Age as a factor for cognitive decline in patients with glial tumors

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Abstract
Introduction: Cognitive impairment appears in almost all patients with glial tumors during the course of this neuro-oncological disease. There are various reasons for this in regards to the glial tumor: grade of malignancy, rate of growth, molecular nature, mass effect, and presence of perifocal edema. But these factors do not always correlate with the degree of patient's cognitive impairment. The present study's aim is to account for age as a factor in the occurrence of cognitive decline in patients with glial tumors.
Materials and methods: The study includes thirty two patients diagnosed with a glial tumor, treated operatively in the Neurosurgery Clinic of University hospital „St. Marina" in Varna between 2019 and 2022 year. Twenty nine of those patients are diagnosed with glioblastoma, two are diagnosed with diffuse astrocytoma and one with astrocytoma grade 3 according to WHO. The mean age of the patients is 58.4 ± 11.4 years. The youngest patient is 25 years old and the oldest is 78 years old. Preoperatively, all patients are subjected to a series of cognitive tests.
Results: From the studied sample, patients diagnosed with glioblastoma showed lower cognitive scores compared to the patients diagnosed with other glial tumors. Patients diagnosed with glioblastoma are significantly older than the patients diagnosed with other glial tumors.
Conclusion: The older age of patients affected by glioblastoma may be an additional reason beside tumor factors for lower cognitive test outcome compared to patients affected by lower-grade gliomas.
Key words: glioblastoma, cognitive deficit, cognitive functions, age-related cognitive impairment

Introduction

Cognitive impairment is a common clinical sign in the development of neuro-oncological diseases. In regard to patients diagnosed with glial tumors the literature demonstrates presence of impairment of cognitive functions in 19% to 95% of cases.[1–4,5,6] Boone et al. argue that the large discrepancy in these results can be attributed to the difference of the sensitivity connected to the used research methods and to the differences of the used statistical data processing methods.[1] Regardless of the percentage of cognitively impaired patients at the time of tumor diagnosis, cognitive impairment occurs in

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almost all patients at some stage during the course of the disease.[7] This cognitive deficit may be due to the tumor itself, its subsequent treatment, or a combination of the two.[8] Factors associated with the tumor itself are: location, side, tumor volume and diffusion of perifocal edema, growth rate, histological group and grade, and molecular grade of agressivness.[2,6,9,10] On the other hand, there are factors outside of the tumor itself leading to cognitive decline. Aging is associated with structural and functional changes in the central nervous system that correlate with age-related cognitive changes, including changes in neuronal structure without neuronal death, loss of synapses, and dysfunction of neural networks.[11]

In the present study we compare the cognitive outcomes of patients with glial tumors, taking into account the correlation between them, the age of the patients and their histological diagnosis.

Material and methods

Ethical approval was granted by the Committee on Scientific Ethics at Medical University – Varna „Prof. Dr. Paraskev Stoyanov", Varna, Bulgaria.

All patients with a clinical diagnosis of a glial tumor from a single tertiary healthcare center – St. Marina University Hospital, admitted from January 2019 to December 2022 year, were included in the study. Initial exclusion criteria were neuroradiology which did not support the diagnosis of a glial tumor and patients previously subjected to central nervous system surgical intervention, previous cerebrovascular incident, preexisting neurocognitive deficit and history of trauma. All patients were preoperatively subjected to a series of neurocognitive tests: Issac set test, Montreal cognitive assessment (MoCA), Trail making test A, Trail making test B, Bender's test, Raven's progressive matrices, Luria's test and Stroop test. Cognitive dysfunction is defined as damage to one or more cognitive areas, including: executive functions, memory, attention, language functions and visuospatial functions.[12]

From the 65 included into the initial cohort, 23 were excluded due to the exclusion criteria.

From the remaining 42 patients included into the secondary cohort a further ten were excluded due to a postoperative histopathological diagnosis of a non-glial histogenetic group (one patient with brain abscess, nine patients with brain metastases).

The collected data from the preoperative cognitive tests was analysed in a descriptive manner to depict the main characteristics of the sample, from the indicators included in the study. Central tendency measures such as arithmetic mean and non-parametric tests such as chi-square are used as the basis of the analysis in search of significant differences in the frequency representation of categorical values. Statistical significance in non-parametric tests was accepted at $p \leq 0.05$. All statistical test were carried out using SPSS statistical software package.

Results

Demographic characteristics:

In the final sample of 32 patients, 13 female and 18 male, 29 were diagnosed with glioblastoma, two with astrocytoma grade 2, and one with astrocytoma grade 3. The mean age of the patients is 58.4±11.4 years (range 25–78). (Fig. 1).

Fig. 1. Age of the patients

Patients	32
Average	58.4
Median	60.0
Standard deviation	11.4
Min. Age	25
Max. Age	78

Correlation analysis between patients' age and histological diagnosis demonstrates that glioblastoma is a diagnosis reserved for older patients (rho = 0.490, p = 0.004) (Fig. 2).

Fig. 2. Correlation analysis

		Age	Diagnose
Age	Spearman's rho	—	
	p-value	—	
Diagnosis	Spearman's rho	0.490 **	—
	p-value	0.004	—
Note. * p < .05, ** p < .01, *** p < .001			

Cognitive results:

The results obtained from the conducted cognitive tests show a correlation between age and cognitive decline. The MoCA test results demonstrate a statistically significant relationship between age and cognitive decline ($r = –0.447$; $p = 0.010$). The inverse correlation signifies the tendency that with increasing age, cognitive test scores decline and more severe cognitive impairment is present. The results of a strong correlation are similar for the TMT B ($r = 0.404$; $p = 0.022$), Bender test ($r = 0.445$; $p = 0.011$) and Raven ($r = 0.503$; $p = 0.003$) tests (Fig.3).

Fig. 3. Results from the conducted cognitive tests.

		Age	MoCA	Issac set test	TMT A	TMT B	Luria	Bender	Raven	Stroop
Age	Pearson‘s r	—								
	p-value	—								
MoCA	Pearson‘s r	-0.447*	—							
	p-value	0.01	—							
Issac set test	Pearson‘s r	-0.295	0.494**	—						
	p-value	0.101	0.004	—						
TMT A	Pearson‘s r	0.331	-0.421*	-0.447*	—					
	p-value	0.064	0.016	0.01	—					
TMT B	Pearson‘s r	0.404*	-0.556***	-0.443*	0.679***	—				
	p-value	0.022	< .001	0.011	< .001	—				
Luria	Pearson‘s r	-0.318	0.627***	0.666***	-0.446*	-0.561***	—			
	p-value	0.076	< .001	< .001	0.011	< .001	—			
Bender	Pearson‘s r	0.445*	-0.524**	-0.449**	0.36*	0.538**	-0.451**	—		
	p-value	0.011	0.002	0.01	0.043	0.002	0.009	—		
Raven	Pearson‘s r	-0.503**	0.728***	0.591***	-0.452**	-0.63***	0.704***	-0.503**	—	
	p-value	0.003	< .001	< .001	0.009	< .001	< .001	0.003	—	
Stroop	Pearson‘s r	-0.151	0.231	0.518**	-0.334	-0.598***	0.415*	-0.348	0.377*	—
	p-value	0.409	0.204	0.002	0.062	< .001	0.018	0.051	0.033	—

Note. * p < .05, ** p < .01, *** p < .001

Discussion

Wefel et al. taking in consideration the IDH1 status of the glial tumors demonstrates reduced cognitive functions in patients with IDH1 wild-type glioblastoma, in contrast to the more preserved cognitive status of patients with IDH1 mutant astrocytomas.[10] In their sample, patients diagnosed with IDH1-wild type glial tumors are significantly older than patients diagnosed with mutant type tumors. The authors focus on the grade of malignancy and do not consider age as a factor for lower cognitive test outcome scores.

A variety of causes can lead to cumulative brain damage with age and can lead to cognitive impairment. These factors include changes in the structure and function of synapses and changes in neuronal networks, brain damage due to cerebral ischemia, head trauma, toxins such as alcohol, excess stress hormones, or the development of degenerative dementia such as Alzheimer’s disease.[11]

Glioblastoma can occur in patients of any age, but predominantly affects older patients, with a peak incidence in patients aged 55-85 years.[13] In contrast, the majority of patients with WHO grade 2 or 3 IDH-mutant Astrocytoma are in their thirties or forties (median age: 38 years).[14] Astrocytoma of IDH-mutant type is rarely found in patients older than 55 years.[15]

Considering the older age of the patients affected by glioblastoma compared to the age group of patients with astrocytoma, it can be argued that age is an additional factor leading to lower test outcomes. The results from the present study demonstrate a correlation between age and cognitive impairment as well as between the age of the patients and the exact histopathological diagnosis of the tumor.

Conclusion

Cognitive decline in patients with glioblastoma compared to patients with lower-grade gliomas may be due not only to tumor growth rate, malignancy, and molecular nature, but also to cognitive impairment invariably associated with the advanced age of patients affected by this group of tumors, relative to the significantly younger age of patients with lower-grade gliomas.

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