PROSPECTIVE STUDY ON THE PRESENCE OF COGNITIVE IMPAIRMENTS IN PATIENTS WITH BRAIN TUMORS

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ABSTRACT

Objective: The purpose of our study was to evaluate the cognitive decline in patients with primitive brain tumors.
Material and methods: We enrolled in our study 188 patients diagnosed with brain tumors, hospitalized in the Clinic of Neurology Craiova between January 2006 and December 2010. Depending on the origin of the brain tumors the group was divided as follows:

- Group A, composed of 45 patients with tumors of the meninges
- Group B, composed of 105 patients with neuroepithelial tumors

Each patient was evaluated by neurological and neuroimaging exam (computed tomography and/or nuclear magnetic resonance). For the evaluation of global disability we used Karnofsky Performance Status Scale. Cognitive function was assessed using: Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). The results were analyzed by Student's T test, considering statistically significant $p<0,05$.
Results: Statistical analysis, in terms of the average age and average years of education didn't show significant differences between the two groups. Evaluation of the global functionality, using Karnofsky score, did not show significant differences between the two groups. On MMSE group A obtained an average score of 26,7 points, while in group B, the average score was 25,6 points. On MoCA scale there was, also, a statistically significant difference between the two groups; group A obtained an average score of 23,3 points and group B an average score of 20,3 points.
Conclusion: Our study demonstrated a statistically significant cognitive decline in patients with neuroepithelial tumors compared with patients diagnosed with tumors of the meninges.

Key words: brain tumors, cognitive deficits, neuropsychological assessment

INTRODUCTION

Primitive brain tumors are a group of neoplasms, each type of tumor presenting its own biology, prognostic and treatment, and each being determined by different risk factors.

Despite marked improvement of both diagnostic and surgical techniques, brain tumors, especially malignant, remain a group of devastating diseases, with a low rate of survival and with significant morbidity, as the disease progresses.

In evolution, most patients diagnosed with brain tumors have cognitive decline, but the mechanisms by which these neoplasms may compromise brain function are varied in different patients. It is well-known that cognitive tests' performances are influenced by patient-related variables (age, level of education) and disease-related variables (the location of the tumor, its growth rate, tumor's size), but was not yet fully explained the nature of interactions between these variables. Cognitive dysfunction is a consequence of neoplastic process but it may be, also, secondary to associated intracranial hypertension or cerebral edema, being evident, at the time of diagnosis, on more than half of patients.

Knowing that tumoral lesions with faster growth tend to manifest clinically with relatively greater cognitive impairment, we wonder whether tumor histology could be more important than patient's

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age, level of education or volume and location of the tumor in determining cognitive performance.

OBJECTIVE

The purpose of our study was to evaluate the cognitive decline in patients diagnosed with primitive brain tumors, knowing that cognitive impairment is one of the most common neurological problems associated with brain tumors, even at the time of diagnosis.

MATERIAL AND METHODS

The study-group consisted of patients diagnosed with brain tumors, hospitalized in the Clinic of Neurology Craiova between January 2006 and December 2010. The exclusion criteria of the study were the following:

- Brain metastases
- Diagnosis of coma at admission
- Previous psychiatric diseases or any other condition that could influence cognitive function
- Aphasic language disorders
- Sever motor deficit in upper limb that could prevent writing.

It was formed a group consisting of 188 patients (102 women and 86 men), diagnosed with primitive brain tumors, aged between 17 and 83 years; patients' level of education was between 4 and 18 years of study. In each patient was noted age, gender, residence, level of education and location of the tumor. Also, each patient was evaluated by neurological and neuroimaging exam (computed tomography and/or nuclear magnetic resonance). The histology of the tumor was taken from personal files of the patients after surgical procedures and anatomopathological diagnosis. Tumor diagnoses used are those of the 1993 WHO classification, technical support didn't permit, in all cases, the precise immunohistochemical and genetic identification at the level of 2000 WHO classification.

For the evaluation of disability we used, in all patients, Karnofsky Performance Status Scale, widely used in patients with brain cancer, to quantify the global functionality. The Karnofsky Scale has 11 possible scores, starting from 100 (no complaints) to 0 (which means the patients is died), with interval of 10 points.

Cognitive function was assessed using: Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). MMSE, a brief 30-point questionnaire test, is a widely used scale for a first impression on patients' cognitive function, assessing the subject's mental abilities in memory, attention and language. MoCA scale, a 30-point test, is used as a screening tool for a rapid evaluation of cognitive dysfunction, assessing different domains of cognition: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculation and orientation.

This evaluation of cognitive performances was realized at the time of diagnosis.

The results were analyzed by Student's T test, considering statistically significant $p<0,05$.

We attempted a correlation between histological type of brain tumors and cognitive performances of the patients.

RESULTS

The study-group consisted of 188 patients diagnosed with primitive brain tumors. In the distribution by gender, we found a slightly predominance of females (102 cases), representing 54,2% of the total number of cases, compared to males (86 cases), representing 42,8%, the difference between the two groups are statistically insignificant, however. Related to the urban/rural origin, 45,8% of the cases come from rural areas. In our study-group, the average age of occurrence of cerebral tumors was 59,02 (range between 17 and 83 years), median age being at 60 years.

Studying the incidence of brain tumors by age, we found a small number of cases up to the age of 30 years; we noticed an obvious increase after the age of 40 years and the maximum incidence in the range 50 – 70 years (Table 1).

The tumors were located, mostly, supratentorial (162 cases, representing 86% of all cases), especially at lobar level (150 cases, representing 79,8% of total number of cases), the rest being located in the corpus callosum (8 cases) and intraventricular (4 cases) (Fig. 1).

Tumors with subtentorial localization were in number of 26 cases (14%). They were located in the cerebellar hemispheres (14 cases), at the level of brainstem and fourth ventricle (4 cases) and in cerebellopontine angle (8 cases) (Fig. 2).

Table 1. *Distribution of patients by age*

Groups of age	17-29 years	30-39 years	40-49 years	50-70 years	> 70 years
No. of patients	8	9	26	101	44

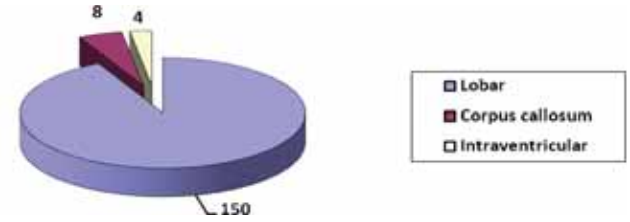

Figure 1. *Distribution of cases with supratentorial localization*

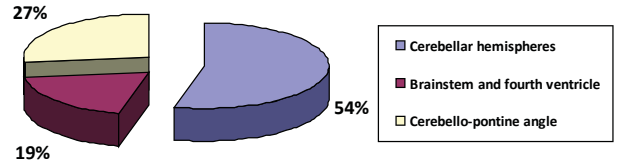

Figure 2. *Distribution of cases with subtentorial localization*

Because, in our study-group, the tumors located in the cerebral lobes are, by far, the most numerous (150 patients), we analyzed in detail this subgroup, the other localizations didn't meeting a sufficient number of cases to permit a proper analysis.

Analyzing the distribution of these 150 cases according to lateralization (left or right hemisphere), we found a slight predominance of the location of tumoral process in the right hemisphere (73 cases) compared with location in left hemisphere (72 cases), while 5 cases have presented, at the time of inclusion, localization in both hemispheres.

In our patients, the most common localization was the unilobar (74 cases), most frequently in the parietal lobe (40 cases), followed by frontal lobe (19 cases) and temporal lobe (15 cases), while the localization in multiple lobes have met a number of 76 cases.

Depending on the origin of the brain tumors, using histological WHO classification of brain tumors (1993), the group, consisting of 150 patients, was divided as follows:

- Group A, composed of 45 patients with tumors of the meninges
- Group B, composed of 105 patients with neuroepithelial tumors

In group A, there was a greater predominance of meningiomas in females (28 cases), compared to males (17 patients, representing 37,8%). The average age in group A was 60,8±12,3 years, median being at 59 years. 62% of patients were from urban areas. In group A, the average level of education was 9,35 years.

Group B showed a greater predominance of tumors in men (58 men) compared with women (47 cases). The average age of group B was 59,7±14,4 years, median being at 61 years, while average years of education were 9,81 years.

Statistical analysis, in terms of the average age and average years of education didn't show significant differences between the two groups (Fig. 3).

Evaluation of the global functionality, using Karnofsky score, did not show significant differences between the two groups, although group B, with neuroepithelial tumors, had a lower mean score than patients with meningiomas (Fig. 4).

Cognitive function was evaluated, in both groups, by using MMSE and MoCA.

On MMSE group A obtained an average score of 26,7 points, while in group B, the average score was 25,6 points ($p<0,05$) (Fig. 5).

On MoCA scale there was, also, a statistically significant difference between the two groups; group A obtained an average score of 23,3 points and group B an average score of 20,3 points (Fig. 6).

Using MoCA, in both groups, we assessed most affected cognitive domains (Table 2). We noticed that over 90% of patients in both groups had at least one impaired cognitive domain. In patients with meningiomas, memory and executive functions were better than in group B. In glioma group, the impairment of executive functions was noticed on 78% of subjects, while memory, visuo-constructional skills and attentions have been affected on more than 60% of patients.

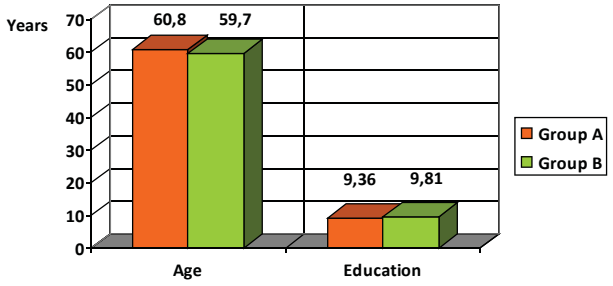

Figure 3. *Statistical analysis of age and level of education in the two groups*

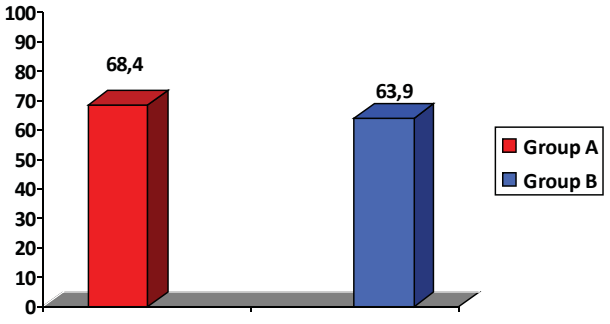

Figure 4. *Average scores obtained by the two groups on the Karnofsky scale*

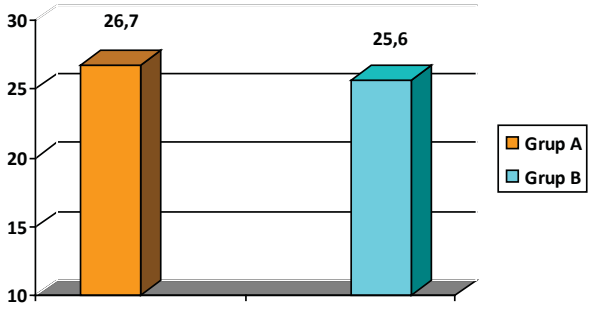

Figure 5. *Average score on MMSE*

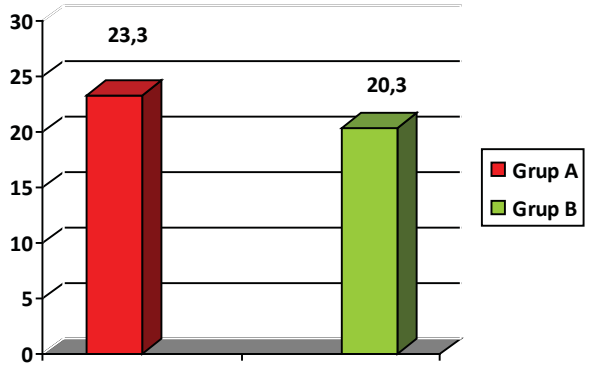

Figure 6. *Average score on MoCA scale*

Table 2. *Affected cognitive domains in patients of both groups*

Domain	Group A N=45 (n%)	Group B N=105 (n%)
Attention and concentration	30(66,6%)	74(70,4%)
Executive functions	19(42,2%)	82(78,1%)
Memory	14(31,1%)	65(62%)
Language	15(33,3%)	56(53,3%)
Vizuo-constructional skills	23(51,1%)	62(59,04)
Thinking	24(53,3%)	53(50,47%)
Calculation	11(24,4%)	44(41,9%)
Orientation	20(44,4%)	34(32,3%)

DISCUSSION AND CONCLUSIONS

In this study, we evaluated cognitive function in patients newly diagnosed with brain tumors. Our study demonstrated a statistically significant cognitive decline in patients with neuroepithelial tumors compared with patients diagnosed with tumors of the meninges, results that are consistent with the data in the literature (1, 2). In our study, in group A, most commonly affected cognitive area was attention (66% of patients with meningiomas showing the decline in this area), followed by thinking and executive functions.

There are few studies on cognitive profile of patients diagnosed with meningiomas. One of these, conducted by Tucha and his collaborators, couldn't show cognitive deficits in specific areas (5). Also, Schubert and his collaborators, examining pre-surgical a series of patients diagnosed with meningiomas, have concluded that there are no specific cognitive deficits in these patients. A possible hypothesis could be that meningiomas, unlike glioma, have a greater possibility of gradual neural reorganization as a result of slow tumor growth. In their study, a large proportion of patients have shown cognitive decline in, at least, one cognitive domain, but, most frequently, in not specific areas. Age, gender and the volume of the tumor were variables that have not significantly influenced cognitive deficit (6).

On the other hand, in our study, in group B, a rate of over 60% of patients had impaired executive function, memory or attention. The data obtained by us are similar to data obtained by Tucha (1).

There are not many studies about cognitive functions at the time of diagnosis (pre-treatment or pre-intervention) in patients with brain tumors. Most of them were conducted to assess post-surgical cognitive function or as a measure for evaluating the effectiveness or adverse effects of treatment (chemo or radiotherapy). One of the few studies in which cognitive function was assessed before any treatment, showed that a large proportion of patients diagnosed with brain tumors in frontal and temporal lobes, had impaired executive function, memory and attention even at the time of diagnosis, aspect that is consistent with results obtained by us (1).

For assessing cognitive function we used MMSE (3) and MoCA (4). Using MMSE in clinical trials of brain tumors is, however, subject of controversy, being, in fact, widely used as a screening tool for dementia. This scale is using to quickly assess aphasia, apraxia, orientation and memory, while the other cognitive domains are not investigated (8). This means that getting a normal score on MMSE (over 27 points), does not mean that the patient does not have any cognitive impairment. In our study, there were patients who fell within normal limits on MMSE, but on MoCA, had at least one impaired cognitive domain. Also, the study of Olson and his collaborators showed that the score obtained on MoCA is a better prognostic factor than that obtained on MMSE (9). Olson concluded that, due to the greater sensitivity and better correlation with quality of life, MoCA should be chosen in clinical practice and clinical trials. On the other hand, Brown and colleagues have shown that an

abnormal MMSE score (less than 26 points) at the time of inclusion, is a bad prognostic factor in low-grade malignant glioma, supporting the idea that the MMSE score to be introduced in assessment of prognostic of brain tumors (10).

In our study, between the two groups, there were no significant differences regarding age, gender or level of education, knowing that these variables could influence the results of neuropsychological tests (11). Also, the patients in both groups had comparable localization of brain tumor. Of the variables related to tumoral process, we did not note tumor volume; this is because there is data in the literature who revealed that the volume of the tumor was not statistically significant related to any of the cognitive domains assessed (1, 12, 13).

In conclusion, the assessment of cognitive function, even at the time of diagnosis, can be extremely useful in clinical trials in patients with brain tumors. It is used to better quantify the neurotoxicity of new therapies and to assess therapeutic response and patients' outcome, these being listed as priority issues to be investigated in the report "Brain Tumor Progress Review Group" (14).

REFERENCES

1. **Tucha O, Smely C, Preier M, Lange KW** (2000): Cognitive deficits before treatment among patients with brain tumors. Neurosurgery 47: 324-333.
2. **Habets E, Walchenbach R, Kloet A, Zwinkels H, Klein H, Vecht CJ, Taphoorn MJ:** The effect of tumor resection on cognition: high-grade glioma versus meningioma, Neuro-Oncology, Volume12, Issue suppl 4.
3. **Folstein MF, Folstein SE, McHugh PR** (1975). ""Mini-mental state". A practical method for grading the cognitive state of patients for the clinician". Journal of psychiatric research 12 (3): 189–98.
4. www.mocatest.org
5. **Tucha O, Smely C, Preier M, Becker G, Paul GM, Lange KW**: Preoperative and postoperative cognitive functioning in patients with frontal meningiomas, J Neurosurg 2003 Jan;98(1):21-31.
6. **Schubert S, Goebel S, Ferstl R, Maximilian Mehdorn H** (2008): Cognitive Deficits In Patients With Intracranial Meningiomas Prior To The Neurosurgical Treatment, JNSPG & Publications, abstract, 2008, September, 4.
7. **Bosma I, Vos MJ, Heimans JJ, Taphoorn MJB, Aaronson NK, Postma TJ, van der Ploeg HM, Muller M, Vendertop WP, Slotma BJ, Klein M** (2007) The course of neurocognitive functioning in high-grade glioma patients. Neuro-oncol 9(1):53–62.
8. **Meyers CA, Wefel J:** The Use of the Mini-Mental State Examination to Assess Cognitive Functioning in Cancer Trials: No Ifs, Ands, Buts, or Sensitivity, Journal of Clinical Oncology, Vol 21, No 19 (October 1), 2003: pp 3557-3558
9. **Olson R, Tyldesley R, Carolan H, Parkinson M, Chhanabhai T, McKenzie M**(2010): Prospective comparison of the prognostic utility of the Mini Mental State Examination and the Montreal Cognitive Assessment in patients with brain metastases, SUPPORTIVE CARE IN CANCER, DOI: 10.1007/s00520-010-1028-1, 1273-1278.
10. **Brown PD, Bruckner JC, O'Fallon JR et al:** Importance of baseline mini-mental state examination as a prognostic factor for patients with low-grade glioma. International Journal of Radiation Oncology Biology Physics Vol. 59, Issue 1, Pages 117-125.
11. **Lezak, M.D.** (1995) Neuropsychological Assessment. 3rd ed. New York, Oxford University Press.
12. **Kayl AE, Meyers CA**: Does brain tumor histology influence cognitive function? Neuro Oncol. 2003 Oct;5(4):255-60.
13. **Dijkstra M, van Nieuwenhuizen D, Stalpers LJ, Wumkes M, Waagemans M, Vandertop WP, Heimans JJ, Leenstra S, Dirven CM, Reijneveld JC, Klein M:** Late neurocognitive sequelae in patients with WHO grade I meningioma, J Neurol Neurosurg Psychiatry. 2009 Aug;80(8):910-5.
14. Report of the Brain Tumor Progress Review Group.