CLINICO-PATHOLOGICAL CORRELATIONS IN MALIGNANT BRAIN TUMORS

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ABSTRACT

Objective. The aim of our study was to evaluate the cognitive impairment in patients diagnosed with malignant brain tumors.

Material and methods. We enrolled in our study 105 patients diagnosed with astrocytomas, hospitalized in the Clinic of Neurology between January 2006 and December 2010. Depending on the histology of the tumor, the study-group was composed of 19 cases diagnosed with diffuse astrocytomas, 13 cases with anaplastic astrocytomas and 73 cases with glioblastomas.

Each patient was evaluated by neurological and neuroimagistic exam (computed tomography and/or nuclear magnetic resonance). Each patient was evaluated in the term of disability using Karnofsky Performance Status, which is a scale commonly used in patients with cancer to quantify functional status. Presurgical cognitive functions of the patients were assessed using Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA),

The results were analyzed using Student's T test and Chi-Squared test, considering statistically significant $p<0.05$.

Results. In the terms of mean age, the statistical analysis didn't show a significant difference between the three groups of patients. Also, we observed that the mean level of education in glioblastomas group was significantly lower than that of anaplastic astrocytomas. On MMSE, the average scores obtained by the patients were: 27.2 points in patients with diffuse astrocytomas, 26.7 points in patients with anaplastic astrocytomas and 25,1 points in patients with glioblastomas. On MoCA, the average scores were: 24.6 points in patients with diffuse astrocytomas, 24.2 points in patients with anaplastic astrocytomas and 21.8 points in patients with glioblastomas.

Conclusion. In our study, the patients diagnosed with glioblastomas showed a statistically significant cognitive decline than the patients with diffuse astrocytomas or anaplastic astrocytomas, respectively. Between patients with grade II tumors and those diagnosed with anaplastic astrocytomas there were no statistically significant differences in terms of scores obtained from the assessment of cognitive functions.

Key words: astrocytoma, glioblastoma, cognitive decline, neuropsychological assessment

INTRODUCTION

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

Cognitive impairment is the most common neurological problem associated with brain tumors, and it is present in many people from the time of diagnosis (1). Cognitive dysfunction results from the neoplastic process, secondarily from shift or compression of intracranial structures or it can be due to associated cerebral edema. In addition, the neurocognitive function in gliomas patients can be affected by treatment (neurosurgery, chemotherapy, radiotherapy), by tumor-related epilepsy, by treatment with antiepileptics or corticosteroids or by patient-related factors, including age or level of education and psychological distress.

Several causes of cognitive deficits can be discerned, but the exact pathopsychology of the impairments is not entirely understood. It is well-

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known that cognitive performances are influenced by tumor-related factors or patient-related factors, but, the nature of interactions between these variables was not fully explained (2).

We consider that it is useful to focus on the relationship between tumor histology and cognitive function in patients diagnosed with malignant brain tumor

OBJECTIVE

The aim of our study was to evaluate the cognitive impairment in patients diagnosed with malignant brain tumors.

MATERIAL AND METHODS

The data presented in this paper comes from a study performed between January 2006 and December 2010. The study-group was composed of 105 patients admitted in the Clinic of Neurology who were diagnosed with astrocytomas with lobar location.

Exclusion criteria from the study were as follows:

- Presence of brain metastases;
- Diagnosis of coma at the time of admission;
- Previous psychiatric illness or any other condition that could affect cognitive function of patients;
- Aphasia;
- Severe motor deficit in the upper limb that could interfere with writing.

The diagnosis of astrocytoma was suspected based on computed tomography and/or nuclear magnetic resonance. Each patient was evaluated in the term of disability using Karnofsky Performance Status, which is a scale commonly used in patients with cancer to quantify functional status (3). Presurgical cognitive functions of the patients were assessed using Mini Mental State Examination (MMSE) (4) and Montreal Cognitive Assessment (MoCA) (5).

The definite diagnosis was established based on anatomopathological examination of the tissue obtained during surgical procedures. For each subject we noted: patient-related data (age, gender, residence, education, neurological assessment, neuroimaging evaluation) and tumor-related data (location, results of the histopathological examination).

The results were analyzed using Student's T test and Chi-Squared test, considering statistically significant $p < 0,05$.

RESULTS

From the 105 cases of astrocytoma, 46 were women and 59 men, noting thus a slight predominance of men (56.2%) than women (43.8%). This slight dominance was found also by the CBTRUS report and has no statistical significance (6).

Our study-group had a mean age of 59.5 ± 14.2 years. The average years of education were 9.95 ± 3.48 years.

We found a small number of tumors up to the age of 44 years, an obvious increase after 45 years and the highest number in the range 65-74 years (Table 1). This maximum incidence, in the seventh decade, is also reported by CBTRUS (6).

TABLE 1. *Distribution of patients by age*

Groups of age	Number of patients	Percentage
17-34 years	6	5.7%
35-44 years	7	6.6%
45-54 years	24	22.9%
55-64 years	23	21.9%
65-74 years	32	30.5%
≥ 75 years	13	12.4%

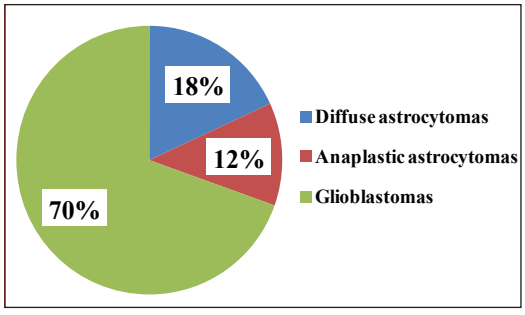

FIGURE 1. *Percentage of tumors by histology*

Depending on the results of the morphopathological examination, our group was composed of 19 cases diagnosed with diffuse astrocytomas, 13 cases with anaplastic astrocytomas and 73 cases with glioblastomas.

1. Diffuse astrocytomas

The 19 cases (12 women and 9 men) of diffuse astrocytomas, that were grading as WHO grade II tumors, had an average age of 51.9 ± 18.5 years and a mean education level of 10.9 ± 3.6 years.

Cognitive function in patients with diffuse astrocytomas

On MMSE scale, the patients with diffuse astrocytomas obtained an average score of 27.2 ± 1.96 points, while the mean score on MoCA scale was 24.6 ± 2.61 points. In these patients, we examined also the cognitive function depending on the site (right or left hemisphere) and location (lobes that

TABLE 2. *MMSE and MoCA scores in patients with diffuse astrocytomas*

	Right hemisphere				Left hemisphere				
	F	P	F-P	T-P	F	T	F-P	T-P	F-T-P
MMSE	28	27.2	26.5	29.3	25.5	25.5	25	24	25
MoCA	25.5	25	24	25.6	19.5	22	20	19	21
Education (years)	10	9.4	14	11.6	7.5	8.5	7	8	12
Age (years)	55	62.4	63.5	38.6	63	69	76	61	52

are involved) and we obtained the following distribution (Table 2).

Depending on the location, when we analyzed the scores obtained, we found that, under the condition of the same lobe involved, the scores were lower in patients with tumors located in the left hemisphere compared to the score obtained in patients with right hemisphere location, but without statistical significance. On the MMSE, the maximum score, very close to the upper limit, was obtained by the patients with right temporo-parietal location. It must however be noted that this group had a significantly lower mean age than the others. For the right hemisphere, except for this location of the tumor, there were no statistically significant differences in scores obtained on MMSE or MoCA. Also, in the patients with involvement of the left hemisphere we did not notice statistically significant differences between the scores obtained on MMSE or MoCA.

2. Anaplastic astrocytomas

The group of patients diagnosed with anaplastic astrocytomas comprised of 9 men and 4 women, with a ratio B:F of 2,2:1. This is consistent with the literature showing higher frequency of this type of tumor in men (7). This group had an average age of 57 ± 10.7 years and a mean level of education of 11.5 ± 3.64 years.

Cognitive function of patients with anaplastic astrocytomas

On MMSE this group obtained a mean score of 26.7 ± 1.44 points. The mean score obtained on MoCA was 24.2 ± 2.05 points.

The cognitive function was analyzed depending on the site and location of the tumor and we observed that, for the right hemisphere, the highest score, either on MMSE or MoCA, was obtained by the patients with frontal lobe involvement. These patients experienced impairment especially of executive functions. The analysis of the scores obtained by patients with involvement of left hemisphere showed the lowest score obtained by the patient with involvement of the parietal lobe, due to the impairment of attention, executive functions and orientation (Table 3).

TABLE 3. *MMSE and MoCA scores in patients with anaplastic astrocytomas*

	Right hemisphere			Left hemisphere			
	F	P	T	P	F-P	P-O	T-O
MMSE	28	27	27	21	23.5	25	28
MoCA	25.5	23	25	18	20.2	22	27
Education (years)	12.5	17	12	4	6.75	10	12
Age (years)	54.5	67	32	54	68	64	51

3. Glioblastomas

Our group comprised a number of 73 cases (30 women and 43 men) which were diagnosed with glioblastomas, classified as WHO grade IV tumors. The average age of this group was 58,2 ± 14,2 years. These values fall within the values published by WHO classification, reporting a peak incidence between 45 and 75 years (2). This group had a mean level of education of 9,95 ± 3,48 years.

Cognitive function in patients with glioblastomas

The patients with glioblastomas obtained on MMSE a mean score of 25,1 ± 2,29 points. The average score obtained on MoCA was 21,8 ± 3,64 points.

Analyzing the cognitive function of these patients according to site and location, we obtained the following distribution (Table 4):

TABLE 4. *MMSE and MoCA scores in patients with glioblastomas*

		MMSE	MoCA	Education (years)	Age (years)
Right hemisphere	F	26.6	22.6	10.6	60.3
	P	25.2	21	9.75	69.5
	T	26	23	9	62
	F-P	24.5	21.2	10.1	65.7
	T-P	25.3	22	9,8	61.7
	P-O	26	23.2	10	59.7
	F-T-P	25	23.3	11.3	59.6
	T-P-O	26.5	24	11	45.5
Left hemisphere	F	27.8	25.6	10.2	44.8
	P	24.9	21.5	8.76	64
	T	26	22	9.33	57.6
	F-P	25.6	23	11.8	54.4
	T-P	25.4	23.2	11.1	53
	F-T-P	23.5	20	7.5	66.5
Bilateral		24	19	5.5	71.5

According to site and location, our study did not show any statistically significant difference between groups of patients.

It must be emphasized that the mean values obtained on assessment of cognitive function was influenced by the average age and level of education. Lower scores were observed in patients with advanced age and lower education level.

4. Analysis of cognitive decline in astrocytic tumors

The summary of demographic, clinical and cognitive characteristics of the patients with astrocytic tumors, according with the grade of malignancy is shown in Table 5.

Analyzing the mean age of the patients depending on the grade of malignancy, we observed that the lowest value was obtained in the group of patients with diffuse astrocytomas and that the highest average age was obtained by the group of patients diagnosed with glioblastomas, but the difference between the three groups was statistically insignificant (Fig. 2).

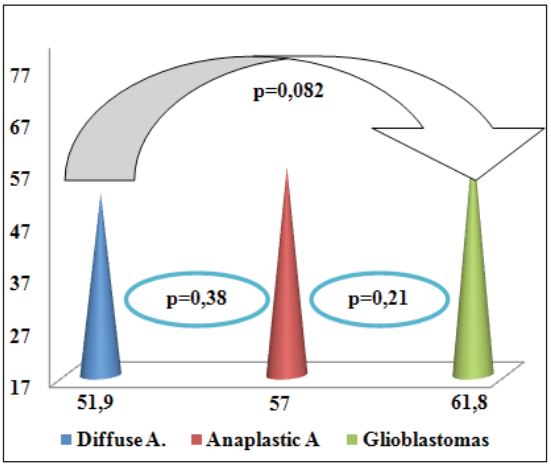

FIGURE 2. *Statistical analysis of age*

Statistical analysis, in terms of average years of education, didn't show significant difference between the group of patients with diffuse astrocytomas and those diagnosed with anaplastic astrocytomas and glioblastomas, respectively. In contrast, the mean level of education in glioblastomas group was significantly lower than that of anaplastic astrocytomas (Fig. 3).

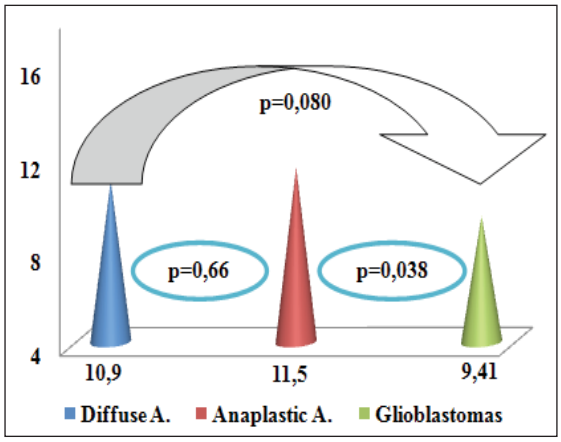

FIGURE 3. *Statistical analysis of education*

When we analyzed the cognitive function using MMSE, we noticed that the group of patients with anaplastic astrocytomas obtained a lower mean score (p = 0,42) than the one obtained by the patients with diffuse astrocytomas, but a significantly higher one than patients with glioblastomas (p = 0.02). The score obtained by the patients diagnosed with glioblastomas was significantly higher than that obtained by the patients with diffuse astrocytomas (Fig. 4).

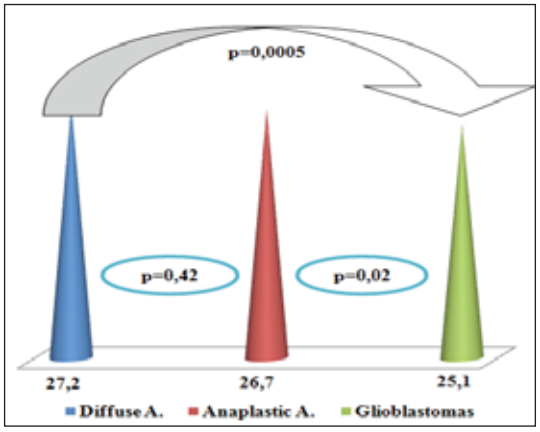

FIGURE 4. *Statistical analysis of MMSE score*

TABLE 5. *Clinical, demographic and cognitive characteristics of the patients*

		A. grade II	A. grade III	Glioblastomas	Total
Number		19	13	73	105
Gender	F	12	4	30	46
	M	7	9	43	59
Mean age (years) ± SD		51.9 ± 18.5	57 ± 10.7	61.8 ± 12.8	59.4 ± 14.2
Education (years) ± SD		10.9 ± 3.66	11.5 ± 3.64	9.41 ± 3.3	9.95 ± 3.48
Karnofski score		68.4 ± 16.8	68.5 ± 12.8	62.5 ± 16.8	64.3 ± 16.5
MMSE		27.2 ± 1.96	26.7 ± 1.44	25.1 ± 2.29	25.7 ± 2.3
MoCA		24.6 ± 2.61	24.2 ± 2.05	21.8 ± 3.64	22.6 ± 3.52

The analysis of cognitive function using MoCA, showed an average score lower in patients with anaplastic astrocytomas than the score obtained by the patients with diffuse astrocytomas (p = 0.65), but higher than that obtained by glioblastomas (p = 0.022). Also, the group of patients diagnosed with diffuse astrocytomas had a mean score obtained on MoCA significantly higher than the patients with glioblastomas (Fig. 5).

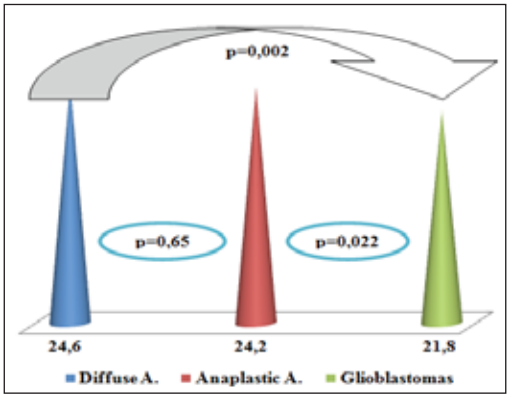

FIGURE 5. *Statistical analysis of MoCA score*

DISCUSSIONS

Primitive brain tumors compose a group of neoplasms derived from different cell types of the central nervous system. Although there is written data showing an increased frequency of primitive brain tumors, their incidence has remained at a low level, representing a percentage between 1 and 5% of all cancers. The incidence of brain tumors in adults older than 20 years was estimated by "The Central Brain Tumor registry of the United States" (CBTRUS) at 25.17/100.000 people/year. About one third of the total number of brain tumors are malignant, the rest being classified as benign or borderline (6).

In our study, the distribution of astrocytic tumors by age showed an increased incidence in the sixth decade, especially due to the increased number of aggressive tumors, results that confirm various articles of international literature, which, analyzing the descriptive epidemiology of cerebral gliomas, suggest an increased frequency at older ages, along with an increased degree of malignancy. Distribution of astrocytomas according to their degree of malignancy showed a statistically significant higher incidence of glioblastomas, which represented a rate of 70% of the astrocytic tumors studied, while anaplastic astrocytomas represented a rate of 18% and diffuse astrocytomas 12%. These results are similar to those reported by CBTRUS.

Our research investigated cognitive function in patients before surgery, using MMSE (4) and MoCA (5). The cognition was analyzed depending on the degree of malignancy, knowing that cognitive decline is the most common neurological problem associated with brain tumors, which is obvious at the time of the diagnosis in many patients (1).

The use of MMSE scale in clinical trials of brain tumors is a subject of controversy, this scale being widely used for dementia screening. By using MMSE we can easily evaluate aphasia, apraxia, orientation and memory, while other cognitive domains are not investigated (8). The study conducted by Meyers and Wefel noted that obtaining a normal score, over 27 points, does not mean that the cognitive function is integral. An assessment of cognitive function is often required using a more detailed scale. The study conducted by Olson demonstrated that the MoCA score is a better indicator of prognosis than those obtained on MMSE (9). Olson concluded that, due to a greater sensitivity and a better correlation with the quality of life, MoCA should be chosen in clinical practice and clinical trials. These findings were evident in our study, too. We administrated MMSE and MoCA to a series of 105 patients with astrocytomas and we found patients who were considered normal on the basis of MMSE score, but they were classified as impaired on the basis of MoCA.

In contrast, another study conducted by Brown demonstrated that an abnormal MMSE score at the time of enrollment is a poor factor of prognostic in the case of patients with malignant gliomas. The authors sustained MMSE score to be introduced as a factor which could assess the prognosis of brain tumors (10).

According to the degree of malignancy, our study didn't show any significant difference between the group of patients diagnosed with diffuse astrocytomas and those diagnosed with anaplastic astrocytomas. In contrast, the cognitive decline in patients with glioblastomas was significantly more pronounced than those of patients with anaplastic astrocytomas. On the other hand, our study demonstrated a statistically significant cognitive decline in patients with glioblastomas compared with patients with diffuse astrocytomas.

Although there are many studies which assessed cognitive function in patients with brain tumors, only a few of them were conducted prior to any treatment. Most of them were conducted to assess post-surgical cognitive treatment or as a measure of evaluating the effectiveness or the adverse effect of treatment. Thus, the study conducted by Kayl AE

on 24 patients diagnosed with anaplastic astrocytomas compared, in terms of cognitive function, with 24 patients diagnosed with glioblastomas showed a more pronounced cognitive decline in the latter group, but the difference between the two groups was statistically insignificant once the tumor-related variables (location and size) and the patient-related variables (age, sex and gender) were taken into account (11).

It should be noted, however, that, unlike our study where the patients were evaluated before surgery or of any specific therapy, the patients evaluated by Kayl were neuropsychological tested after surgery. Thus, although the results of the study were interpreted as a measure of the damage related to tumor size, the effects of the neurosurgery must, however, be considered.

We can conclude that the assessment of cognitive function, even at the time of the diagnosis, can be useful in clinical trials to understand what cognitive problems exist before any specific therapy and to establish a baseline by which the effect of treatment is judged. Thus, it can be determined whether different treatments could improve neurocognitive function due to a better tumor control, or have more or less neurotoxicity.

CONCLUSION

In our study, the patients diagnosed with glioblastomas showed a statistically significant cognitive decline than the patients with diffuse astrocytomas or anaplastic astrocytomas, respectively. Between patients with grade II tumors and those diagnosed with anaplastic astrocytomas there were no statistically significant differences in the terms of scores obtained from the assessment of cognitive functions.

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