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Study on cognitive decline in patients diagnosed with brain tumors

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Abstract

Aim: The purpose of our study was to assess the cognitive performance in patients with primitive brain tumors and to analyze the cognitive status of these patients, correlated with histological type of brain tumors. *Patients, Materials and Methods*: The study enrolled 52 patients diagnosed with primitive brain tumors, hospitalized in Neuropsychiatry Hospital of Craiova, Romania, from December 2013 to December 2015. According to the histological type of tumors, the patients were classified into three groups: Group A included 22 patients with meningioma, Group B composed of 16 patients diagnosed with glioblastoma, and Group C including 14 patients diagnosed with diffuse astrocytoma. Neurological examination, neuroimaging assessment [computed tomography (CT) or magnetic resonance imaging (MRI) for skulls] to diagnose primitive brain tumors, then the confirmation of clinical and histopathological diagnoses were performed for these patients. For cognitive assessment performed before surgery, Montreal Cognitive Assessment (MoCA) and Cambridge Cognitive Examination (CAMCOG) scales were used. The results were statistically analyzed using the Student's *t*-test; *p*-values less than 0.05 were considered statistically significant. *Results*: In terms of age, we did not observe statistically significant differences between the three groups of patients. The group of patients with diffuse astrocytoma presented a higher educational level compared to patients with glioblastoma or meningioma. MoCA score obtained in glioblastoma group was 21.7 points, while in the group of patients with diffuse astrocytoma was 23.5 points, and in the group of patients with meningioma 24.2 points. The cognitive assessment using CAMCOG scale led to the following results: group of patients diagnosed with glioblastoma showed an average score of 83.5 points, the diffuse astrocytoma group had an average score of 88.9 points and the group with meningioma an average score of 90.1 points. *Conclusions*: Patients diagnosed with glioblastoma showed a statistically significant cognitive decline in comparison to patients diagnosed with diffuse astrocytoma ($p<0.05$). We did not notice statistically significant differences in the cognitive decline of patients with meningioma compared to those diagnosed with diffuse astrocytoma ($p>0.05$).

Keywords: cognitive decline, meningioma, astrocytoma, glioblastoma.

Introduction

Primary central nervous system tumors represent a heterogeneous group of neoplasms characterized by a wide diversity of clinical features and ways of evolution [1, 2].

The annual global age-standardized incidence of primary malignant brain tumors is 3.7 per 100 000 for males and 2.6 per 100 000 for females [3–5].

Rates appear to be higher more developed countries (males 5.8 and females 4.1 per 100 000) than in less developed countries (males 3 and females 2.1 per 100 000) [5].

Males also generally have higher rates of primary malignant brain tumors, while females have higher rates of non-malignant tumors, primarily meningiomas [4].

Worldwide age standardized mortality for primary malignant brain tumors is 2.8 for males and 2 for females per 100 000 [3].

The mortality is higher in more developed countries (4.1 and 2.7 per 100 000 for males and for females, respectively). The survival rates differ significantly by histology and age. For example, glioblastoma multiforme has a five-year survival rate of 3.3%, while lower grade gliomas, such as pilocytic astrocytoma, oligodendroglioma and ependymoma have a five-year survival rates of over 70%, while astrocytoma, malignant glioma and lymphoma have a five-year survival rates less than 40% [6].

Overall, five-year survival rates decrease with age.

Caucasians had a five-year relative survival of 33.5%, while African-Americans had a five-year relative survival rate of 37% [6].

Regarding the clinical picture of primitive brain tumors, cognitive impairment is one of the major neurological problems of these patients [7, 8]. Cognitive disorder can be caused either by the tumor itself, or brain swelling around the tumor [9]. Tumor spectrum is broad, including glial tumors (astrocytoma, glioblastoma), oligodendroglioma, ependymoma, primitive neuroectodermal tumors, etc. [10, 11].

As is known, cognitive performance is influenced by factors related to the patient and tumor-related factors, but we still do not know precisely the nature of their interaction [12–14].

The purpose of our study was to assess the cognitive decline in patients with primitive brain tumors previously surgery and to analyze the severity of cognitive decline according to tumor histology.

Patients, Materials and Methods

In this study, we included 52 patients (22 men and 30 women) aged 17–78 years, and the educational level of between five and 18 years of education. They were diagnosed with primitive brain tumors and hospitalized in Neuropsychiatry Hospital of Craiova, Romania, during December 2013–December 2015.

Depending on the histopathological type of tumor, the patients were classified into three groups: Group A comprising 22 patients diagnosed with meningioma, Group B including 16 patients diagnosed with glioblastoma, and Group C with 14 patients diagnosed with diffuse astrocytoma. Exclusion criteria for the study were the comatose patients with language disorders, patients with secondary brain determinations.

Patients were analyzed by age, area of origin, gender, educational level and last but not least, by histopathological type of tumor.

The patients of our study were subjected to surgery with total or partial resection of the tumor in "Bagdasar–Arseni" Hospital, Bucharest, Romania. Brain tumors were defined as tumor of the brain indicated by clinical features and computed tomography (CT) or magnetic resonance imaging (MRI) examination and histopatologically verified after surgery.

Although MRI has distinct advantages over CT scan, contrast-enhanced CT scan is still used as the imaging modality for the evaluation of intra-axial mass lesions. The sensitivity of contrast-enhanced CT scan is 65–100% and the specificity is 72–100% [15].

The histopathology grading was performed according with the most recent *World Health Organization* (WHO) Classification [3, 4].

The tissue fragments were fixed in 10% formalin and processed by standard histological techniques based on Hematoxylin and Eosin (H-E) staining. Single immunohistochemistry (IHC) was performed on consecutive seriate sections with anti-glial fibrillary acidic protein (GFAP) antibody (rabbit anti-human, Z0334 clone, 1:30 000 dilution, Dako), anti-epithelial membrane antigen (EMA) antibody (mouse anti-human, M0725 clone, 1:100 dilution, Dako), and anti-S100 (rabbit anti-human, Z0311 clone, 1:500 dilution, Dako).

Briefly, after microwaving in citrate buffer for 21 minutes as antigen retrieval, endogenous peroxidase was blocked in 1% water peroxide, and unspecific binding sites were blocked in 1% skimmed milk (Biorad). The sections were next incubated with the primary antibody for 18 hours at 4°C, and the next day the signal was amplified for 30 minutes utilizing a specific peroxidase polymer-based system (Nikirei-Bioscience, Tokyo, Japan). The signal was finally detected with 3,3'-diaminobenzidine (DAB) (Dako, Glostrup, Denmark) and the slides were coverslipped in DPX (Sigma-Aldrich, St. Louis, MO, USA) after a H-E staining. We evaluated the proliferative activity by the Ki67 immunoreactivity (MIB-1 clone, 1:10 dilution, 30 minutes incubation time, at room temperature). The tissue sections were previously subjected to microwave antigen unmasking in citrate buffer. Ki67 labeling index was defined as the percentage of Ki67-positive nuclei for 10 high-power fields (HPFs) (×400), counting at least 500 tumor cells per cross-section.

Cognitive status of patients was assessed using the Montreal Cognitive Assessment (MoCA) scale and the Cambridge Cognitive Examination (CAMCOG) scale is making this assessment prior neurosurgical intervention.

We compared the results obtained from the three study groups, and also watched from the cognitive domains assessed showed significant damage depending on the type of tumor histopathology.

The results were statistically analyzed using Student's *t*-test; *p*-values less than 0.05 were considered statistically significant.

Results

Depending on the patient's gender, we observed that the percentage of women (57.69%) was higher than that of men (42.3%), the difference between the two genders being not statistically significant ($p>0.05$). The average educational level of the patients studied was 9.1±4.5 years.

Regarding the average age of patients included in the study, it was 50.04 years (between 17 and 78 years). We noticed a growth rate of diagnosis after age of 40, the maximum being reached in the age range between 50 and 70 years (Table 1).

Table 1 – ***Distribution of patients by age***

Age range	17–29 years	30–39 years	40–49 years	50–70 years	70–78 years
No. of patients (n%)	5 (9.615%)	5 (9.615%)	12 (23.077%)	21 (40.385%)	9 (17.308%)

Histopathological analysis reporting the appearance of tumors, the results showed that 22 (42.31%) patients had meningioma, 16 (30.77%) patients had glioblastoma, and 14 (26.92%) patients had diffuse astrocytoma (Figure 1).

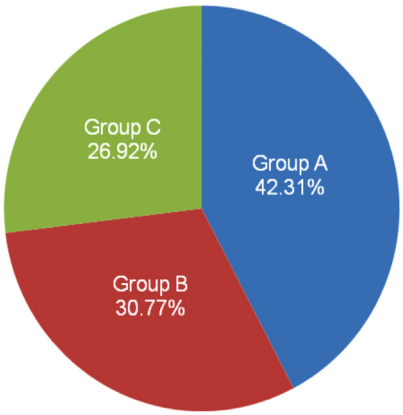

Figure 1 – ***Distribution of patients depending on the type of tumor histopathology.***

Evaluation of patients in Group A, those diagnosed with meningioma, led to the following results: a greater number of women presenting meningioma (12, 54.54%), compared with men (10, 45.45%). The average age of patients diagnosed with meningioma was 45±12 years, 59% of them coming from rural area. Patients diagnosed with meningioma had an average educational level of 10.24 years.

In Group B (patients diagnosed with glioblastoma), we also noticed that the number of women was higher (nine, 56.25%), when compared to men (seven, 43.75%). The mean age of patients in Group B was 46.23±10 years, 56% of them coming from rural area. The average educational level of these patients was 10.01 years.

In Group C (patients diagnosed with diffuse astrocytomas), we noticed eight women (57.14%), compared to six men (42.85%). The average age of patients diagnosed with diffuse astrocytoma was 48.5±8 years, 52% of them coming from rural area. The average educational level was 11.02 years.

Statistical analysis of the data obtained in the three groups did not show statistically significant differences in terms of age or educational level (Figures 2 and 3).

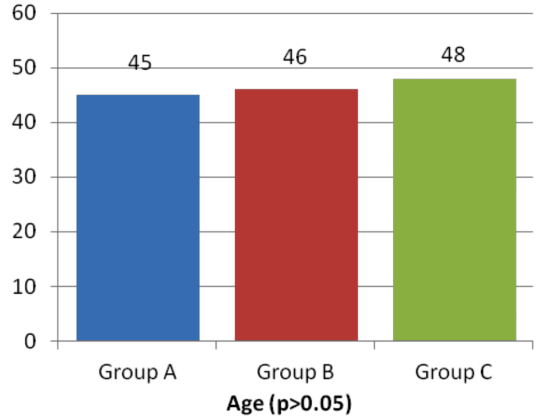

Figure 2 – ***Statistical analysis of the age in the three groups of patients.***

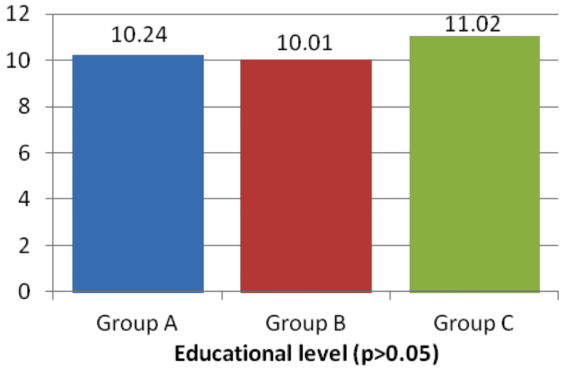

Figure 3 – ***Statistical analysis of the educational level in the three groups of patients.***

Cognitive assessment in the three study groups showed the following results: MoCA score in the group of patients with meningioma was 24.2 points, in the group of patients with glioblastoma was 21.7 points, and in the group of patients with diffuse astrocytoma 23.5 points (Figure 4).

CAMCOG assessment scale showed the following results: meningioma patients had a score of 90.1 points, 83.5 points for those diagnosed with glioblastoma, and those suffering from diffuse astrocytoma had 88.9 points (Figure 5).

Figures 6 and 7 show CT features in some of our patients. In both of these two cases, their final diagnosis was diffuse astrocytoma (WHO grade II). Tumor components consisting of diffusely growing malignant astrocytoma is difficult or impossible to delineate by CT. Necrotic areas within the tumors were accurately outlined by post-contrast CT but growth of diffuse astrocytoma or the presence of astrocytic gliosis within this edematous area seems difficult to evaluate by current CT techniques. In the first frame of Figure 6, we observe a hyperdense mass in the left temporal region and in the second frame, there is an after contrast image showing the homogeneous enhancement of the mass. Figure 7 contains a right parietal region of low density with mass effect, without calcification or hemorrhage, also representing an image who finally was diagnosed as a diffuse astrocytoma. MRI increased the sensitivity and specificity in imaging astrocytomas, as we observe in Figure 8, showing a right occipital mass with central necrosis and intense surrounding enhancement in T1+Gado (Gadolinium).

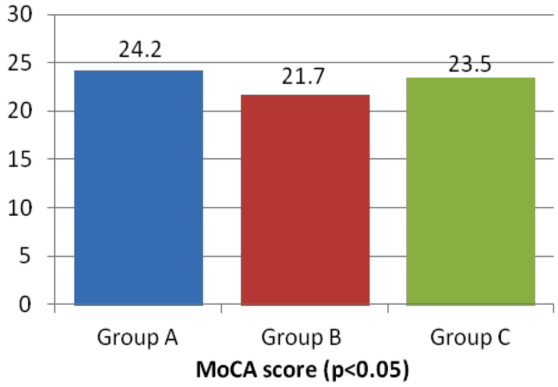

Figure 4 – ***Assessment of the cognitive status using MoCA scale. MoCA: Montreal Cognitive Assessment.***

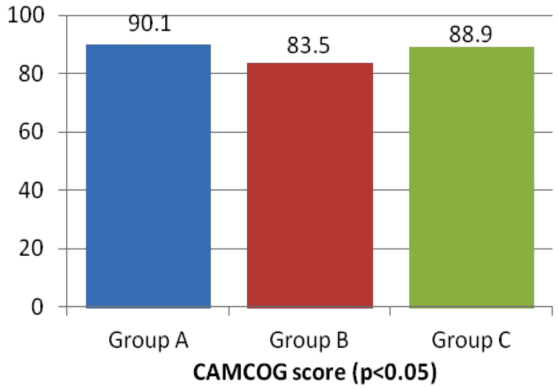

Figure 5 – ***Assessment of the cognitive status using CAMCOG scale. CAMCOG: Cambridge Cognitive Examination.***

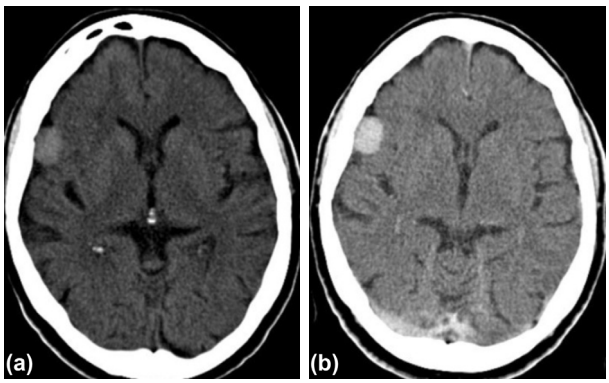

Figure 6 – ***(a) CT scan hyperdense mass in the left temporal region; (b) After contrast, there is an homogeneous enhancement of the mass. CT: Computed tomography.***

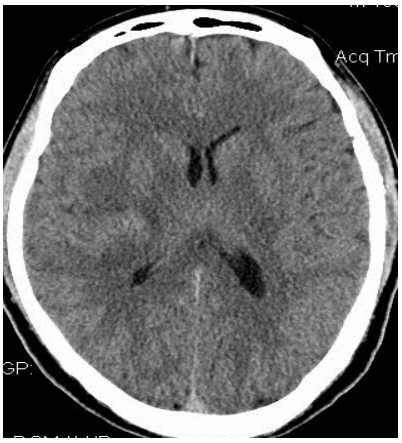

Figure 7 – ***CT scan. A right parietal region of low density is present with mass effect, without calcification or hemorrhage. A small curvilinear region of increased density is noted, which is of uncertain significance. The final diagnosis was diffuse astrocytoma (WHO grade II). CT: Computed tomography.***

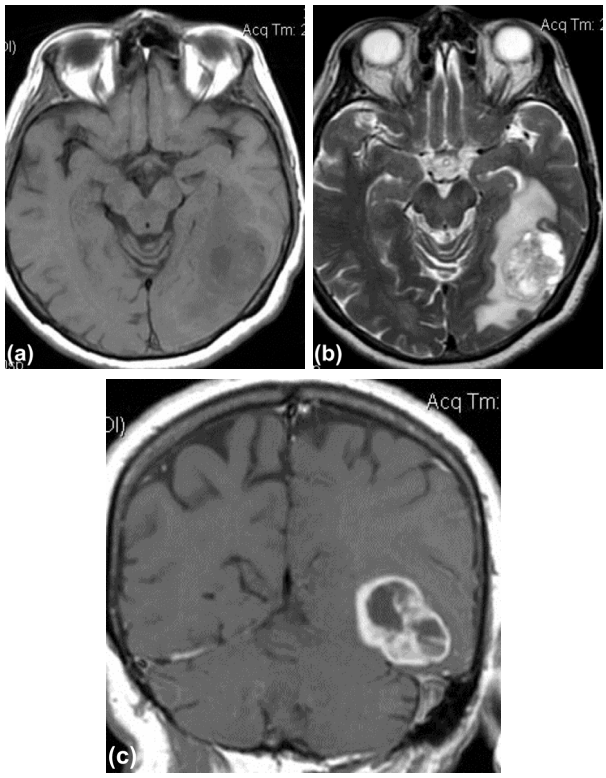

Figure 8 – ***MRI shows a right occipital mass with central necrosis [(a) T1W; (b) T2W] and intense surrounding enhancement in T1+Gado (c). MRI: Magnetic resonance imaging; W: Weighted; Gado: Gadolinium.***

In Group A, consisted of 22 patients with meningioma, 14 of them had WHO grade I and eight of them had WHO grade II. Ten of these patients were diagnosed with meningothelial meningioma, with meningothelial cells wrapped around small blood vessels, a very important vascular component of this tumor. We observed in their tumor areas lobules of cells separated by thin strands of collagen, with uniform and oval nuclei, showing on occasion central clearing. We also found at these tumors avacuolation of the cytoplasm. Eight patients of the Group A had the tumors composed of spindle cells with indistinct cell boundaries, an architecture without lobules or classic meningothelial whorls. Four of the patients diagnosed with meningioma showed tumoral cells with elongated processes, without myxoid background. They presented variable pleomorphism. We did not observe cords/trabeculae or inflammatory infiltrate (Figures 9–12).

In Group B, including 16 patients diagnosed with glioblastoma, both intra- and inter-tumoral histological appearance was highly variable. In these tumors, we observed fibrillary astrocytes and also endothelial vascular proliferation. Four of these patients had glioblastomas composed almost entirely of large cells, often with prominent nucleoli. In six patients of the Group B, we found pseudopalisading necrosis, with tumor cells oriented in a perpendicular fashion. In some areas of pseudopalisading necrosis, we observed the presence of surrounding vessels exhibiting profound tortuosities and multiple lumina.

Group C, including 14 patients with diffuse astrocytoma, showed a modest hypercellularity, nuclear polymorphism, increased intercellular edema and small microcysts. In the sections greater than 1×1 cm, the cellular density was uniform with little variation between gray and white matter. Most of the tumors from the Group C had astrocytic tumor cell cytoplasm elongated, located trailing away from the nucleus, resulting in a unipolar appearance. In the intercellular spaces, we found abundant eosinophilic fibrillary cytoplasm, with compact pattern.

MoCA and CAMCOG assessment scales showed that over 85% of patients with primitive brain tumors had at least one affected cognitive domain. Patients with meningioma had affected especially visual-spatial skills. Patient's memory and skills of Group B, diagnosed with glioblastoma, showed a significant impairment of memory, attention and executive functions. Patients diagnosed with diffuse astrocytoma have deficiencies, especially in terms of attention, orientation and memory (Table 2).

Table 2 – ***The cognitive domains affected in the three groups of patients***

Cognitive domain	Group A *N*=22 (*n*%)	Group B *N*=16 (*n*%)	Group C *N*=14 (*n*%)
Attention	16 (72.72%)	12 (75%)	12 (85.71%)
Executive functions	10 (45.45%)	10 (62.5%)	8 (57.14%)
Language	11 (50%)	8 (50%)	7 (50%)
Visual-spatial skills	16 (72.72%)	9 (56.25%)	10 (71.42%)
The memory	18 (81.81%)	12 (75%)	12 (85.71%)
Calculation	12 (54.54%)	8 (50%)	10 (71.42%)
Concentration	10 (45.45%)	7 (43.75%)	8 (57.14%)
Orientation	9 (40.9%)	7 (43.75%)	11 (78.57%)

Discussion

A great number of studies have focused their attention towards cognitive decline in patients diagnosed with brain tumors. Cognitive impairment is the most common neurological problem associated with brain tumors. Cognitive functioning of patients with brain tumors is an important outcome measure, because of the impact on quality of life. Treatment of primary brain tumors using surgery, radiotherapy or chemotherapy impaired cognitive function, too.

Cognitive function is now recognized as an independent prognostic factor in the survival of these patients. Also, the cognitive decline can be the first indicator of the progressive disease after treatment. Some studies showed that radiotherapy in brain tumors is the main cause of cognitive decline [16]. This decline is recognized as the most frequent complication among long-term survivors [17].

During our study, we watched the cognitive assessment of patients diagnosed with primitive brain tumors and the correlation of their cognitive status with histopathological type of tumor.

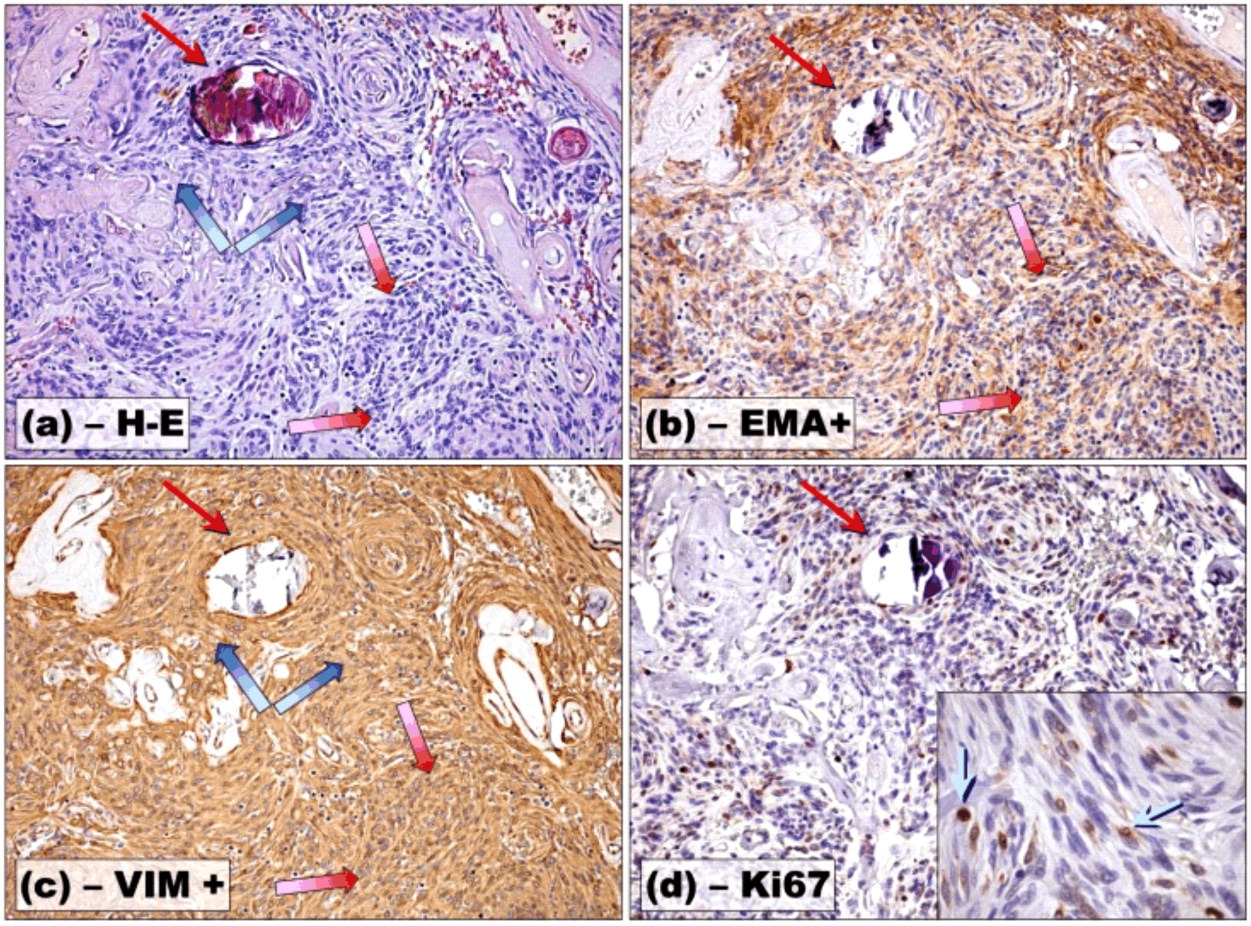

Figure 9 – ***Transitional (mixed) meningioma: (a–d) Areas with uniform lobules made by uniform tumor cells and surrounded by thin collagenous septae (thick red arrows) and areas with intersecting fascicles of spindle-shaped cells resembling fibroblasts, embedded in a collagen-rich and reticulin-rich matrix (thick blue arrows); (a–d) Psammoma bodies (thin red arrows). (a) H-E staining, ×100; (b) Tumoral cells positive for EMA (Immunomarking with anti-EMA antibody, ×100); (c) Tumoral cells positive for VIM (Immunomarking with anti-VIM antibody, ×100); (d) Ki67 proliferative index 10.3% (thin blue arrows) (Immunomarking with anti-Ki67 antibody, ×100; inset, ×400). H-E: Hematoxylin and Eosin; EMA: Epithelial membrane antigen; VIM: Vimentin.***

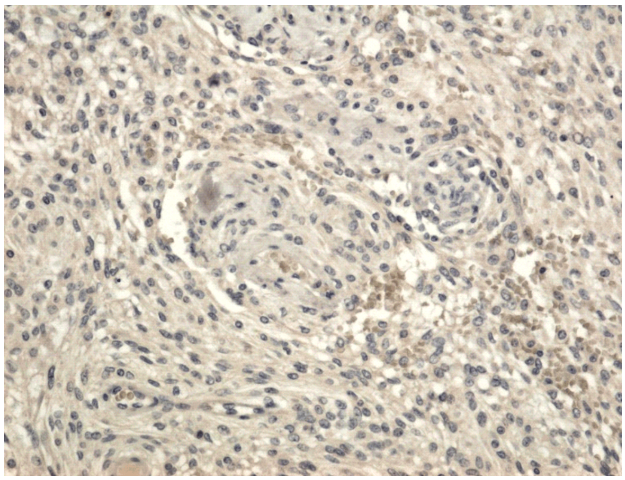

Figure 10 – ***Meningioma, tumoral cells are negative for GFAP (Anti-GFAP antibody immunostaining, ×200). GFAP: Glial fibrillary acidic protein.***

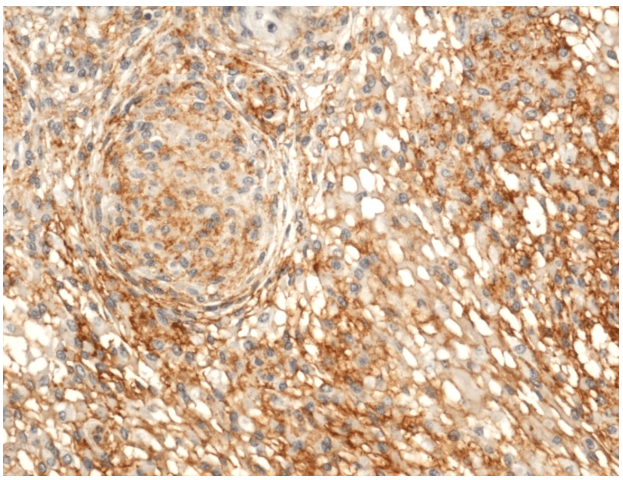

Figure 11 – ***Meningioma, strong immunoreactivity for EMA (Anti-EMA antibody immunostaining, ×200). EMA: Epithelial membrane antigen.***

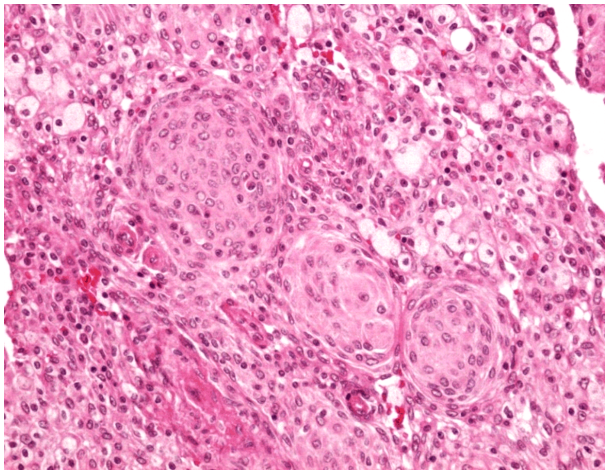

Figure 12 – ***Tumoral areas of meningioma, with relatively uniform cells, with a tendency to form psammomatous bodies (H-E staining, ×200). H-E: Hematoxylin and Eosin.***

MoCA is a cognitive assessment test in which the maximum score that can be obtained is 30 points. It rates attention, concentration, orientation and visual-spatial abilities. A MoCA score more than 26 points is considered normal [18].

CAMCOG is a cognitive scale that assesses multiple cognitive domains: attention, memory, language, praxia, orientation and perception. The maximum score that can be obtained from a subject with normal cognitive status is 105 points. As the score decreases reveals a cognitive decline. Scoring border between cognitive decline and dementia is 80 points [19].

Following the evaluation, we observed that patients who had glioblastoma showed a statistically significant cognitive impairment compared to those suffering from diffuse astrocytoma's or meningioma. We observed that the patients with glioblastoma who showed an important cognitive decline had endothelial vascular proliferation in their tumors.

The pathogenesis of these vascular deformities is not known but seem to be related to tumoral production of vascular endothelial growth factor (VEGF). The vascular density is highly variable and may be an independent prognostic factor [20].

Patients with meningioma have shown the lowest cognitive decline. Among the patients with diffuse astrocytoma and the patients with meningioma, we noticed that those with diffuse astrocytoma had a more pronounced cognitive decline compared to those with meningioma but statistically insignificant.

Regarding cognitive domains affected, meningioma presented the highest percentage compared to the other two groups concerning only the influence over visual-spatial abilities.

Our data are consistent with those from the literature; both Tucha *et al.* [21] and Meskal *et al.* [22] studies led to the conclusion that patients with meningioma had no specific cognitive deficits. It is possible that one of the explanations is linked to the fact that meningiomas have a higher possibility of gradual reorganization, with slower growth [21, 22].

Regarding our results on the correlation with age and gender of patients, they were consistent with the data from the literature, meaning that statistically significant differences were not detected in any of the three study groups [21–23]. In our study, we observed a growth rate of diagnosis after the age of 40. More data will show the relationship between brain tumors and age and gender. Generally, brain cancer develops with age, commonly occurring in individuals aged 65 and older.

The brain tumors are the second type of cancer in terms of frequency, occurring in children less than eight years old. Age is a factor of utmost importance in showing variety regarding the cell type and tumor location. The risk of developing medulloblastomas is very low in adults, but on the other hand, they develop gliomas highly commonly. The adults over the age of 50 are prone to meningiomas. Women are twice likely to develop certain cancers, like meningiomas. In patients with meningiomas, Yoshii *et al.* reported that temporal and spatial orientation, writing and first recall decreased after surgery [24].

In patients with glioblastomas, we noticed a pronounced cognitive impairment in terms of memory, attention and executive functions; data also are consistent with the literature [25, 26]. Verbal memory decline was observed in the resection of dominant temporal lobe [27], while visual-spatial memory decline was associated with the resection of non-dominant temporal lobe [28].

Specific cognitive domain deficits after tumor removal were observed in some studies. One of these, conducted by Goldstein *et al.*, showed a minimal deterioration in attention after right parenchymal frontal resection [29].

From what we observed in the literature, there are many studies regarding cognitive assessment based on histopathological type of tumor in the pre-neurosurgical intervention or radio/chemotherapy [30–32]. Most studies in the literature noticed that the cognitive status of the patients was evaluated postoperatively or post-radio-/chemotherapy; therefore, we became interested in a study of cognitive status for patients with brain tumors of primitive stage or pre-interventional/preoperative therapy [33–35].

For many patients, cognitive changes are part of the disease process. Some studies found that the pattern of impairment can vary markedly in different patients. These studies show that after surgical therapy, an improvement of cognitive domains was obtained. For example, Teixidor *et al.* reported long-term improvement of verbal memory after a transient immediate postoperative worsening, following frontal premotor and anterior temporal area resection [36].

In their study, Zucchella *et al.* reported a cognitive impairment, as follows: 16.25% of patients presented language deficits, 13.75% had limited to memory, 8.75% to attention, 6.25% to executive functions, and 1.25% to visual-spatial abilities. The rest of the patients with brain tumors presented multi-domain cognitive impairment [37].

Referring to the scales, which we have used in the cognitive assessment of patients included in our study, there is a discussion concerning the representation and cognitive areas that they cover these scales.

We chose the above-mentioned cognitive assessment scales (MoCA and CAMCOG) because their structure is complementary, the combination of these two scales providing a better assessment for a wider range of cognitive domains. As the palette is broader cognitive domains studied, the results are striking.

As noted, we did reporting in tumor volumes, as data from the literature that we found shows that there is a statistically significant correlation between tumor volume and assessment of cognitive domains [26, 38, 39].

Conclusions

After conducting this study, we conclude that cognitive assessment of patients diagnosed with primitive brain tumors is useful in earlier stage therapeutic intervention, at least as useful as it is in the post-interventional step, as it helps us to track the dynamic status of cognitive patient, both pre- and post-interventional. In this way, we can have a broader vision on the evolution of the patient's cognitive level, and we can quantify the possible neurotoxic effects of some new therapies. We believe in importance of multidisciplinarity in the diagnosis of brain tumors and the subsequent cognitive impairment, based on clinical, radiological and pathological data.

Conflict of interests

The authors declare that they have no conflict of interests.

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