Article

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Cognitive impairments in patients with low grade gliomas and high grade gliomas

Eliane C. Miotto[1], Aluizio Silva Junior[2], Clemar Corrêa Silva[1], Hector Navarro Cabrera[1], Melissa A.R. Machado[2], Glaucia R.G. Benute[2],Mara C.S. Lucia[2], Milberto Scaff[1], Manoel Jacobsen Teixeira[1]

ABSTRACT

Objective: The relationship between brain tumors and cognitive deficits is well established in the literature. However, studies investigating the cognitive status in low and high-grade gliomas patients are scarce, particularly in patients with average or lower educational level. This study aimed at investigating the cognitive functioning in a sample of patients with low and high-grade gliomas before surgical intervention. **Method:** The low-grade (G1, n=19) and high-grade glioma (G2, n=8) patients underwent a detailed neuropsychological assessment of memory, executive functions, visuo-perceptive and visuo-spatial abilities, intellectual level and language. **Results:** There was a significant impairment on verbal and visual episodic memory, executive functions including mental flexibility, nominal and categorical verbal fluency and speed of information processing in G2. G1 showed only specific deficits on verbal and visual memory recall, mental flexibility and processing speed. **Conclusion:** These findings demonstrated different levels of impairments in the executive and memory domains in patients with low and high grade gliomas.

Key words: low grade gliomas, high grade gliomas, brain tumors, cognitive functions.

Comprometimentos cognitivos em pacientes com gliomas de baixo grau e gliomas de alto grau

RESUMO

Objetivo: A associação entre tumores cerebrais e déficits cognitivos é bem estabelecida na literatura. No entanto, estudos sobre a cognição de pacientes com gliomas de baixo e alto grau são escassos, especialmente, em sujeitos com baixa escolaridade. Este estudo investigou o funcionamento cognitivo de uma amostra de pacientes com gliomas de baixo e alto grau antes da intervenção cirúrgica. **Método:** Os pacientes com glioma de baixo grau (G1, n=19) e alto grau (G2, n=8) foram avaliados quanto à memória, funções executivas, habilidades visuo-perceptivas e visuo-espaciais, nível intelectual e linguagem. **Resultados:** Houve prejuízo significativo em G2 na memória episódica verbal e visual, funções executivas incluindo flexibilidade mental, fluência verbal nominal e categórica e velocidade de processamento de informações. G1 demonstrou apenas déficits específicos de evocação verbal e visual, flexibilidade mental e velocidade de processamento. **Conclusão:** Estes achados demonstraram níveis diferenciados de comprometimento nos domínios executivos e mnésticos de pacientes com gliomas de baixo e alto grau.

Palavras-chave: gliomas de alto grau, gliomas de baixo grau, tumores cerebrais, funções cognitivas.

Correspondence
Eliane C. Miotto
Av. Dr. Enéas de Carvalho Aguiar 155
PAMB Térreo
05403-000 São Paulo SP - Brasil
E-mail: ecmiotto@usp.br

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[1]Department of Neurology, Hospital das Clinicas, University of São Paulo, Medical School, São Paulo SP, Brazil; [2]Psychology Division, Central Institute, Hospital das Clinicas, University of São Paulo, São Paulo SP, Brazil.

The gliomas are the most frequent primary tumors of the central nervous system (CNS). They originate from the neuroglial, astrocyte, oligodendrogliocyte, ependymal and microglial cells, which are responsible for the maintenance and protection of the neuron. The oligodendrogliomas, astrocytomas, mixed gliomas (combined oligodendroglial and astrocytic elements) and ependymomas represent 60% of all brain tumors[1,2].

The astrocytomas are derived from the astrocytes. They correspond to 30% of the gliomas and are more frequent in males (World Health Organization - WHO). They are also described according to the degree of malignancy as low-grade or high-grade[3]. The low-grade astrocytomas are of grade I and II[4] and the patients with this type of tumor have an average survival of more than 10 years for grade I and from 8 to 10 years for grade II[5]. They are typically seen in adults with age under 40. However, the low-grade astrocytomas are infiltrative and present a potential for malignancy[6]. The anaplastic astrocytoma (grade III) and the glioblastoma (grade IV) are the high-grade astrocytomas[4]. The multiform glioblastomas (MGB) correspond to 55% of the intracranial gliomas and are considered the most anaplastic form of the primary neoplasms of the CNS. It can result from a malignant transformation of another glioma or it can be an MGB from the beginning. This is the most aggressive subtype of glioma[3] with a survival rate between 8 and 18 months[7]. The oligodendrogliomas represent 5% of the gliomas and are usually present in the frontal lobes[4]. In other studies, however, it represented 10% of cases[3] or 25 to 33% of gliomas[8]. They can be seen at any age, although the initial diagnosis has two peaks of incidence: at 6 to 12 years and at 35 to 44 years. This tumor is also more frequent in males and more than 90% of them originate in the supratentorial white matter including the frontal lobes and less than 10% begin in the posterior fossa[9]. There are two category grades, namely grade II and III, nevertheless the commonest tumor is the anaplastic or grade III[4].

In general, the cognitive alterations resulted from the neoplastic processes are related to the compression, displacement, destruction or isquemia of intracranial structures, as well as, associated cerebral edema. These cognitive deficits are present at the moment of the diagnosis in 50 to 80% of pacients[10]. It's impact on daily life activities (DLA) and quality of life of patients are recognized especially in patients with high-grade malignant gliomas with a relatively short survival[11]. On the other hand, studies in patients with low-grade glioma indicate that this type of brain tumor also produces cognitive deficits[12].

The majority of the studies showed that cognitive functioning in patients with glioma can be affected by the tumor, the epilepsy related to the tumor, the surgical treatment, the radiotherapy, the chemotherapy, antiepileptic or corticosteroid drugs and factors related to the patient, including age[7,9-12].

Memory is frequently impaired, particularly in patients with tumors in the frontal and temporal lobes and in the region of the thalamus[13]. Executive functioning is usually impaired in patients with low-grade gliomas in the frontal lobes. In this context, the assessment of the intellectual abilities is important since high intellectual level subjects present a greater cognitive reserve and adaptive skills, which allow for compensation of the cognitive symptoms at the beginning of the tumor development[14]. Klein et al.[15] showed that individuals with low-grade glioma also present reduced processing information speed. Hahn et al.[16] evaluated the cognitive functioning of patients with high-grade glioma and demonstrated that the subjects with tumors in the left hemisphere showed more memory problems, impaired verbal fluency and verbal learning. These cognitive alterations also affect patients DLA, occupational status and quality of life[17].

Systematic and detailed assessment of cognitive functioning in these patients is of relevance allowing for an early detection of these changes and therapeutic interventions, which can minimize the worsening of these symptoms. However, studies in the literature on the neuropsychological alterations in patients with high and low-grade gliomas and low educational level are scarce. The aim of the current study was to investigate and compare the performance of patients with diagnoses of high and low-grade glioma before surgical intervention.

METHOD

Subjects

The participants were recruited from the Neuro-Oncology Group of the Hospital das Clinicas, FMUSP. They had diagnoses of astrocytomas, oligodendroglioma and multiform gliobastoma (MGB) and were allocated into two groups (Table 1): patients with low-grade glioma or G1 (n=19) and with high-grade glioma or G2 (n=8). Neuroimaging and histopathological examinations confirmed the diagnoses.

All patients were assessed before the surgical procedure and they had no previous history of cerebral tumors, use of medication for psychiatric symptoms or history of psychosis, depression or alcohol abuse. They were selected at the multidisciplinary meeting day and assessed by neuropsychologists on the same day of their medical appointment as outpatients. Illiterate subjects were excluded due to the need of reading of some instruments.

The study was approved by the hospital ethical committee board (CAPPESQ nº 086/06) and before entering the study all patients signed an informed consent form.

The testes included in the current study and the functions assessed by them are described on Table 2.

RESULTS

Initially, the two groups of patients (G1 and G2) were compared in terms of age and education with Anova tests using the SPSS v.16 program. There were no significant differences between the two groups on these variables (age: F=3.63, P=0.068; schooling: F=0.38, P=0.546). The average age for G2 was 54.63 years (SD=7.95) and 46.0 years (SD=11.64) for G1. The average years of education for G2 was 7.0 (SD=2.83) and 7.94 years (SD=3.30) for G1.

Subsequently, the results of each group were analyzed according to the percentiles obtained by the patients and the norms of the tests taking into account the age and education of the subjects (Table 3). In general, the two groups of patients with gliomas (G1 and G2), particularly G2, were impaired on more than two cognitive domains including nominal and categorical verbal fluency (executive function), episodic visual recognition memory and episodic immediate verbal recall. G1 was impaired on immediate and delayed verbal memory recall as well as on the nominal verbal fluency and processing speed (Figure).

Both groups of patients fell into the below average range on testes of estimated general intelligence (G1: IQ=84.84, SD=15.63; and G2: IQ=84.25 SD=16.43). The two groups did not show significant differences in terms of total IQ (F=0.08, P=0.93).

Next, the results of each group were described considering the injury location.

Results for G1

Out of the five patients with left frontal lesions, 3 (60%) were in the impaired range on tests of immediate verbal recall and information processing speed, 2 (40%) on mental flexibility and nominal verbal fluency and 1 (20%) on categorical verbal fluency. One subject was in the borderline range on immediate verbal recall, processing speed, nominal verbal fluency, as well as in categorical verbal fluency.

Out of the three patients with right frontal lesions, 2 (66.6%) were in the impaired range on the tests of immediate verbal and visual memory recall and 1 (33.3%)

Table 1. Distribution of the sample according to area and hemisphere of the lesion.

		Gliomas	
Type	Hemisphere	High grade (n=8)	Low grade (n=19)
Frontal	Left	1	5
	Right	3	3
Temporal	Left	0	2
	Right	1	3
Occipital	Left	0	1
	Right	0	1
Fronto-temporal	Left	0	1
	Right	0	1
Fronto-parietal	Left	0	1
Fronto-insular	Left	0	1
Fronto-temporo-insular	Left	0	1
Temporo-parietal	Left	1	0
Temporo-occipital	Right	1	0
Temporo-parieto-occipital	Right	1	0
Intraventricular		0	1

Table 2. Tests and neuropsychological functions.

Neuropsychological functions	Tests
Intellectual functions	Vocabulary and Matrix Reasoning (WASI-III)[18]
Memory functions	
Short-term memory	Digits (WAIS-III)[21]
Verbal episodic memory (immediate and delayed recall and recognition)	Hopkins Verbal Learning Test - R (HVLT-R)[19]
Visuo-spatial episodic memory (immediate and delayed recall and recognition)	Brief Visual Memory Test - R (BVMT-R)[20]
Visuo-perceptual and visuo-spacial functions	
Fragmented letters	VOSP[22,23]
Discrimination of points	
Executive functions	
Nominal verbal fluency	FAS-Test[22,23]
Categorical verbal fluency	Category Fluency - Animals[22,23]
Mental flexibility	WCST[26]
Processing speed	Symbol Digit Modality Test - Oral Version[25]
Naming	Boston NamingTest[22-24]

Table 3. Results of the neuropsychological tests administered expressed as average and standard deviation and percentiles for the patients with high grade (n=8) and low grade (n=19) glioma.

		High grade glioma (G2)		Low grade glioma (G1)	
Neuropsychological tests		Average (SD)	Percentile average (SD)	Average (SD)	Percentile average (SD)
WASI	Vocabulary	34.6 (15.8)	15.8 (20.7)	38.6 (16.2)	23.8 (26.9)
	Matrix Reasoning	13.4 (8.62)	35.95 (39.06)	13.4 (6.09)	30.13 (33.75)
	IQ estimated	84.25 (16.43)	22.5 (28.99)	84.84 (15.63)	22.3 (23.73)
Digits	Direct Order	5.43 (1.27)	28.0 (13.5)	6.74 (2.13)	48.0 (27.5)
	Inverse Order	3.14 (1.07)		4.63 (2.19)	
HVLT-R	Immediate Recall	14.5 (5.68)	4.88 (10.6)	18.1 (6.61)	10.1 (20.9)
	Delayed Recall	4.5 (3.78)	12.25 (23.49)	5.47 (3.45)	13.74 (23.11)
	Recognition	10.0 (2.27)	40.9 (28.1)	9.16 (2.63)	30.5 (32.0)
BVMT-R	Immediate Recall	14.5 (10.54)	13.63 (26.69)	17.26 (8.12)	15.89 (26.33)
	Delayed Recall	5.25 (4.2)	15.75 (38.8)	5.84 (3.55)	16.0 (28.44)
	Recognition	4.95 (1.08)	10.25 (7.23)	5.13 (1.13)	47.8 (3.54)
VOSP	Fragmented Letters	15.75 (6.78)	29.38 (38.61)	17.95 (3.27)	25.32 (25.53)
	Discrimination of Points	18.63 (3.89)	64.88 (26.27)	18.68 (2.38)	42.95 (24.62)
FAS (Nominal verbal fluency)		15.0 (5.81)	9.75 (8.21)	18.89 (10.52)	9.16 (7.65)
Categorical verbal fluency (Animals)		9.33 (2.94)	5.67 (4.93)	11.1 (4.79)	18.37 (24.21)
WCST categories		2.98 (2.19)	7.0 (10.43)	3.19 (2.01)	10.0 (9.29)
Symbol Digit (time)		28.75 (21.25)	21.5 (26.41)	22.0 (8.35)	4.11 (5.71)
Boston Naming Test		42.13 (15.72)	54.4 (37.4)	46.83 (11.84)	52.6 (31.1)

*Percentiles obtained according to the normative data for each test.

on mental flexibility and nominal and categorical verbal fluency. All of these patients were in the impaired range on tests of information processing speed.

The two individuals with the single lesion on the left temporal lobe were impaired on tests of immediate verbal recall and processing speed.

Out of the three patients with a single lesion on the right temporal lobe, 2 (66.6%) were impaired on immediate visual and verbal recall and information processing speed. One subject (33.3%) was impaired only on processing speed.

The patient with the lesion in the left occipital lobe was impaired on immediate verbal recall and information processing speed. The subject with the lesion in the right occipital lobe fell in the low average range on processing speed and nominal verbal fluency.

The patient with left frontal-temporal lesion was impaired on immediate and delayed verbal memory recall, nominal and categorical verbal fluency.

In the only case of intraventricular lesion, the patient was impaired on immediate verbal recall and processing speed.

Results for G2

The only case of frontal lobe lesion in the left hemisphere was impaired on mental flexibility, immediate verbal recall and nominal verbal fluency. Out of the 3 subjects with frontal lesion on the right, 2 (66.6%) were impaired on immediate visual and verbal memory and 1 (33.3%) on mental flexibility.

In the only right temporal lesion case, the individual was in the deficient range on immediate and delayed vi-

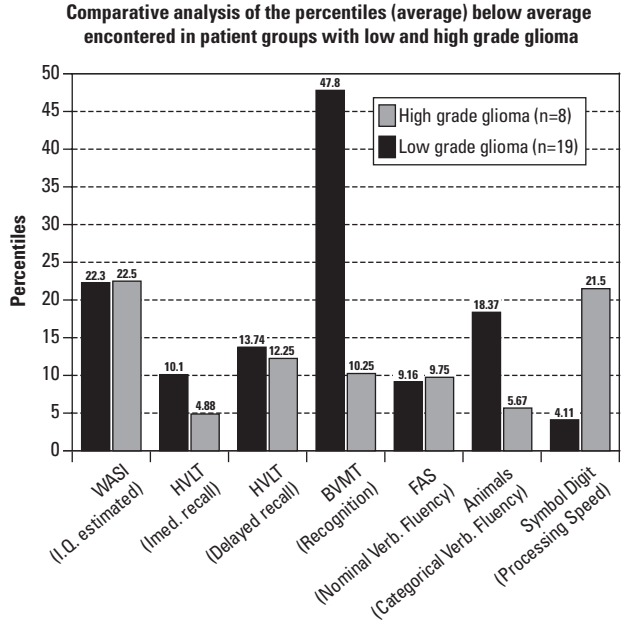

Figure. Results in percentiles for both G1 and G2 on the neuropsychological tests.

sual and verbal recall. In the only case of temporal-occipital lesion on the right, the subject was in the deficient range on immediate visual and verbal memory recall and visual recognition. In the only incident of parietal-temporal-occipital lesion on the right, the individual was moderately impaired on immediate visual and verbal recall.

DISCUSSION

This study aimed to investigate the cognitive functioning of patients with low and high-grade gliomas before surgery. The main results demonstrated an impaired performance in G1 and G2 on tests of executive functions, especially of mental flexibility, nominal and categorical verbal fluency, as well as on immediate and delayed verbal and visual memory recall. These findings corroborate with some studies in the literature showing the involvement of the executive and memory domains specifically in patients with frontal-temporal lesions[13,14,27-30].

The majority of the high-grade glioma patients (88%) showed impairments on speed of information processing, executive functions, verbal and visual memory independently of the lesion location. This could possible be explained by the fact that most tumor lesions in this group involved subcortical or white matter regions. There is evidence that these regions are directly associated with such functions[5,7,10,14]. Also in this group, patients with left hemisphere lesions were impaired on verbal immediate memory recall. These results are in line with studies demonstrating memory deficits in patients with injuries in the left hemisphere[14,16,28-30]. The patients with right hemisphere lesions also had immediate verbal memory recall deficits. It is possible that the diffuse growth of the tumor cells could have infiltrated the normal cerebral tissue invading areas of the left hemisphere. There is also some evidence showing that impairment of executive function can alter verbal memory and learning[14,27-30]. The deficits of visual recognition episodic memory were found in patients with tumors in the right hemisphere and these findings have already been shown in other patients with right side lesions[5,7,14,27,29,30].

In patients with low-grade gliomas, those with left hemisphere tumors were impaired on immediate and delayed verbal memory recall. Those with intraventricular and posterior fossa tumors (occipital region on the left) were impaired on immediate verbal memory recall and executive functions particularly speed of information processing. Here again, this could also be associated with the involvement of subcortical and white matter regions[14,29].

Some studies on patients with gliomas reported that the educational and intellectual levels are relevant to the presence of cognitive deficits. Individuals with high intellectual level can demonstrate better adaptive skills or cognitive reserve which allows to compensate for their cognitive impairments and postpone their appearance[7,14]. Since most of the patients in the current study had less than eight years of education, this perhaps explains the largest number of cognitive alterations in patients with either low or high-grade gliomas. Nonetheless, patients with high-grade gliomas performed at the impaired range on more functions than those with low-grade gliomas including, executive functions and episodic memory.

These findings demonstrate that a comprehensive cognitive assessment is relevant to the identification of the presence and level of extent of cognitive deficits in patients with low and high-grade gliomas prior to the surgical treatment.

One of the limitations of the present study was the small sample. Future studies with larger populations, range of educational level and comparisons between the pre- and post-operative cognitive status are necessary.

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