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CLINICAL-PATIENT STUDIES

Assessment of verbal working memory before and after surgery for low-grade glioma

Pilar Teixidor · Peggy Gatignol · Marianne Leroy · Cristina Masuet-Aumatell · Laurent Capelle · Hugues Duffau

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Abstract
Object While scarcely reported in low-grade glioma (LGG), accurate assessment of higher functions is essential to evaluate then preserve the quality of life. We assessed verbal working memory (vWM) in patients with LGG in language areas, before and after surgery, to evaluate the effect of glioma and resection on cognition, respectively.
Methods About 23 patients harboring a LGG in language areas underwent awake surgery. All patients had a vWM assessment, before and immediately after the resection, in addition to KPS. vWM was also evaluated 3 months after surgery in eight patients (KPS in all cases), who performed postoperative rehabilitation.
Results Preoperatively, 91% of patients had vWM disorders (KPS ≥90 in 22 patients). Immediately after surgery, 96% of patients had vWM worsening (50% of KPS ≥90). At 3 months, among the eight patients examinated, five recovered their preoperative vWM score, and three significantly improved it (KPS ≥90 in 23 patients).
Conclusion In LGG, neuropsychological assessment is encouraged in addition to KPS. vWM evaluation before treatment showed that most patients had a cognitive deficit. Moreover, surgery induced a transient vWM worsening, which nevertheless recovers within 3 months. Specific rehabilitation might help to recover and even to improve the preoperative cognitive status.

Keywords Brain mapping · Language · Low-grade glioma · Surgery · Working memory

Introduction

The primary objective of low grade glioma (LGG) surgery is to preserve eloquent brain areas whilst obtaining the maximum degree of tumor resection [1, 2]. Currently, in addition to the preoperative neurofunctional imaging, intraoperative direct cortico-subcortical electrical stimulation enables to optimize the benefit-to-risk ratio of surgery, since definitive morbidity is less than 5% and the resection is total or subtotal in approximately 80% of cases [2, 3]. Thus, the development of functional brain mapping has allowed resective surgery to be focused on one of the basic principles of neuro-oncology: maintaining and even improving the patient's quality of life (QoL) [4].

Nevertheless, neurosurgeons must not forget that this concept also includes cognitive aspects. Therefore, the effect of surgery on patients' higher functions should be considered, as previously extensively

P. Teixidor
Department of Neurosurgery, Hospital Germans Trias I Pujol, Ctra del Canyet s/n, 08916 Badalona (Barcelona), Spain

P. Gatignol · M. Leroy · L. Capelle · H. Duffau
Department of Neurosurgery, Hôpital Salpêtrière, 75651 Paris, Cedex 13, France

M. Leroy · L. Capelle · H. Duffau (✉)
Department of Neurosurgery and UMR-S678 Inserm, Hôpital Salpêtrière, 47-83 Boulevard de l'hôpital, 75651 Paris, Cedex 13, France
e-mail: hugues.duffau@psl.ap-hop-paris.fr

C. Masuet-Aumatell
Department of Preventive Medicine and Public Health, Hospital de Bellvitge, Feixa Llarga s/n 08907 Hospitalet del Llobregat, Barcelona, Spain

reported in epilepsy surgery [5]. In this way, before being able to analyse this effect, it is mandatory to demonstrate if such functions are really intact in LGG patients before surgery. Indeed, although it was reported for a long time that most of patients harboring a LGG had normal higher functions (only 10% of mental status abnormalities described by De Angelis in 2001 [6]), recent studies have found that, if extensive neuropsychological assessment was performed, approximately 91% of patients with LGG have in fact cognitive disorders before any treatment [7].

With the aim to test neurocognition accurately, working memory (WM) represents a sensitive and reliable task. Indeed, any WM dysfunction has a negative impact on higher functions. The theoretical concept of WM assumes that a limited capacity system, which temporarily maintains, stores and allows manipulation of information, supports human thought processes by providing an interface between perception, long-term memory and action [8]. Therefore an objective decrease in this WM capacity reflects a cognitive function disorder.

Here, we report a homogeneous series of 23 patients who underwent surgical resection for LGG in the dominant hemisphere whilst operated on under local anaesthesia using intrasurgical electrical mapping. Due to the location of the tumors in language regions, the preoperative status of the verbal WM (vWM) was systematically assessed using specific neuropsychological tests, in addition to the classical functional scale in neuro-oncology—Karnofksy Performance Status (KPS)—in order to better evaluate the QoL. The same battery of vWM tests was also used to analyse the effect of surgery in the immediate postoperative period in all patients, and 3 months later in eight patients (KPS score was evaluated in all cases). The aim was to determine (i) the patients' higher functions before any treatment, (ii) the effect of surgery on these functions in the immediate and delayed postoperative periods and (iii) the actual contribution of the vWM assessment in addition to the classical functional scale.

Patients and methods

Patient population

This is a longitudinal study of a consecutive surgical series of 23 patients harboring a LGG located in language areas, who underwent surgical resection under local anaesthesia with intraoperative functional mapping using direct cortico-subcortical electrical stimulations, and who benefited from a vWM assessment before and after operation. All patients were operated on by the two senior neurosurgeons (H. D. and L. C.) in the Pitié-Salpêtrière hospital between 2002 and 2005.

The socio-demographic variables collected were sex, age, education level, handedness and past medical history of major illness. The education level was defined as a qualitative variable with two categories: less than or equal to 9 years of schooling, or over 9 years of schooling, in accordance with the French educational system. Handedness was evaluated using the Edinburgh Inventory. The language hemispheric dominance was assessed by functional MRI using a protocol associating a semantic fluency task, a covert sentence repetition task, and a story listening.

Clinically, patients who presented with seizures were recorded, and classified according to their seizure. In cases that did not present with seizures, the symptoms leading to a brain tumor diagnosis were recorded. The preoperative KPS score was defined and a conventional neurological examination was carried out the day before of the surgical intervention.

The patients undergoing antiepileptic treatment before surgery were determined.

Radiologically, the characteristics of the lesion, its homogeneity or heterogeneity, and whether or not there was contrast uptake, were defined using T1, T2 and FLAIR weighted MRI. In addition, the tumor location was defined according to the criteria described by Duffau et al. [9] and the tumor volume was systematically evaluated.

Preoperative neuropsychological assessment

Since all tumors were located within language areas in the dominant hemisphere, a preoperative neuropsychological assessment was systematically performed by a speech therapist (P. G.), using the picture naming test (DO80) [10] and the Boston Diagnostic Aphasia Examination (BDAE) (French adaptation 1982) [11]. Subtests of BDAE requiring the greatest involvement of vWM were selected for the assessment (see below).

DO80 looks for a possible disturbance in the process of naming, which involves three levels: visual-perceptive, semantic and lexical. Indeed, naming disorder is one of the troubles that are detected earliest in many types of aphasias. The test is based on 80 pictures and is scored according to the age of the patient (between 20 and 59 years, and between 60 and 79 years) and the education level (9 years or less, and over 9 years) [10]. Its standardization is related to a total of 108 subjects distributed in a homogeneous way according to individual factors' of age (three classes from 20 to

75 years), duration of schooling (up to 9 years included and higher than 9 years) and sex [10]. In order to balance possible regional linguistic particularisms, the subjects were recruited in different geographical regions. The test proposes two modes of quotation: one known as ''strict'' with finality of research, and the other, more adapted with the standard clinical practice. Results of the DO80 test were considered pathological if they were below the limits of normality, established according to age and years of education.

Eight subtests were selected from the BDAE [11]. All subtests had a minimum store of 0 and a maximum score that varied according to the test. Scores for the BDAE subtests were considered normal if they fell between twice the standard deviation and the maximum score for each subtest. The test of commands and the test of logic and reasoning were selected from the auditory comprehension section of the BDAE. Indeed, when both the language's syntax and semantics, and the order of more complex sentences, are detected and understood, these tests involve vWM. The maximum score was 15 for the first test, and 10 for the second one. In the written comprehension section, the vWM is also essential for decoding and recognizing the words, and for recalling the words that have already been read. The vWM is equally crucial to maintain the thematic thread so that the meaning of the ideas read can be understood. The test of reading phrases aloud was used. This test has a maximum score of 10. Furthermore, the vWM is involved in the repetition section, as information about each word segment entering through the auditory pathways needs to be converted. This information needs to be stored in the memory and then converted into material to be correctly pronounced. The greater the length and complexity of the material to be recalled, the greater are the demands on the vWM. Three subtests were selected: word repetition, concrete phrase repetition and abstract phrase repetition. The maximum score was 10 for the first test, and 8 for the second and third one. The spelling test was also selected from the written language comprehension section. This was because, unusually, the subject first has to identify the letters from their sound and then subsequently associate them with vocabulary. This test requires considerable attention capacity and vWM. The scores ranged between 0 and 8. Finally, in the sentence dictation test taken from the writing section, the patient receives information through the auditory pathway. This information must then be converted into graphemes, which also requires the manipulation of information. The maximum score for this test was 12.

Surgical variables

The surgical technique, i.e. the on-line cortico-subcortical electrical functional mapping guiding the limits of the resection under local anaesthesia, was widely detailed in previous reports [1–3]. The double aim was first to track and preserve the eloquent structures at each moment and each site of the resection, in order to avoid postoperative sequelae, second to continue the LGG removal until essential functional areas were encountered, in order to optimize the quality of resection. Briefly, following the detection of glioma boundaries using intraoperative ultrasonography, a 5-mm spaced tips bipolar electrode delivering a biphasic current (pulse frequency of 60 Hz, single pulse phase duration of 1 ms, amplitude from 2 to 6 mA under local anaesthesia) was applied on the brain. First, the electrical mapping was realized at the cortical level, before tumor removal, to identify the essential eloquent sites which must be avoided, thus to define the boundaries of the resection according to functional data. In addition to sensorimotor mapping, language tasks including counting, picture naming and reading were systematically performed [2, 3]. A trained speech therapist and/or neuropsychologist was systematically present in the operative room all along the awake period, in order to accurately interpret the tasks. Second, direct stimulations, with the same electrical parameters as those used at the cortical level, were *continuously* applied during glioma removal at the subcortical level to detect sensorimotor and/or language pathways, which represent the deep functional limits of resection [2, 3]. As a consequence, the resection was systematically continued until the language areas were encountered, with no any margin.

It is worth noting that WM was not mapped intraoperatively, because it was never demonstrated previously that this function was altered before and after LGG surgery. This was exactly the goal of our study, in order to propose or not to add WM mapping during the resection for future operations according to the results of the present pre- and post-surgical assessments.

Factors which could have a negative impact on the tolerance of the awake procedure have been evaluated, namely seizures, anxiety or extreme tiredness. The accurate intensity of the electrical stimulations and the duration of surgery were also recorded.

Postoperative assessment

Postoperatively, the results of neurological examination and KPS were detailed in all cases. In addition, the 23 patients had neuropsychological vWM assessment using the same test battery than preoperatively, within seven days after surgery, depending on the patient's state.

A control MRI has evaluated the quality of resection within 48 h after surgery, according to the classification proposed by Berger et al. [1], namely: partial resection in cases of residual tumor larger than 10 cc, subtotal resection in cases of residual tumor lesser than 10 cc, and total resection in cases of no signal abnormality on MRI.

Histological results were recorded according to WHO classification criteria.

Three months after surgery, KPS and clinical examination were reassessed in all patients. Moreover, the eight last patients of the series, who underwent a specific language rehabilitation primarily focussed on strengthening vWM in the three postoperative months, were tested again using the same battery of vWM than described above. The rehabilitation was carried out by a speech therapist. It began after the discharge and took place in one hour sessions three times a week. The exercises performed were presented through auditory or visual channels and arranged in an increasing hierarchy.

Statistical methods

Statistical analyses were performed with SPSS 11.0 software (version 11.0). Nonparametric test were used, since the sample was relatively small and the variables did not meet criteria for normality, evaluated by the Kolmogorov–Smirnov test and even the logarithmic transformation.

Comparisons between patients, before and after surgery (immediate and later postoperative) were performed using the two-sided Wilcoxon rank sum test for continuous variables and comparisons variables means assessed more than twice were performed using the Friedman test. All statistical tests were two-tailed; a p value of 0.05 or less was considered significant.

Results

Demographic characteristics of the 23 patients

There were twelve (52.2%) men and eleven (47.8%) women. The average age was 34 years. The educational level was of 9 years or less in 39.1% of patients, while over 9 years in 60.9% of patients. Nineteen patients were right-handed, two were ambidextrous, and two were strongly left-handed.

Two patients had a past medical history: one patient had congenital hemiparesis and the other suffered from seizures since childhood.

Clinical history

The diagnosis was made after inaugural seizures in all cases but two. Ten patients presented with generalized tonico-clonic seizures, four with sensory partial seizures, four with motor partial seizures and three with mild language disorders. Moreover, one patient experienced an intracranial hypertension. Finally, the diagnosis of one patient was incidental.

At the onset of the illness, 95.6% of the patients had a normal conventional neurological examination, except for the patient who presented with signs of intracranial hypertension. This examination was normalized after a first cytoreductive surgery performed in emergency. The examination of the patient with congenital hemiparesis was considered to have no new deficit, taking into account the past medical history.

The preoperative KPS score was of 100% in four patients, 90% in 18 patients and 80% in one patient.

MRI examination

In all cases, the tumor was hypointense on the T1 images and hyperintense on T2 and FLAIR images. On the T1-weighted images, the tumor was homogenous in 16 patients and heterogeneous in the other patients, with a punctiform contrast uptake observed in six cases. The tumors were located in the following areas: 6 in the supplementary motor area (1 right, 5 left), 5 in the left premotor cortex, 1 in the left frontal operculum, 1 in the left operculo-insular region, 4 within the sole insula (2 right, 2 left), 1 in the left parieto-retrocentral area and 5 in the parieto-temporo-occipital junction (3 left, 2 right). The average tumor volume was 48.2 cc, with extremes of range of 10 cc to 140 cc.

Preoperative neuropsychological vWM examination (Table 1.)

The percentage of patients scoring below normal levels were: DO80 14.3%; auditory comprehension: commands 38.1% and logic 90.4%; written comprehension : reading 23.8%; repetition: word repetition 23.8%, concrete phrase repetition 19%, abstract phrase repetition 14.3%; written language comprehension: spelling 14.2%; writing: sentence dictation 5.2%.

Table 1 Preoperative and immediate postoperative vWM assessment in the 23 patients

Patient	D080		Commands		Logic		Reading		Word repetition		Concrete phrase repetition		Abstract phrase repetition		Spelling		Sentence dictation	
	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop
1	75	**55**	**14**	**8**	**9**	**5**	**6**	**4**	**8**	**8**	**7**	**6**	7	**4**	6	**1**	12	11
2	78	76	15	**13**	12	**11**	10	10	10	10	8	8	8	**6**	8	7	10	10
3	79	79	15	**13**	**9**	**7**	**8**	**9**	10	**9**	8	**6**	7	**2**	8	**5**	**4**	**4**
4	**52**	**64**	**13**	**14**	**6**	**11**	**7**	**9**	**9**	10	**6**	**7**	**4**	**7**	8	8	12	12
5	77	80	15	**10**	**10**	**8**	9	9	10	10	8	**7**	8	7	8	7	12	9
6	78	78	15	**13**	**10**	**8**	9	9	10	10	**7**	**7**	8	7	8	6	12	
7	**76**	**78**	**13**	**13**	**10**	**8**	10	10	10	**9**	8	**7**	8	7	8	8	12	
8		**76**		**13**		**7**		10		10		8		**8**		5		**6**
9	80	78	15	**14**	**11**	**10**	**8**	**9**	10	10	8	8	8	**5**	8	8	12	10
10		77		15		**9**		**6**		10		8		8		8		12
11	80	80	15	15	**11**	**11**	10	10	10	10	8	8	8	7	8	7	12	12
12	80	78	15	15	**11**	**8**	10	10	10	10	8	8	6	**8**	7	6	12	**6**
13	80	80	**14**	15	**10**	12	10	10	10	10	8	8	8	8	7	8	12	12
14	78	**16**	15	**13**	**7**		10		**9**	**7**	8	**6**	8	**4**	**5**	2	-	10
15	**75**	**70**	15	**14**	**8**	**4**	10	10	10	**7**	8	**4**	7	**4**	8	6	11	**5**
16	76	78	15	**14**	**7**	**10**	10	9	**9**	10	8	**5**	8	8	**5**	**5**	12	
17	78	77	15	**13**	**9**	**9**	10	**8**	10	10	8	8	8	8	6	**5**	12	10
18	78	**76**	**14**	**12**	**10**	**6**	10	9	10	**9**	8	8	8	8	8	7	12	
19	78	76	**14**	**14**	**10**	**11**	10	**8**	10	10	8	8	7	7	7	8	12	10
20	80	79	15	15	**11**	**11**	10	10	10	10	8	8	8	8	8	8	12	12
21	78	**63**	15	15	12	**11**	10	10	10	10	8	**7**	7	7	7	6	12	10
22	80	80	**14**	15	**10**	**10**	10	10	10	10	8	**8**	8	8	8	8	12	10
23	77	79	**14**	**13**	**8**	**8**	**7**	**5**	**9**	**9**	**7**	**7**	**6**	**5**	**6**	**5**	-	**6**
%**Pbn**	**14.2**	34.7	**38.1**	69.5	**90.4**	91.3	**23.8**	21.7	**23.8**	30.4	**19**	47.8	**14.2**	34.7	**14.2**	30.4	**4.7**	26

%pbn: percentage of patients scoring below normal level

Surgical treatment

All patients in this series were operated on from 3 to 9 months after the first symptoms. The average duration of surgery was 5 h (SD 1.2 h) and the average duration of the awake period was 2 h. The average intensity of the electrical stimulation was 4.3 mA (SD 1.4 mA). The operation was carried out without incidents in 20 patients. One patient presented repetitive seizures: therefore, electrostimulation was stopped. Another patient had an excessive anxiety, which imposed a rapid procedure with no extensive repeated mappings. Due to the prolongation of the surgery, one patient presented extreme fatigue that led to stop the procedure, which was completed in a second stage. There was no case of complication due to the anaesthetic procedure or cerebral oedema.

In all cases, cortical and/or subcortical stimulation induced transient language disturbances, demonstrating the presence of essential language structures in the immediate vicinity of the tumor. More precisely, slowness of initiation was elicited in the six patients with a lesion involving the supplementary motor area, anomia in the five patients with a lesion in the premotor area, anarthria in the six patients with a lesion involving the operculum and/or the insula, phonemic paraphasia in the patient with a lesion in the parietal area, and semantic paraphasias in the five patients with a lesion involving the parieto-temporo-occipital junction. In the 23 patients, the resection was stopped into the contact of these functional boundaries, provided by electrical mapping.

Immediate postoperative period (Table 1.)

No focal deficit was observed in 34.8% of the patients in the immediate postoperative period. Four patients presented a transient supplementary motor area syndrome (which recovered in a few days), six presented language disorders, one had a pure motor deficit and two a sensory deficit. Two patients presented a combined motor, sensory and language deficit.

In the immediate postoperative period, the KPS score was of 90% for 12 patients, 80% for ten patients, and 70% for one patient.

The results of the neuropsychological vWM assessment in the immediate postoperative period, expressed as the percentage of patients below normal limits in each test, were: DO80 30.4%; commands 69.5%; logic 91.3%; reading 21.7%; word repetition 30.4%; concrete phrase repetition 47.8%; abstract phrase repetition 34.7%; spelling 30.4%; and dictation 26.08%. Only one patient had results within the limits of normality (Table1.). Statistically significant differences between the preoperative and immediate postoperative results were observed in the auditory comprehension commands test ($p = 0.005$), concrete phrase repetition ($p = 0.031$), abstract phrase repetition ($p = 0.029$), spelling ($p = 0.008$) and sentence dictation ($p = 0.007$). There was no change in vWM function related to the completeness of resection, nor related to tumor location in primary or supplementary cortex (NS).

The histological examination revealed the diagnosis of WHO grade II glioma in the 23 cases (seven astrocytomas and 16 oligodendrogliomas).

Delayed postoperative examination at 3 months (Table 2.)

Seven patients had a normal clinical situation 3 months after surgery. Seizures persisted in three patients and they underwent an increase of antiepileptic therapy. One patient presented a slight right-sided paresis (who recovered almost to within normal limits 3 months later). Another patient had still mild language disorders. Finally, 11 patients mentioned slight difficulties in attention, in performing two tasks at the same time and mental fatigue among other symptoms.

The KPS score at this time was of 100% in seven patients, 90% in 13 patients and 80% in three patients.

The rehabilitation treatment, primarily focused on language and vWM, was carried out for all patients by our speech therapist (P. G.). In the eight last patients of the series, a neuropsychological assessment 3 months after surgery was again performed, and expressed as the percentage of patients with scores below normal value (Table 2.). Five patients recovered their preoperative vWM score, and three significantly improved it. The result for the DO80 test was 12.5%. The results for the BDAE subtests were: commands 62.5%; logic 87.5%; word repetition 25%; concrete phrase repetition 50%; abstract phrase repetition 12.5%; spelling 0%; reading 12.5%. *A statistical comparison of the results of both DO80 and global BDAE scores, before and three months after surgery, revealed that there was no significant difference (p > 0.05).* More precisely, in three BDAE subtests, the postoperative scores after 3 months were better than the preoperative scores, in reading, abstract phrase repetition and sentence dictation. The scores were equal in DO80 and word repetition, while the scores were slightly lower in commands, logic, concrete phrase repetition and spelling.

Discussion

Preoperative study of cognitive functions

The conventional neurological examination is ''classically'' thought to be normal in most patients harboring a LGG. Moreover, the majority of QoL assessement has been based on the sole KPS. However, this score is very incomplete, since it does not record data such as the emotional, social nor in particular cognitive status of the patient. As a consequence, in 2001, DeAngelis [6] has reported that patients with LGG had normal higher functions in 90% of cases.

Yet, our results call into question such a proposition. Indeed, while 22/23 patients had a KPS ≥90%, only two patients' results before surgery felt within the limits of normality for all the neuropsychological tests here performed. *Especially, it is significant that in tests requiring a greater involvement of vWM, up to 90.4% of the patients' results were below normal levels.*

Table 2 Postoperative vWM 3 months following LGG resection in eight patients

Patient	D080			Commands			Logic			Reading			Word repetition		
1	75	**55**	**64**	**14**	**8**	**12**	**9**	**5**	**4**	**6**	**4**	**7**	**8**	**8**	**9**
2	78	76	78	15	**13**	15	12	**11**	**10**	10	10	10	10	10	**9**
3	79	79	78	15	**13**	**14**	**9**	**7**	**10**	**8**	9	10	10	**9**	10
4	**52**	**64**	79	**13**	**14**	**14**	**6**	**11**	**7**	**7**	9	10	**9**	10	10
5	77	80	79	15	**10**	**14**	**10**	**8**	**11**	9	9	10	10	10	10
12	80	78	79	15	15	15	**11**	**8**	**10**	10	10	10	10	10	10
21	78	**63**	80	15	15	15	12	**11**	12	10	10	10	10	10	10
22	80	80	80	14	15	**14**	**10**	**10**	**11**	10	10	10	10	10	10
%Pbn	12.5	37.5	12.5	37.5	62.5	62.5	75	100	87.5	37.5	12.5	12.5	25	25	25

Patient	Concrete phrase repetition			Abstract phrase repetition			Spelling			Sentence dictation		
1	**7**	**6**	**7**	7	**4**	7	6	1	5	12	11	12
2	8	8	**7**	8	**6**	8	8	7	7	10	10	12
3	8	**6**	**7**	7	**2**	8	8	**5**	8	**4**	**4**	12
4	**6**	**7**	**7**	**4**	7	**6**	8	8	8	12	12	12
5	8	**7**	8	8	7	8	8	7	8	12	**9**	12
12	8	8	8	**6**	8	8	7	6	8	12	**6**	12
21	8	**7**	8	7	7	8	8	6	8	12	10	12
22	8	8	8	8	8	8	8	8	8	12	10	12
%Pbn	25	62.5	50	25	37.5	12.5	0	25	12.50	12.5	37.5	0

WM is a common instrument of the higher functions since it enables to temporarily retain information to be manipulated [8]. For language, i.e. vWM, the information is maintained through the articulatory process. In the framework of Baddeley's model, vWM is divided into a phonological store and an articulatory rehearsal module. The former would involve the left supramarginal gyrus, whereas the latter would be distributed rather over the left inferior frontal (Broca's) area. This manipulation is essential for carrying out complex cognitive tasks [8]. Thus, a systematic study of LGG patients' vWM enables to provide a representation of their higher functions' overall performance. If the vWM is slightly affected, this only leads to a dysfunction in those tasks requiring a high degree of vWM, such as for instance more abstract problems. Moreover, recent articles suggest a close interaction between the WM neural networks and the processes of selective attention and decision making [12]. Test efficiency could therefore be optimized by including additional examination of these functions, and by refining cognitive assessment tools, as previously suggested in stroke and brain injury [13].

Interestingly, our results are in accordance with recent publications, which have reported that, in fact, LGG were most often associated to cognitive deficits, identified only if accurate neuropsychological assessments were made [7]. Indeed, extensive examinations of higher functions in patients harboring LGG have shown cognitive deficits, in particular involving executive functions [14], picture and word recognition memory [15] or verbal fluency performance.

However, antiepileptic drugs may also have an adverse effect on cognition [7]. In addition, seizures themselves can affect higher functions, whilst also causing significant obstacles to the patient's psychosocial adaptation [7]. In 38% of patients from our series, the seizures had not been completely controlled before surgery even though anticonvulsivant medications were used.

On the other hand, it is remarkable that patients with voluminous LGG located within eloquent regions have only mild deficits, since necessitating extensive neuropsychological assessment to be detected. One likely explanation is the potential of brain plasticity, which allows constant functional reorganization whilst the tumour proliferates and spreads [16]. Such functional compensation is especially based on the recruitment of perilesional areas. Consequently, since even mild cognitive disorders could be interpreted as a limit of brain plasticity potential, it is crucial for LGG resection that a very accurate and reliable intraoperative functional mapping can be performed, in order to preserve imperatively the peritumoral eloquent sites essential for recovery [16].

Immediate postoperative study of cognitive functions

In the immediate postoperative period, the neurocognitive assessement worsened in 22 out of 23 patients, despite 52% of KPS ≥ 90%. In five out of the 9 tests, the differences between preoperative and postoperative scores were statistically significant. These findings confirm that LGG surgery within eloquent areas has temporary negative effects on cognition. While in accordance with the well-known possible neurological (sensorimotor and language) worsening when the resection comes into contact of the functional cortico-subcortical pathways [2, 3], these data also show that vWM assessment is more sensitive than classical KPS to detect post-operative impairment (as described preoperatively). However, tests requiring less involvement of the vWM are not notaby affected after surgery, whereas tests requiring higher vWM participation had lowest scores. Indeed, in the logic and reasoning tasks, 91.3% of the patients obtained scores below normal levels. Such data are important, since as for sensorimotor functions, neurosurgeons should inform patients and their families about this risk of worsening, albeit transient, of cognition. This would also help to plan an intensive and specific rehabilitation program for the immediate postoperative period, to recover more effectively and rapidly.

Delayed postperative study of cognitive functions

Complete data is only available for the last eight patients of the series. While this is a very small sample, the great interest is to benefit, for the first time to our knowledge, *from a longitudinal neuropsychological study of vWM before and following surgical resection of LGG* – moreover, before and after specific rehabilitation during the postoperative period.

Scores for sentence dictation, abstract phrase repetition and reading tests were higher 3 months after surgery than in the preoperative period. In two more tests, the scores were unchanged. Thus, the patients not only recover their cognitive functions, but also they may surpass certain preoperative test scores 3 months after surgery in comparison to the preoperative status. At least three explanations could be suggested. First, a decrease of loco-regional mass effect due to the resection of the more bulky LGGs, in particular the left insular tumors, allowing decompression of perilesional areas often involved in the functional compensation [16]. Second, a potential unmasking of latent cognitive networks induced by the cortical hyper-excitability due to the surgical act itself, as previously described for sensorimotor and language functions [17]. Third, a likely important participation of the specific neurocognitive rehabilitation on vWM [18], as already demonstrated in aphasia [19]. In this way, the incomplete normalization of scores 3 months after surgery in the three last tests in which vWM is highly involved (auditory comprehension tests of commands and logic, and concrete phrase repetition), could be due to the need for a longer or more adapted WM rehabilitation.

Finally, from an oncological point of view, we suggest to perform regular neuropsychological examinations during a longer follow-up, to detect an eventual LGG recurrence through a worsening of the cognitive functions without any other symptoms—as recently reported [20]. Moreover, the rapidity of the neuropsychological worsening might be correlated to the aggressiveness of the glioma [16].

Conclusions

Our study shows that patients harboring a LGG in language areas, even if they usually have a ‘‘normal’’ clinical examination, and a ‘‘normal’’ score according to functional scales classically used in neuro-oncology (e.g. KPS), present in fact an actual cognitive deficit more frequently than previously thought. Such a decline of higher functions can be detected by performing a more systematic neuropsychological assessment, especially by examining vWM, before any treatment. Furthermore, despite the use of intraoperative functional mapping, particularly for language, surgical resection induces most of the time an immediate postoperative cognitive worsening, again identified if a neuropsychological examination is performed—and not systematically by KPS alone.

Therefore, in order to improve the QoL of patients operated on for a LGG, it can be considered:

– to better recognize cognitive deficits before and after surgery. To do that, it is essential to establish new batteries to complete the assessment of higher functions, and to perform such extensive neuropsychological examination, not limitated to the vWM, in all the patients with a LGG (whatever the location of the tumor). Moreover, such batteries would also enable to better understand the brain reshaping due to LGG growth and to surgery, then to adapt specific cognitive rehabilitation programm;
– and to monitor WM during glioma resections, in the same way than motor, sensory and language functions, at least in selected patients (e.g. in relation to their preoperative cognitive status);

Finally, from a fundamental point of view, such systematic studies should increase our knowledge of the functional anatomy of WM, which is an essential function for cognition thus for QoL, in order to complete the model proposed by Baddeley [8].

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