, we need a specific battery of tests. Beside the impact of preoperative status on surgical decision, the quantification of postoperative function alteration is essential in neurorehabilitation. *Patients, Materials and Methods*: We proposed a battery of tests to assess the neurocognitive function, with an accent on language adapted to Romanian population. The 43 cases included in the study were tested preoperatively, seven days postoperatively and at one month, and correlated with the images and histological results. *Results*: At admission, from all participants, 11.6% were affected across all measured items and 6.9% on none of them. A rate of impairment significantly higher, four or more items, was observed in glioblastoma (GB) cases (23.3%) in contrast with low-grade glioma (LGG) (0%), meningioma (0%) and metastases (6.9%). From all cases, we performed seven awake craniotomies. At one-month evaluation, general decrease in neurocognitive function was observed in 20.93% cases, among them 88.88% being GB and favorable outcome in 32.55% patients with dominance of LGG and meningioma cases. *Conclusions*: A neurocognitive assessment of brain tumor patients is important for preoperative and postoperative evaluation and secondary adjustment of the surgical resection in order to improve or, at list, meantime the initial status. The role and the link between the histological type and tests alteration were observed. The results can be used for a better understanding and management of language area tumors.

Keywords: neurocognitive assessment, aphasia, language area tumor, glioma, meningioma.

Introduction

Brain tumors represent a common cause of mortality and high morbidity worldwide. There are many histological subtypes among these neoplasias, beside high-grade glioma (HGG), metastases are frequent and most of them have an infaust prognosis [1–3]. The incidence of intracranial neoplasias is increasing, especially in the case of atypical and anaplastic meningiomas, and some authors took into consideration the effects of Chernobyl nuclear accident [4].

About 60–90% of patients with intracranial tumors have some degree of cognitive impairments along the course of the disease [5, 6]. Neuropsychological deterioration has been found to be related to tumor recurrence and prognosis. Negative tests changes may be more sensitive in predicting early recurrence than even imaging evaluation [7]. Furthermore, it is important to identify, manage and prevent neurocognitive dysfunction especially in asymptomatically patient. Quality of life (QoL) being important not only in cases with good survival rate (due to histological type or innovation in the adjacent treatment), but also in patients with grade IV tumors, where the neurosurgeon should achieved symptoms remission or at least to avoid their worsening [8, 9].

Tests for language and other neurocognitive function were created for evaluation of stroke patients, but the difference in psychopathological mechanisms, onset of symptoms made the necessity for a battery of tasks especially for tumor patients.

Worldwide, there are some tests designed for evaluation of glioma patients. We can mention Papagno *et al.* (2012), who proposed Milano–Bicocca Battery (MIBIB) for evaluation of low-grade glioma (LGG) cases, De Witte *et al.* (2015) introduced a Dutch set of tasks for awake craniotomy in brain tumor cases [10, 11] and Faulkner *et al.* (2017), who developed a set of tests named Brief Language Assessment for Surgical Tumor Patients (BLAST) [12].

Aim

In this study, we attempted to achieve this goal by adapting and developing a Romanian neurocognitive battery

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of tests for patients with brain tumors located in and near the language areas and to obtain some correlation with the histopathological (HP) subtype of these neoplasias.

Patients, Materials and Methods

We conducted a retrospective analysis of collected data from 43 patients with brain tumors, who were admitted in the Third Department of Neurosurgery, "Prof. Dr. Nicolae Oblu" Emergency Clinical Hospital, Iaşi, Romania, between January 2015 and July 2018. Inclusion criteria were: (*1*) patients diagnosed by contrast-enhancement magnetic resonance imaging (MRI) with tumors located in or near language areas, (*2*) age >18 years old, (*3*) could cooperate and accepted to be included in the study, (*4*) presented at one-month postoperative evaluation, (*5*) no history of neurological, psychiatric pathology nor speech/ language development.

For each case, we recorded the demographic data (age and gender of the patients), tumor location, imaging aspects, and HP diagnosis of the lesions.

All the patients have been examined with a battery of tests, adapted to Romanian population, to assess the neurocognitive function with an accent on language before surgery, at seven days and one month postoperatively. The tests were chosen from different international protocols: Boston Diagnostic Aphasia Examination (BDAE), Denomination d'Object (DO80), Hopkins Verbal Learning Test, Trail Making Part B, BLAST and speech exercise tests. The battery included items for language (spontaneous speech, repetition of words, object naming and reading special speeches texts), memory, praxis and executive function evaluation, modified for Romanian patients. We prepared practice items to ensure that patients understood the task. The assessment was made by the same neurosurgeon. All cases were operated by the same team of surgeons. We evaluate the effect of resection on overall cognitive function and the relationship between the degree of resection, histological type of tumor and changes in language and neurocognitive function. The lesions were distinguished according to *World Health Organization* (WHO) Classification.

Spontaneous speech included questions about the patient as he was asked to tell: his full name, if he is married, his/her wife/husband name, if he has children, the reason for hospital presentation and was let to talk freely. For word repetition, we used five words and request the patient to repeat them. Object naming constituted in shown images representing geometric figures, animals, instruments, different things and he had to recognize them. To assess reading capacity, we utilized fragments from speech exercises. For short memory evaluation, we used five words. The words were repeated three times and the patient was asked five minute later to recall them. For every word remembered, he got one point (minimum – 0 points; maximum – 5 points). Cards with name of a color written on them with the ink in another color were utilized for executive function. The patient needed to read the word and not to say the ink color. For praxis function, we ask the patient to close the eyes, salute and pretend to knock at the door or imitate an action made by the examiner.

All the surgical samples were placed in containers with 4% neutral formalin for fixation and sent to the Laboratory of Pathology, "Prof. Dr. Nicolae Oblu" Emergency Clinical Hospital, Iaşi, for standard HP processing and microscopic examination, in order to establish the HP diagnosis. Briefly, after the samples were extracted from the formalin containers, the tissue was processed and embedded in paraffin. Three µm thick sections were cut with a microtome and then were stained with Hematoxylin–Eosin (HE). Selected histological sections were immunostained with a two-step detection system, using anti-cytokeratin 19 (CK19), anti-glial fibrillary acidic protein (GFAP), anti-p53, anti-isocitrate dehydrogenase 1 (IDH1), anti-adenosine triphosphate (ATP)-dependent helicase ATRX (ATRX), and anti-Ki67 antibodies (Table 1), according to the presumptive diagnosis of the case on the standard (HE) staining. Finally, the histological slides were viewed on a Leica DMC 2900 (Germany) light microscope. Brown staining of cytoplasm (in cases of immunostaining with anti-CK19 and anti-GFAP antibodies) or nuclei (in cases of immunostainings with anti-Ki67, anti-p53, anti-ATRX, and anti-IDH1 antibodies) were considered positive reactions.

Table 1 – *Immunohistochemical panel of antibodies used for our cases*

Antibody	Manufacturer	Clone	Antigen retrieval	Dilution	Detection system
CK19	Dako, Denmark	RCR 108	Citrate, pH 6.5	1:100	Dako EnVision™+ Dual Link System–HRP
GFAP	BioSB, USA	EP 13	Citrate, pH 6.5	Prediluted	UltraVision™ Quanto Detection System–HRP
p53	BioSB, USA	D07	Citrate, pH 6.5	1:340	UltraVision™ Quanto Detection System–HRP
IDH1	BioSB, USA	IHC 132	Citrate, pH 6.5	1:75	UltraVision™ Quanto Detection System–HRP
ATRX	BioSB, USA	BSB-108	Citrate, pH 6.5	1:150	UltraVision™ Quanto Detection System–HRP
Ki67	BioSB, USA	EP5	Citrate, pH 6.5	Prediluted	UltraVision™ Quanto Detection System–HRP

CK19: Cytokeratin 19; GFAP: Glial fibrillary acidic protein; IDH1: Isocitrate dehydrogenase 1; ATRX: Adenosine triphosphate (ATP)-dependent helicase ATRX; HRP: Horseradish peroxidase.

Results

At the beginning of our study, we identified a total of 48 cases, but we excluded five patients, as follows: three patients were lost from the study by not presenting to the postoperative follow-up, in one case we practiced only biopsy and other patient had only 11 years old.

The demographic data showed a male/female ratio of 1.3/1, with a slight dominance of male patients (24 males *vs.* 19 females), the median age of presentation was 57 years old, with an interval between 23–73 years. We divided the education level of patients in three categories: basic (1–8 years of education), high school (9–12 years) and university (13–18 years). We classify symptoms duration in >1 month (19 cases) and <1 month (24 cases).

The histological results were: HGGs [*i.e.*, glioblastoma

(GB)] 23 cases, LGGs (*i.e.*, diffuse astrocytoma) six cases, metastasis of carcinoma (MTS) six cases, meningiomas eight cases.

We present the imagistic and histological aspects of some illustrative cases from our study: a metastases form a moderately differentiated colon adenocarcinoma (Figure 1), a grade I meningioma in a left-handed patient (Figure 2), a diffuse astrocytoma also in a left-handed patient (Figure 3) and a GB (Figure 4).

The degree of resection for intra-axial lesions was: gross total resection (GTR) seven cases, near total resection (NTR) 16 cases, subtotal resection (STR) 12 cases. For meningioma, we used Simpson grading system and the results were: S1 – two patients, S2 – five patients, and S3 – one patient.

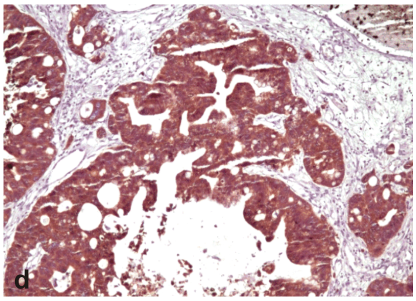

Figure 1 – ***Cerebral metastases of moderately differentiated colon adenocarcinoma: (a) T2 MRI axial view – left temporal iso- to hyperintense mass with relatively good cleavage plane and important perilesional edema; (b) T1 with enhancement sagittal view – heterogeneous enhancement pattern with perilesional edema which extends temporo-parietal including Wernicke area; (c) The tumor was well delineated by the adjacent gliotic nervous tissue and consisted of glandular or tubular structures situated in a desmoplastic stroma (HE staining, ×100); (d) The immunohistochemical staining with anti-CK19 antibody was very strong in the tumor cells, confirming the diagnosis (×100). MRI: Magnetic resonance imaging; HE: Hematoxylin–Eosin; CK19: Cytokeratin 19.***

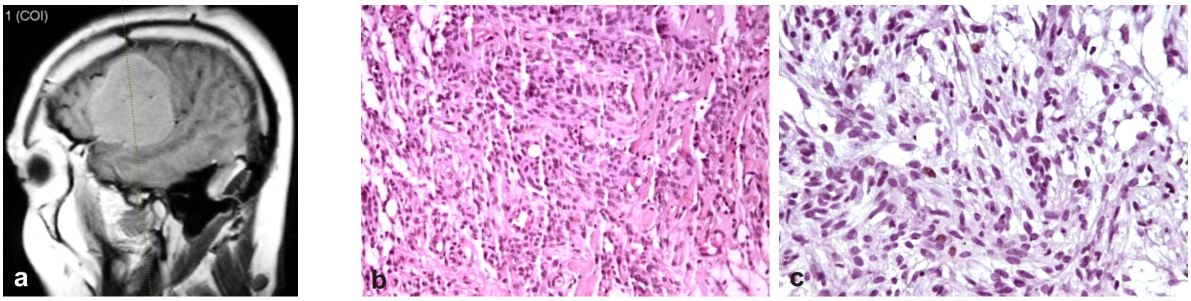

Figure 2 – ***Meningothelial meningioma, WHO grade I: (a) T1+C MRI sagittal view – extra-axial homogenous contrast-enhancement fronto-temporal lesion; (b) The tumor was made up of meningothelial cells, with a syncytium-like appearance – some hyaline bundles could be seen between tumor cells (HE staining, ×200); (c) The growth fraction as determined by the Ki67 proliferation index was 5% (Anti-Ki67 antibody immunostaining, ×200). WHO: World Health Organization; MRI: Magnetic resonance imaging; HE: Hematoxylin–Eosin.***

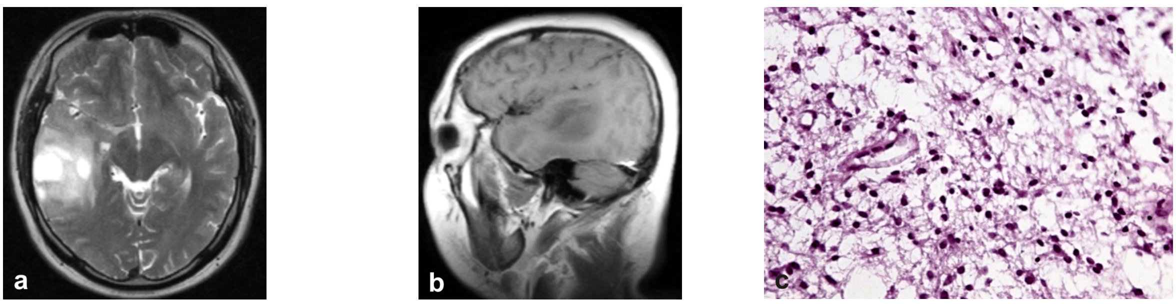

Figure 3 – ***Diffuse astrocytoma, WHO grade II: (a) T2 axial MRI view – right medio-temporal infiltrative mass with surrounding edema in a left-handed patient; (b) Sagittal T1+gadolinium view – hypo- to isointense lesion with no contrast enhancement; (c) Astrocytic tumor with an infiltrative, diffuse growth pattern – a fibrillary background could be seen; tumor nuclei presented moderately atypia as they were hyperchromatic and enlarged; tumor cells also presented variable amount of cytoplasm, mostly scant (HE staining, ×400). WHO: World Health Organization; MRI: Magnetic resonance imaging; HE: Hematoxylin–Eosin.***

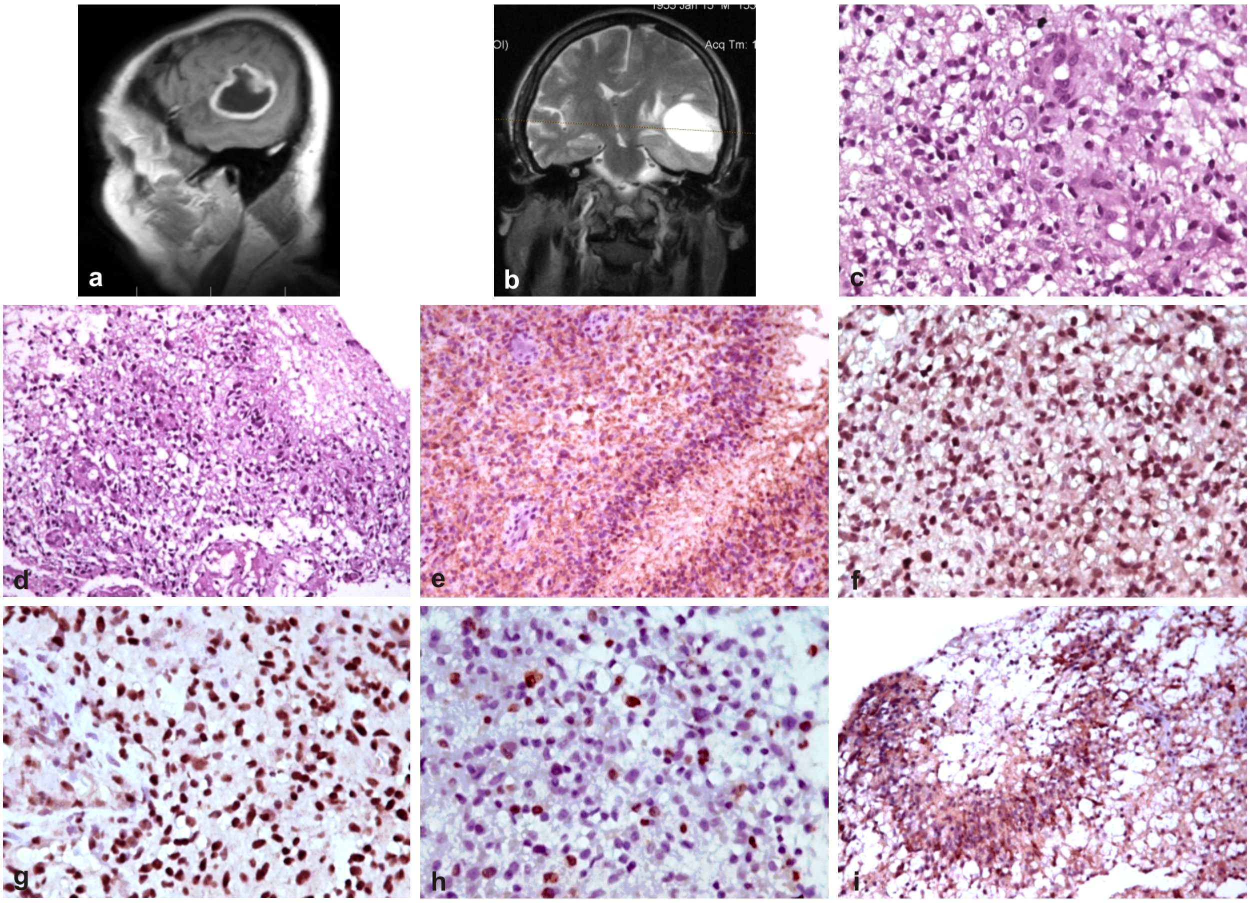

Figure 4 – ***Glioblastoma, WHO grade IV: (a) T1+C MRI sagittal view – left temporo-parietal lesion with peripheral irregular enhancement, nodular and cystic (central necrosis) components; (b) T2 MRI coronal view – edematogenic cystic left temporo-parietal lesion with mass effect, 7 mm midline shift; (c) Marked nuclear pleomorphism of the tumor cells, with a prominent atypical mitosis in the centre and endothelial proliferation of the intratumoral vessels (HE staining, ×200); (d) An area of necrosis with pseudopalisading of the tumor cells in its periphery (HE staining, ×200); (e) The tumor cells expressed strong immunopositivity for anti-GFAP antibody (×200); (f) The nuclei of the tumor cells expressed strong immunopositivity for anti-p53 antibody (×400); (g) The nuclei of the tumor cells expressed strong immunopositivity for anti-ATRX antibody (×400); (h) The growth fraction as determined by the Ki67 proliferation index was 5% (Anti-Ki67 antibody immunostaining, ×200); (i) Only tumor cells located around the necrotic foci expressed IDH1 – mutant type (Anti-IDH1 antibody immunostaining, ×200). WHO: World Health Organization; MRI: Magnetic resonance imaging; HE: Hematoxylin–Eosin; GFAP: Glial fibrillary acidic protein; ATRX: Adenosine triphosphate (ATP)-dependent helicase ATRX; IDH1: Isocitrate dehydrogenase 1.***

On the one hand, the preoperative neurocognitive evaluation showed that the most affected item was the ability of reading, almost all the patients, 39 (90.6%) of them presented some degree of aphasia. The next item quite altered was object naming, 27 (62.7%) patients having anomia. On the other hand, no impairment was the dominate result for spontaneous speech in 37 (86.04%) patients, praxis in 30 (69.7%) patients, executive function in 29 (67.4%) patients and word repetition in 27 (62.7%) patients (Figure 5).

The seven-day postoperative neurocognitive evaluation revealed amelioration for the reading tests in 20 (51.2%) patients from those affected preoperatively, for object naming in 18 (66.6%) patients, for executive function in 12 cases (85.7%) and for word repetition in 13 (81.2%) cases. Aggravation was observed in seven cases in reading task and in three cases in object naming task. More results are shown in Figure 6.

The one-month neurocognitive assessment showed a favorable evolution compared with the seventh day post-operative evaluation in 16 (42.1%) cases with aphasia and in 10 (33.3%) cases with anomia. Aggravation was found in four (22.6%) cases for executive function, praxis (28.5%) and spontaneous speech testing (9.3%). The details of the results are shown in Figure 7.

Preoperative results for memory consist in: 0 points – 12 patients; 1 point – 10 cases; 2 points – 13 cases; 3 points – seven cases; 4 points – one case; 5 points – 0 cases. The evaluation from seven-day postoperative reveals that 28 patients were stationary, seven had at least one point regression and eight had an increase in the final score. At one-month revaluation, the results showed: 19 cases – stationary, five cases – increase in scores, nine cases – decrease, and 10 cases had favorable evolution (increase in scores in stationary patients).

The most affected item was reading (90.6%). From all the patients with reading impairment, 19 had sensitive aphasia and 15 had motor aphasia. At seven-day post-operative, seven patients presented decrease in reading ability. Three cases with only episodes of motor aphasia at admission presented symptoms worsening, with true aphasia in two patients and mutism in one, but all of them remitted the symptoms at one-month evaluation. In two cases without language disturbance preoperatively, we observed, in the early postoperative period, transient speech worsening with episode of aphasia (one motor and one sensitive) which remitted after antiedematous treatment. Two patients with preoperative aphasia had speech worsening at seven days postoperative evaluation, with stationary evolution in one case and aggravation in the other.

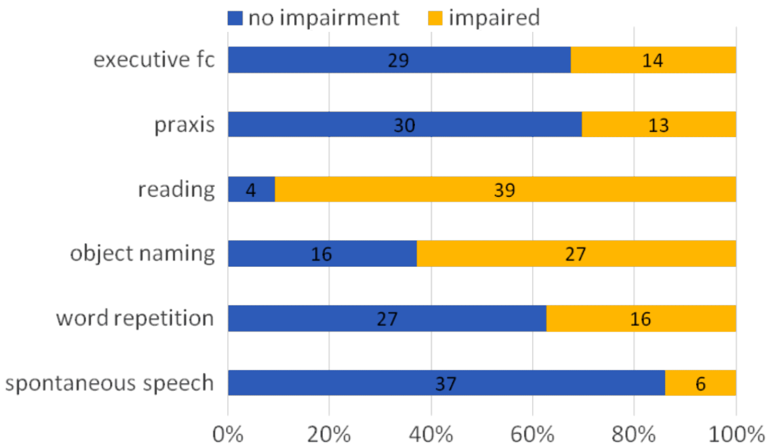

Figure 5 – ***Preoperative neurocognitive status: for every item tested is presented the number of patients with impaired/no impairment function found of them all. fc: Function.***

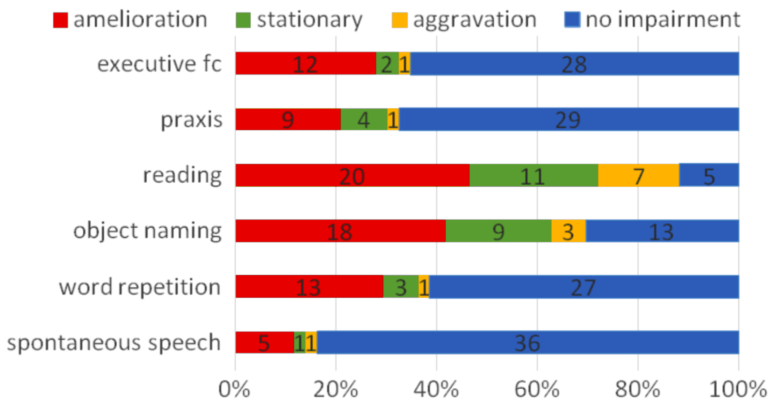

Figure 6 – ***Seven days postoperative neurocognitive evaluation results: for every item tested is presented the number of patients with different function evolution found of them all. fc: Function.***

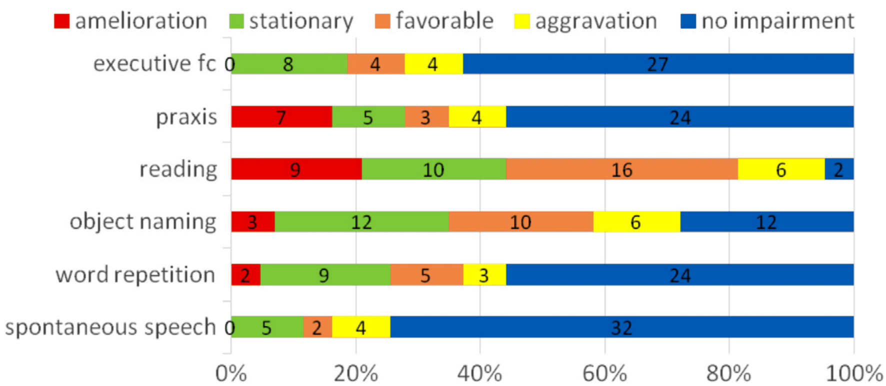

Figure 7 – ***One-month postoperative neurocognitive results: for every item tested is presented the number of patients with different function evolution found of them all. fc: Function.***

From all 43 participants, four of them were left-handed and the lesion was located on the right hemisphere (two in the frontal lobe and two in the temporal lobe). From all the cases, we performed seven awake craniotomies, in cases with no language disturbance or only slight dysfunction, which permitted intraoperative cooperation and evaluation. In two cases at the seven-day post-operative evaluation, we observed new neurocognitive dysfunction, with decrease in preoperative scores in two to three items. The deficit remitted at one-month assessment. The degree of resection was GTR in one and NTR in the other.

At admission, from all participants, 6.9% (four patients) were unimpaired across all measured items, 23.3% (10 patients) exhibited impaired performance in one task, 30.2% (13 patients) on two tasks, 11.6% (five patients) on three tasks, 9.3% (four patients) on four tasks, 9.3% on five tasks, 11.6% (five patients) on all tasks. A rate of impairment significantly higher on four or more items was observed in cases with GBs (23.3%; 10 patients) compared with LGGs (0%), meningioma (0%) and metastasis (6.9%; three patients).

At one-month follow-up evaluation, general decrease in neurocognitive function was observed in 20.93% cases (nine patients). From a HP point of view, these cases were eight GBs and one metastases of adenocarcinoma. The degree of resection in these cases was STR in five patients and NTR in four patients. Impairment on two tasks was noticed in four cases, on three tasks in two cases, on more than four in three cases. The MRI showed signs of increases of contrast-enhancement residual areas in GB cases at one-month postoperatively and the presence of the recurrence of metastases, which needed reintervention.

A favorable outcome, remission of symptoms and no impairment of items measurement at one-month post-operative evaluation was obtained in 14 patients (five cases – meningiomas, four cases – metastasis, three cases – LGGs, two cases – GBs), p=0.001 for spontaneous speech, word repetition, praxis, executive function, p=0.003 for object naming and p=0.028 for reading. Before surgery, these patients had: one item affected – 35.7% (five cases), two items – 28.5% (four cases), three items – 21.4% (three cases) and four or more items – 14.2% (two cases).

Discussions

Standardized tests for language evaluation were created for patients with stroke, to help their categorization inside one of the classical aphasic syndromes, one example being BDAE [13]. Although it was designed for cardiovascular disease, BDAE was largely used in the neurological assessment of brain tumor patients [14]. However, some important impairment in language skills, usually frequently found in those cases is not proper evaluated with conventional aphasia tests. One reason is that there are difference in the pathophysiological mechanisms responsible for language impairment, between infiltrative, slow growing, diffuse tumors and an acute event – *i.e.*, stroke – associated with sudden brain damage. Hence, the need for adapted and standardized battery of tests for tumor evaluation, capable and sufficiently sensitive to reveal even the slight dysfunctions [10, 15, 16].

We proposed a set of tests to evaluate the patients with brain tumors, especially those located in and near language areas, adapted for Romanian demographic population and culture. The items we used were adjusted and modified from BDAE and DO80 [17, 18]. For memory assessment, we used as a model Hopkins Verbal Learning Test [7, 19]. It is well known that the tumor location is related with specific, focal neurological impairment, but the presence of an intracranial process is associated with more diffuse and generalized neurocognitive dysfunctions reflected in memory and executive function impairment [20]. For this reason, we included in our study the evaluation of these tasks too.

In the literature, the rates of neurocognitive impairment vary in an interval between 12.5% to 91%, depending very much on the modality of evaluation [21]. Talacchi *et al.* found that, using test- and domain-based criteria, 79% and 38% of his patients were impaired [22]. Dwan *et al.* (2015) observed that 61–73% of participants were affected at a domain-specific test and 32–50% at a global level [7]. Sanai *et al.* (2008) reported 36.4% language-specific domain dysfunction [23]. The results from our study correspond with those found in the literature: more than half of them (90.6%) had dysfunction at test-specific analyses, with a dominance of those with just one item impaired (23.3%), compared with the patients how had all the items affected (11.6%).

Beside the overall view of tumor impact, neurocognitive evaluation with domain specific for language helps in recruiting and finding the most suitable candidates for awake craniotomy and for guiding the rehabilitation program. Nowadays, it is well known that the golden standard for lesions located in and near language area is awake craniotomy with neurophysiological intraoperative monitoring and some of the items from the preoperative evaluation are used for patient assessment in time of tumor resection. From our patients, 16.27% met this criterion. Further neurological deterioration was prevented by stopping the intervention when direct cortical and subcortical stimulation generates speech disturbance, even though the cavity borders were infiltrated with tumoral cells. In cases with incomplete resection, Duffau proposes multistage approach, meanwhile the neuroplasticity process comes into action and reshapes the eloquent cortex. This type of management it is sometime used in young patients with few clinical symptoms and a histological type correlated with relatively good survival rate [24]. These features corresponded with more than half of our selected patients, found in an age interval being between 20–35 years old and with a histological dominance of LGG. But also, it is well known that the extent of resection has an impact on the survival rate and progression free survival, in glioma patients [25, 26]. Thus, even supramarginal resection had been advocate in some cases, but to perform this approach in language area tumors, the risks of complication increases and the patient selection must be very accurate [27, 28].

One of the most used intraoperative tasks is picture naming in evaluation of language performance. This task assesses the phonological, semantic, lexical processing and articulating process. In our cases, the intraoperative testing was performed by a physiologist and it consisted of picture naming, number counting and spontaneous speech. Neurocognitive testing during resection and cortical/subcortical stimulation helps to perform the intervention that is tailored based on functional result, with the aim to preserve the eloquent areas and subcortical tracts, minimizing the risk of permanent neurological deficit [17, 29, 30].

The outcome after awake surgery reported by Sanai *et al.* was as follows: 77.6% – stationary, 14% – new speech deficit and 8.4% – worsened [23]. A review of the literature made by Duffau (2018) has shown that among all the studies, it was noted a relatively high rate of immediate postoperative worsening from 33% to 100%, but with no severe permanent deficits [31]. Although we had a small number of cases, we too register transient neurological deficit in two patients (motor aphasia with degradation in two and three items from the test battery) at day 2 and respectively day 4 after surgery, but with complete remission at one-month evaluation and even with increase in score result compared with the preoperative performance. These results show the significance of a good correlation between the preoperative neurocognitive evaluation, intraoperative patient's response and tumors characteristics.

Another important role of these evaluations and consequently surgical function preservation lays in the fact that it appears to be a relationship between QoL and neurocognitive integrity. This hypothesis was tested by

Moritz-Gasser *et al*. (2012), who reported that naming tests evaluation and especially the speed of the answer is significantly correlated with QoL, more precisely with the patient social reintegration, *i.e.*, his return to work [32]. Reduced autonomy, inability to accomplish daily activities and incapacity to perform his job may represent a greater disability than physical dysfunction [33]. The preoperative evaluation must represent a base for follow-up care. An impact of the overall neurocognitive functions, assessment it on patients' own capacity of decision-making on treatment options [34]. An evaluation on 103 gliomas with temporal location (both right and left) concluded that function independency is associated with the neurocognitive status (p<0.001) [35].

It seems that the histological type of the intracranial tumors has an important influence on the overall neurocognitive functions. For this reason, the preoperative differential diagnosis has great significance in order to distinguish between a brain tumor and a non-tumor lesion, such as Fahr's disease, which can manifest by episodes of grand mal seizures, just like a brain tumor [36].

However, high-grade and rapid-growing tumors were associated with more severe neurocognitive deterioration compared with low-grade, slow-progressing tumors. This is the cases and with our patients with LGG and meningioma, they had modification on 0–3 items, none of them exceeding dysfunction in more than three tasks. One plausible explanation is represented by the activation of neuroplasticity process, which appears in slow-developing lesions. As a result, the degree of impairment is lower because the compensatory mechanisms assume some parts of the disturbed function. It was shown that 90% of cases with brain metastases, enrolled in a randomized Phase III treatment, had at least one neurocognitive item affected [12, 37]. Half of our metastatic patients had four or even more items affected. A study realized on 82 cases of GB published by van Loenen *et al.* (2018) showed that more than 80% of them had impairment of at least one cognitive domain on the evaluation at preoperative time and after three months post-surgery. Although postoperative improvement was found that did not mean a returning to normal state [38]. It is clear that between our patients preoperative neurocognitive impairment were significantly higher in GB cases compared with the rest of the tumor types and unfortunately almost half of them were severely altered (four or more items).

The goal of tumor removal is to prevent further neurological deterioration and to improve the deficit already presented. The impact of surgery on neurocognitive function may be linked with an increase in task performance [39]. However, on the contrary, another postoperative outcome may manifest with performance decrease [40]. One explanation for the first situation is represented by reduction of peritumoral edema from tumor debulking with secondary decompression. This is showed in an article published by Meskal *et al.*, in 2014. The authors made a study on 68 meningiomas and observed that 69% of all revealed significant overall improvement [41]. The overall result of tumor resection in our patients had a good influence and was associated with statistical improvement in scores in more than half of them (reading p=0.028; object naming p=0.003 and p=0.001 for spontaneous speech, word repetition, praxis, executive function).

Knowing that different manifestations of neurological and functional impairment are an indicator of tumor location, it was postulated that a decline in neurocognitive score may be a predictor factor for tumor recurrence. Among the first to test this theory was Meyers & Brown (2006), which evaluate monthly 80 GB and anaplastic astrocytoma. Some function (memory recall, word recognition task) deterioration preceded the images of lesion relapse [42]. In our study, the one-month control MR images 20.9% of cases showed enlargement of residual and new contrast-enhancement area with diffuse, infiltrative and irregular aspects, suggestive for recurrence. Interestingly, all these patients presented with neurocognitive score decline and the histological type was GB (except one) how had NTR or STR, matching the literature reports. Obviously these tests will not replace the radiological explorations, but detecting subtle neurocognitive decline may help identifying the perfect timing for MRI evaluation and so a better adaptation of the adjuvant treatment [7, 43].

Our battery of test included, beside specific language tasks were executive function, praxis and memory assessment. Executive function evaluation in patients diagnosed with brain tumors, regardless of location, has a role in discovering the general effects of the lesion on neurocognitive performance. It involves the capacity of decision making, problem solving, intuition, organization, being connected with working memory and utilizes learnt skills in different situation. Praxis assessment may be linked with executive function because it consists in executing some movement (*i.e.*, ideomotor form), in which planning and executive functions are part of it [33, 44]. New studies found that executive function may be related to survival in GB patients. A poor performance was associated with a rate of survival of 17.1 weeks and a good performance it was a positive factor for survival in the first six postoperative months [45]. Likewise, in our study, a stationary or even decrease score in the postoperative was associated with bad prognosis in GB cases.

Memory plays a major role in maintaining the neurocognitive function. It is usually a frequent self-reported complain [46]. Different degrees of impairment are linked with compromised QoL; verbal memory playing an important role and is characterized by storage, encoding and recall of verbal information after it was presented [8, 47]. Santini *et al.* compared the preoperative and postoperative (three months) memory domain and found out a significant deterioration on verbal and working memory in a series of 22 left-hemisphere glioma operated awake [48]. In our study, at one-month evaluation, one fifth of the patients suffered a decrease in memory. This change was found in addition to other function impairment and the dominant histological tumor type of those cases was GB. On the contrary, half of the meningiomas and metastases showed an increase in the final score. And once again, we observed the link between the histological tumor type and degree of neurocognitive function impairment, not only those related to precise lesion location but also with general impact.

Conclusions

A baseline assessment of brain tumor cases is important for evaluation of preoperative status and the postoperative outcome concerning neurocognitive function and to adjust the surgical resection in order to, at least, maintains the admission scores. Hence, the necessity for standardized battery of test designed for those cases, as nowadays QoL has a significant role in patient's outcome. Although from a histological point of view our study had an unbalanced types of tumors, with clear dominance of GB, the results of our proposed battery of tests match the literature in which is shown the correlation between the tumor type and the degree of preoperative dysfunction, on the one hand, and on the other hand, with the rate of recovery of neurocognitive function in the postoperative period, a positive impact having on low-grade tumors and extra-axial lesions. This study emphasis the necessity of an adapted neurocognitive evaluation and opens new ways for further developments in language area tumors management.

Conflict of interests

The authors report no conflict of interests concerning the materials or methods used in this study or the findings specified in this paper.

References

[1] Costea CF, Anghel K, Dimitriu G, Dumitrescu GF, Faiyad Z, Dumitrescu AM, Sava A. Anatomoclinical aspects of conjunctival malignant metastatic melanoma. Rom J Morphol Embryol, 2014, 55(3):933–937.

[2] Turliuc MD, Sava A, Dumitrescu GF, Cucu A, Eşanu A, Tudorache C, Costache II, Costea CF. Right visual loss due to choroidal metastasis of a papillary adenocarcinoma of the lung: a case report. Rom J Morphol Embryol, 2015, 56(3): 1173–1177.

[3] Sava I, Sava A, Şapte E, Mihailov C, Dumitrescu G, Poeată I, Sava F, Haba D. Intraventricular metastatic clear cell renal carcinoma. Rom J Morphol Embryol, 2013, 54(2):447–450.

[4] Cucu AI, Costea CF, Carauleanu A, Dumitrescu GF, Sava A, Scripcariu IS, Costan VV, Turliuc S, Poeata I, Turliuc DM. Meningiomas related to the Chernobyl irradiation disaster in north-eastern Romania between 1990 and 2015. Rev Chim (Bucharest), 2018, 69(6):1562–1565.

[5] Bondari S, Bondari D, Pîrşcoveanu M, Moroşanu DV, Muşetescu AE, Tudorică V, Pîrşcoveanu DFV. Study on cognitive decline in patients diagnosed with brain tumors. Rom J Morphol Embryol, 2017, 58(4):1185–1192.

[6] Dhandapani M, Gupta S, Mohanty M, Gupta SK, Dhandapani S. Trends in cognitive dysfunction following surgery for intracranial tumors. Surg Neurol Int, 2016, 7(Suppl 7):S190–S195.

[7] Dwan TM, Ownsworth T, Chambers S, Walker DG, Shum DHK. Neuropsychological assessment of individuals with brain tumor: comparison of approaches used in the classification of impairment. Front Oncol, 2015, 5:56.

[8] Veretennikoff K, Walker D, Biggs V, Robinson G. Changes in cognition and decision making capacity following brain tumour resection: illustrated with two cases. Brain Sci, 2017, 7(10): 122.

[9] Georgiu C, Mihuţ E, Raus I, Mirescu ŞC, Szabo L, Şovrea AS. Pediatric glioblastoma with giant cells and "supratentorial" primitive neuroectodermal component – case report and review of the literature. Rom J Morphol Embryol, 2015, 56(3):1165–1171.

[10] Papagno C, Casarotti A, Comi A, Gallucci M, Riva M, Bello L. Measuring clinical outcomes in neuro-oncology. A battery to evaluate low-grade gliomas (LGG). J Neurooncol, 2012, 108(2):269–275.

[11] De Witte E, Satoer D, Robert E, Colle H, Verheyen S, Visch-Brink E, Mariën P. The Dutch Linguistic Intraoperative Protocol: a valid linguistic approach to awake brain surgery. Brain Lang, 2015, 140:35–48.

[12] Faulkner JW, Wilshire CE, Parker AJ, Cunningham K. An evaluation of language in brain tumor patients using a new cognitively motivated testing protocol. Neuropsychology, 2017, 31(6):648–665.

[13] Rohde A, Worrall L, Godecke E, O'Halloran R, Farrell A, Massey M. Diagnosis of aphasia in stroke populations: a systematic review of language tests. PLoS One, 2018, 13(3):e0194143.

[14] Duffau H, Gatignol P, Moritz-Gasser S, Mandonnet E. Is the left uncinate fasciculus essential for language? A cerebral stimulation study. J Neurol, 2009, 256(3):382–389.

[15] Mogoantă L, Pirici D, Pop OT, Bălşeanu AT, Rolea E, Dahnovici RM. Study of vascular microdensity in areas of cerebral ischemia on experimental model. Rom J Morphol Embryol, 2010, 51(4):725–731.

[16] Grosu F, Ungureanu A, Bianchi E, Moscu B, Coldea L, Stupariu AL, Pirici I, Roman-Filip CC. Multifocal and multicentric low-grade oligoastrocytoma in a young patient. Rom J Morphol Embryol, 2017, 58(1):207–210.

[17] Migliaccio R, Boutet C, Valabregue R, Ferrieux S, Nogues M, Lehéricy S, Dormont D, Levy R, Dubois B, Teichmann M. The brain network of naming: a lesson from primary progressive aphasia. PLoS One, 2016, 11(2):e0148707.

[18] Pineda DA, Rosselli M, Ardila A, Mejia SE, Romero MG, Perez C. The Boston Diagnostic Aphasia Examination – Spanish version: the influence of demographic variables. J Int Neuropsychol Soc, 2000, 6(7):802–814.

[19] Lahti J, Saunamäki T, Salo J, Niemelä A, Jehkonen M. Cognitive impairment and in meningiomas and low-grade gliomas. J Behav Brain Sci, 2018, 8(8):473–484.

[20] Chang WH, Pei YC, Wei KC, Chao YP, Chen MH, Yeh HA, Jaw FS, Chen PY. Intraoperative linguistic performance during awake brain surgery predicts postoperative linguistic deficits. J Neurooncol, 2018, 139(1):215–223.

[21] Tucha O, Smely C, Preier M, Lange KW. Cognitive deficits before treatment among patients with brain tumors. Neurosurgery, 2000, 47(2):324–333; discussion 333–334.

[22] Talacchi A, Santini B, Savazzi S, Gerosa M. Cognitive effects of tumour and surgical treatment in glioma patients. J Neurooncol, 2011, 103(3):541–549.

[23] Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. N Engl J Med, 2008, 358(1):18–27.

[24] Robles SG, Gatignol P, Lehéricy S, Duffau H. Long-term brain plasticity allowing a multistage surgical approach to World Health Organization grade II gliomas in eloquent areas. J Neurosurg, 2008, 109(4):615–624.

[25] Jakola AS, Skjulsvik AJ, Myrmel KS, Sjåvik K, Unsgård G, Torp SH, Aaberg K, Berg T, Dai HY, Johnsen K, Kloster R, Solheim O. Surgical resection *versus* watchful waiting in low-grade gliomas. Ann Oncol, 2017, 28(8):1942–1948.

[26] Roelz R, Strohmaier D, Jabbarli R, Kraeutle R, Egger K, Coenen VA, Weyerbrock A, Reinacher PC. Residual tumor volume as best outcome predictor in low grade glioma – a nine-years near-randomized survey of surgery *vs.* biopsy. Sci Rep, 2016, 6:32286.

[27] Duffau H. A new philosophy in surgery for diffuse low-grade glioma (DLGG): oncological and functional outcomes. Neurochirurgie, 2013, 59(1):2–8.

[28] Gerritsen JKW, Arends L, Klimek M, Dirven CMF, Vincent AJPE. Impact of intraoperative stimulation mapping on high-grade glioma surgery outcome: a meta-analysis. Acta Neurochir (Wien), 2019, 161(1):99–107.

[29] Leal RTM, Barcellos BM, Landeiro JA. Technical aspects of awake craniotomy with mapping for brain tumors in a limited resource setting. World Neurosurg, 2018, 113:67–72.

[30] Sanai N, Berger MS. Extent of resection influences outcomes for patients with gliomas. Rev Neurol (Paris), 2011, 167(10): 648–654.

[31] Duffau H. Is non-awake surgery for supratentorial adult low-grade glioma treatment still feasible? Neurosurg Rev, 2018, 41(1):133–139.

[32] Moritz-Gasser S, Herbet G, Maldonado IL, Duffau H. Lexical access speed is significantly correlated with the return to professional activities after awake surgery for low-grade gliomas. J Neurooncol, 2012, 107(3):633–641.

[33] Back M, Back E, Kastelan M, Wheeler H. Cognitive deficits in primary brain tumours: a framework for management and rehabilitation. J Cancer Ther, 2014, 5(1):74–81.

[34] Flechl B, Sax C, Ackerl M, Crevenna R, Woehrer A, Hainfellner J, Preusser M, Widhalm G, Kiesel B, Lütgendorf-

Caucig C, Dieckmann K, Steffal C, Marosi C, Hassler MR. The course of quality of life and neurocognition in newly diagnosed patients with glioblastoma. Radiother Oncol, 2017, 125(2):228–233.
[35] Noll KR, Bradshaw ME, Weinberg SJ, Wefel JS. Neurocognitive functioning is associated with functional independence in newly diagnosed patients with temporal lobe glioma. Neurooncol Pract, 2018, 5(3):184–193.
[36] Sava A, Dumitrescu G, Haba D, Hodorog D, Mihailov C, Şapte E. The Fahr syndrome and the chronic lymphocytic thyroiditis. Rom J Morphol Embryol, 2013, 54(1):195–200.
[37] Talacchi A, d'Avella D, Denaro L, Santini B, Meneghelli P, Savazzi S, Gerosa M. Cognitive outcome as part and parcel of clinical outcome in brain tumor surgery. J Neurooncol, 2012, 108(2):327–332.
[38] van Loenen IS, Rijnen SJM, Bruijn J, Rutten GJM, Gehring K, Sitskoorn MM. Group changes in cognitive performance after surgery mask changes in individual patients with glioblastoma. World Neurosurg, 2018, 117:e172–e179.
[39] Barzilai O, Ben Moshe S, Sitt R, Sela G, Shofty B, Ram Z. Improvement in cognitive function after surgery for low-grade glioma. J Neurosurg, 2018, 1:1–9.
[40] Charras P, Herbet G, Deverdun J, de Champfleur NM, Duffau H, Bartolomeo P, Bonnetblanc F. Functional reorganization of the attentional networks in low-grade glioma patients: a longitudinal study. Cortex, 2015, 63:27–41.
[41] Meskal I, Gehring K, van der Linden SD, Rutten GJM, Sitskoorn MM. Cognitive improvement in meningioma patients after surgery: clinical relevance of computerized testing. J Neurooncol, 2015, 121(3):617–625.
[42] Meyers CA, Brown PD. Role and relevance of neurocognitive assessment in clinical trials of patients with CNS tumors. J Clin Oncol, 2006, 24(8):1305–1309.
[43] Armstrong CL, Goldstein B, Shera D, Ledakis GE, Tallent EM. The predictive value of longitudinal neuropsychologic assessment in the early detection of brain tumor recurrence. Cancer, 2003, 97(3):649–656.
[44] Johnson DR, Sawyer AM, Meyers CA, O'Neill BP, Wefel JS. Early measures of cognitive function predict survival in patients with newly diagnosed glioblastoma. Neuro Oncol, 2012, 14(6):808–816.
[45] Lee ST, Park CK, Kim JW, Park MJ, Lee H, Lim JA, Choi SH, Kim TM, Lee SH, Park SH, Kim IH, Lee KM. Early cognitive function tests predict early progression in glioblastoma. Neurooncol Pract, 2015, 2(3):137–143.
[46] Pranckeviciene A, Deltuva VP, Tamasauskas A, Bunevicius A. Association between psychological distress, subjective cognitive complaints and objective neuropsychological functioning in brain tumor patients. Clin Neurol Neurosurg, 2017, 163:18–23.
[47] Cheng H, Chen H, Lv Y, Chen Z, Li CSR. Prospective memory impairment following whole brain radiotherapy in patients with metastatic brain cancer. Cancer Med, 2018, 7(10):5315–5321.
[48] Santini B, Talacchi A, Squintani G, Casagrande F, Capasso R, Miceli G. Cognitive outcome after awake surgery for tumors in language areas. J Neurooncol, 2012, 108(2):319–326.

Corresponding authors
Roxana Şerban, MD, PhD Student, Department of Pathophysiology, "Grigore T. Popa" University of Medicine and Pharmacy, 16 Universităţii Street, 700115 Iaşi, Iaşi County, Romania; Phone +40726–194 420, e-mail: roxana_serban10@yahoo.com

Mihaela Coşman, MD, PhD Student, Department of Neurosurgery, "Grigore T. Popa" University of Medicine and Pharmacy, 16 Universităţii Street, 700115 Iaşi, Iaşi County, Romania; Phone +40749–147 194, e-mail: mihaelacosman@yahoo.com

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