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CLINICAL STUDY - PATIENT STUDY

Neurocognitive training in patients with high-grade glioma: a pilot study

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Abstract Although their neurocognitive performance is one of the major concerns of patients with high-grade gliomas (HGG) and although neurocognitive deficits have been described to be associated with negative outcome, neurocognitive rehabilitation is usually not integrated into the routine care of patients with malignant gliomas. In this pilot trial, a weekly group training session for attention, verbal, and memory skills was offered to patients with HGG with pre and post-training evaluation. Eleven patients, six with glioblastoma multiforme and five with WHO grade III gliomas, median age 50 years, with a Karnofsky performance score of 80–100 participated in ten group training sessions of 90 min. For evaluation at baseline and after the training by a neuropsychologist not involved in care or training of the patients, Trail Making Tests A and B (TMTA and TMTB), Hopkins Verbal Learning Test (HVLT), and the Controlled Oral Word Association Test (COWA) were used. Comparison of mean group differences between baseline and at post-training evaluation after 12 weeks revealed improvement across all neurocognitive variables. The patients showed a great diversity in their performances, with worsening, improvement, and stabilization. However, a significant group difference was detected only for the HVLT (score 19.6 $\pm$ 8.9 at baseline, 23.6 $\pm$ 8.8 after 12 weeks, $P = 0.04$). This pilot study shows that neurocognitive training in patients with HGG is feasible as group training with weekly sessions and might be able to induce improvements in attention and memory skills.

Keywords Neurocognitive training · Hopkins Verbal Learning Test · High-grade glioma

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Introduction

Losing one's personality, cognitive skills, and memory is a terrifying vision for everyone, yet it is a realistic imminent threat for patients living with malignant gliomas. The outcome of cognitive abilities in patients with brain tumours has been repeatedly addressed, mostly for children surviving after brain tumours and adults with low-grade gliomas [1–7, 8–16]. There are fewer data for patients with high-grade gliomas (HGG) and their cognitive outcome [17–19]. As more and more patients with HGG survive for longer periods, this issue becomes more relevant with time. Bosma et al. evaluated prospectively the course of neurocognitive functioning in a cohort of 32 patients with HGG [18]. Compared with baseline assessment after surgery and before radiotherapy, at eight and sixteen-month follow-up they found deterioration in attention, information capacity, and psychomotor speed. Cognitive decline was more pronounced in patients with tumour recurrence and in patients under medication with either corticosteroids and/or antiepileptic drugs. Of note, patients with tumour recurrence

already performed worse at baseline, thus confirming the negative prognostic impact of a neurocognitive deficit in patients with HGG. The same group has shown that cognitive deficit is associated with shorter survival in patients with GBM and that in patients with low-grade glioma, cognitive functioning was negatively affected by epilepsy and by the use of antiepileptic drugs [20, 21]. In 80 patients with recurrent HGG, Meyers et al. demonstrated that performance in a test of verbal memory was independently and strongly associated with survival duration, when adjustments were made for age, Karnofsky performance score (KPS), and number and extent of surgical resection [22]. Interestingly, performance in the activities of daily living (ADL), although strongly influencing the patient's quality of life, failed to impact on the duration of survival. Corn et al. recently demonstrated a continual deterioration in cognitive functioning in patients with GBM [23], Steinbach, Bahr, and Hottinger mentioned significant prevalence of cognitive deficit in long-term-surviving patients with glioblastoma in Germany and the USA [24–26]. Previous series demonstrate the impact of the volume of the radiation field, the extent of resection, and the duration of follow up as adverse factors on cognitive functioning in patients with HGG [27–31]. Furthermore, tumour histology was not predictive for cognitive performance in 24 patients with GBM compared with 24 patients with anaplastic astrocytomas [32].

Nevertheless, neurocognitive training or "cognitive rehabilitation" is not included in the routine care of patients with HGG. Until recently this would have been regarded as futile—time and resource consuming for patients, relatives, care givers, and personnel.

On the other hand, because neurocognitive deficits in long-term-surviving patients with malignant gliomas are well described and involve attention deficits and verbal memory, methods of neurocognitive training addressing these issues could potentially be effective in reducing cognitive decline. The holistic mnemonic training developed by Dr Stengel in Vienna in the 1950s fulfils all the criteria of effective neurocognitive training and has been proved as effective in children as in adults with various handicaps, for example demented patients [33].

In order to answer a previously unmet need of patients with malignant gliomas at our centre, we started a pilot study on neurocognitive training, in accordance with Dr Stengel's memory training.

Patients and methods

Patients

Patients were recruited from the outpatient clinic. Patients with good performance status (KPS 80–100%) were asked in a non-directive setting to consider their participation in the training course with pre and post-training evaluation. For feasibility reasons, we asked patients living in the proximity of the hospital, who were not professionally active, able to speak and to read German, without aphasia, and without evidence of tumour recurrence according to the most recent MRI control. All patients had been treated by maximal feasible tumour resection (biopsy, subtotal resection, gross total resection), radiation with 60 Gy over six weeks with 2 Gy per fraction and concomitant and adjuvant chemotherapy at the Medical University of Vienna, Austria).

Methods

The protocol had been reviewed and was approved by the local Ethics Committee.

The training includes ten weekly sessions of 90 min according to Dr Stengel's holistic mnemonic training, and pre and post-training assessment.

Holistic mnemonic training

This training discipline is based on a "holistic form of memory empowerment" using all the senses, emotions, and intellect of an individual. It engages the whole spectrum of mental activities through exercises referring to skills useful in every day's life. The objective of the training is to promote mental capacity, to preserve the functional potential for intellectual ability and memory, and to reactivate actually restricted capacities. Patients perform the training in a relaxed ambiance without pressure to perform or time pressure. The opportunity to perform the training in a small group allows the development of social skills and group dynamics. Each patient has the opportunity to watch and to listen to other attendees, to experience their proposed solutions to the exercises, and to train to accept their contributions and personalities.

In each training session all aspects of mental activity are separately addressed, using exercises to train perception, concentration, attention, memory, retentiveness, verbal memory, and creativity. Special emphasis has to be put on training concentration skills and letting patients experience their range of concentration and further proving directing exercises to enhance their power of concentration.

Another important task is to empower short term memory in order to facilitate the processes of learning new information, putting it into context and providing mnemotechniques. To enable attendees to achieve these objectives, the training motivation of each participant has to be maintained. For patients with handicaps special attention is needed to avoid stress because of time or performing pressure. The role of the trainer is to provide

impulses as tools for solution of a problem, not the solution itself. He/she has to encourage autonomous thinking processes in order to enable the attendees to use their newly acquired skills in their every day life. The objectives of this holistic training are to develop not only intellectual capacity but also physical and emotional well being, as this enables humans to maximize their capacities in thinking, recalling, formulating, and creating.

Assessment

Pre and post-course assessments were done by a psychologist not involved in the care for the patients. No other person, neither physician nor family members, were present in the same room during testing. The psychologist used the a test battery consisting of Hopkins Verbal Learning Test (HVLT) for verbal memory, Trail Making Tests A and B (TMTA and TMTB) for visual motor speed and executive function, and the Controlled Oral Word Association (COWA) test for verbal fluency for three letters in 3 min, as published earlier by Herman et al. [34]. The interval between pre and post-course testing was 12 weeks.

The same tests were administered for pre and post-course assessment.

Statistics

The primary results measured in this pilot study were recorded using standard descriptive statistical terms as mean, median, range, and standard deviation (SD). Statistically significant impairment was defined as deviation of more than 1.5 SD from the mean for healthy age-matched subjects for the Hopkins Verbal Learning Test and a score below the 10th percentile for the normative population in the Trail Making Tests and in COWA, similar to the study by Herman et al. [34].

Results

Patients

In the pilot training, we included 11 patients with histologically confirmed high-grade glioma, who gave informed consent after being informed about modalities, expenditure of time, and timing of the training and the neurocognitive assessments before and after the training course.

Of twenty-six screened patients, eleven (seven men, four women, aged 23–73 years with a median of 50 years) agreed to undergo the training. Their biographical details are given in Table 1. There were six patients with glioblastoma multiforme and five patients with HGG, including two patients with anaplastic astrocytomas, two with anaplastic oligodendrogliomas, and one with an anaplastic oligoastrocytoma. Two identical courses were held, one for patients 1–6 and one for 7–11. The time elapsed since the first diagnosis of glioma ranged from to 10 to 42 months, median 15 months. All patients were right handed and suffered from supratentorial gliomas, five gliomas of the right hemisphere and six gliomas of the left. Three patients had already suffered from tumour recurrence, none had undergone second surgery after recurrence. The time since diagnosis of the recurrence was 19 months for patient 2, 3 months for patient 3 and 28 months for patient 5. At the beginning of the training, only one patient was treated with dexamethasone (patient 3). All patients received anti-epileptic drugs because of symptomatic epilepsy during the course of their disease.

Eleven patients were admitted and performed the whole training and assessment. Fortunately, no disease progression occurred within the study period. Subsequently, however, progression of the disease occurred in five patients.

Outcome of cognitive training

Cognitive testing pre and post-course demonstrated that the patients showed great diversity in the performances measured by the tests and also in the changes observed after the training course. At baseline examination, the performances of patients below 1.5 SD of the normal population ranged from 9% for TMT-A up to 57% for HVLT. At post-training, the performances of patients below 1.5 SD of normal population ranged from 9% for TMT-A up to 43% for HVLT (Table 2).

Comparison of mean group differences between baseline and post-training assessment revealed improvement across all five neurocognitive variables. However, because of the small sample size, separate dependent *t*-tests detected no statistical significant group differences for neurocognitive variables (all P values > 0.05) except for HVLT total learning (P value < 0.05) (Table 3).

Patients' performances in the tests are shown in Fig. 1a–d as an overview of improvement, stabilization, or worsening in the individual tests for the patients. In total, every patient showed some improvement in at least one test.

After their last training session, the patients were asked by an anonymous questionnaire to evaluate the training program, the trainer, and their own performance, and their satisfaction with the course. All of the patients were satisfied with the program, with the trainer, and would like to participate in a refresher course.

Table 1 Patients' characteristics, treatment modalities, anti-epileptic medication, and outcome

Patient no.	Sex	Age in years at diagnosis	Date of diagnosis	Tumour location	Left/right	Extent of surgery	Histology	KPS	Chemo-therapy regimen	AED	Professional activity after training course	Follow up
1	m	30	12/2006	Frontal	R	S	OD WHO III	90	TMZ conc + adj	Phenytoin	Student	Alive and well
2	m	70	8/2006	Parietal	L	S	GBM	90	TMZ conc + adj Imatinib + HU	Phenytoin	Retired	Alive and well
3	f	55	7/2006	Frontal	R	B	GBM	90	TMZ conc + adj	Levetiracetam	Clerk	Alive and well
7	m	61	8/2006	Temporal	L	S	GBM	80	TMZ conc + adj	Carbamazepine	Retired	Recurrence 4/08, died 12/08
5	f	23	2/2004	Fronto-parietal	R	S	AA	100	TMZ conc + adj	Carbamazepine	Student	Alive and well
6	m	31	9/2005	Parieto-occipital	R	S	GBM	90	TMZ conc + adj	Carbamazepine Lamotrigine	20 h/week air traffic controller	Recurrence 10/07, died 12/07
7	f	37	4/2004	Fronto-temporal	R	S	AA	80	TMZ 5/28	Carbamazepine	Housewife	Alive and well
8	m	73	2/2008	Parietal	R	T	GBM	90	TMZ 5/28	Carbamazepine	Retired	Relapsed
9	m	49	4/2005	Fronto-parietal	L	T	GBM	90	TMZ conc + adj	Levetiracetam zonisamide	None	Alive and well
10	m	53	3/2007	Frontal	L	S	AOA	100	TMZ conc + adj	Carbamazepine	40 h/week clerk	Alive and well
11	f	44	5/2008	Temporal	L	S	GBM	80	TMZ conc + adj	Carbamazepine	Housewife	Relapsed 12/08

Extent of surgery: B, biopsy; S, subtotal resection; T, gross total resection

Tumour location: L, left hemisphere; R, right hemisphere

GBM, glioblastoma multiforme; AA, anaplastic astrocytoma; AOA, anaplastic oligoastrocytoma; OD, oligodendroglioma; KPS, Karnofsky performance score at begin of the training; TMZ, temozolomide; conc + adj, concomitant + adjuvant; 5/28, temozolomide 200 mg/m^2, day 1–5, every 28 days for 6 months; HU, hydroxy-urea; AED, anti-epileptic drug

Table 2 Percentage of patients with significant impairment for each test

	Baseline *N* (%)	Post-training
Psychomotor speed (TMT-A)[a] ($N = 11$)	1 (9)	1 (9)
Sustained attention (TMT-B)[a] ($N = 11$)	2 (29)	3 (42)
Verbal fluency (COWAT)[a] ($N = 11$)	3 (27)	2 (18)
Verbal Memory Total Learning (HVLT)[a] ($N = 11$)	4 (57)	3 (42)
Verbal Memory Delayed Recall (HVLT)[a] ($N = 11$)	4 (57)	3 (42)

TMT, Trail Making Test; COWA, Controlled Oral Word Association; HVLT, Hopkins Verbal Learning Test

[a] Age-adjusted impairment 1.5 × SD below mean for a normal population

Discussion

Providing cognitive training to patients with glioblastoma multiforme is not part of current standard treatment. This pilot study demonstrates that over a period of 3 months patients with HGG and even with glioblastoma improved markedly in attention and memory skills after weekly group training sessions. Neurocognitive assessment revealed a broad spectrum of cognitive impairment in patients compared with a normal population at baseline testing. Whereas a single patient showed difficulties in visual motor scanning speed at baseline testing, almost half of the patients showed a verbal memory deficit. After 10 weeks of training, assessment detected improvements across all cognitive functions on a group basis. As expected, neuropsychological testing showed both improvement and deterioration in cognitive performances in individual patients.

It can be stated that the duration of survival of patients with malignant gliomas is still very restricted, that the probability of reintegration into an independent or professional life is unlikely or exceptional, and that cognitive rehabilitation is futile or even cruel because it reminds them their deficits. The time spent on training and on transport to the training is time spent in a hospital based environment, and not part of the patient's choice for private activities. On the other hand, the whole initiative was started in response to repeated demands from patients whether there was a meaningful way to perform cognitive training and to prevent cognitive decline. Moreover, it has been established that neurocognitive function is an independent predictor of survival in patients with brain tumours [5, 22, 35, 36]. The patients participating voluntarily in the training course of this study adhered to the program, came regularly to the training sessions, practised at home, and gave a positive evaluation to the whole course and to the coach who performed the training. This coach had undergone special training to work with handicapped persons and demented patients and handled skilfully to maintain motivation and participation of all individuals in the group in a respectful and validating manner. The small size of the training group allowed, on the one hand, activation of the participation of each patient while considering individual needs and, on the other hand, pausing or listening to individual patients only according to their preferences or temper. The great diversity of age, sex, and professional and educational background in this small pilot group enabled the patients to avoid stressful comparisons and competition, and, as guided by the coach, supported mutual assistance and respect. The training helped the patients to regain some self confidence. They all showed some improvement in the skills tested, at least in one of the four tests—and not the lack of improvement in repetitive testing which is frequently seen in patients with cognitive sequelae after systemic cancer therapy [1, 28, 37–45]. Of note, all of the patients of this series were treated with antiepileptic drugs during the course and at both assessments. Antiepileptic drugs have been shown to reduce neurocognitive performance in patients, but less than uncontrolled epileptic seizures would do [35, 36, 46]. Taphoorn et al. have also shown that the tumour itself was the most important factor affecting cognitive function in patients with brain tumours. Nevertheless, after completion of the course, two

Table 3 Means and standard deviation for baseline, 3 months post-training and change score for each neuropsychological measure

	Baseline	Post-training	Difference score	Dependent *t*-test (*P*-value)
Psychomotor speed (TMT-A)[a] ($N = 11$)	34.8 ± 15.4	32.5 ± 14.6	−2.2 ± 5.8	0.22
Sustained attention (TMT-B)[a] ($N = 7$)	121.3 ± 87.4	101.9 ± 69.8	−19.4 ± 33.4	0.17
Verbal fluency (COWAT)[b] ($N = 11$)	6.9 ± 4.0	8.7 ± 4.8	1.8 ± 5.4	0.29
Verbal Memory Total Learning (HVLT)[b] ($N = 11$)	19.6 ± 8.9	23.6 ± 8.8	4.0 ± 4.2	0.04
Verbal Memory Delayed Recall (HVLT)[b] ($N = 11$)	5.6 ± 4.7	7.3 ± 4.0	1.7 ± 2.4	0.11

TMT, Trail Making Test; COWA, Controlled Oral Word Association; HVLT, Hopkins Verbal Learning Test

[a] Negative values of the difference score indicate improvement

[b] Positive values of the difference score indicate improvement

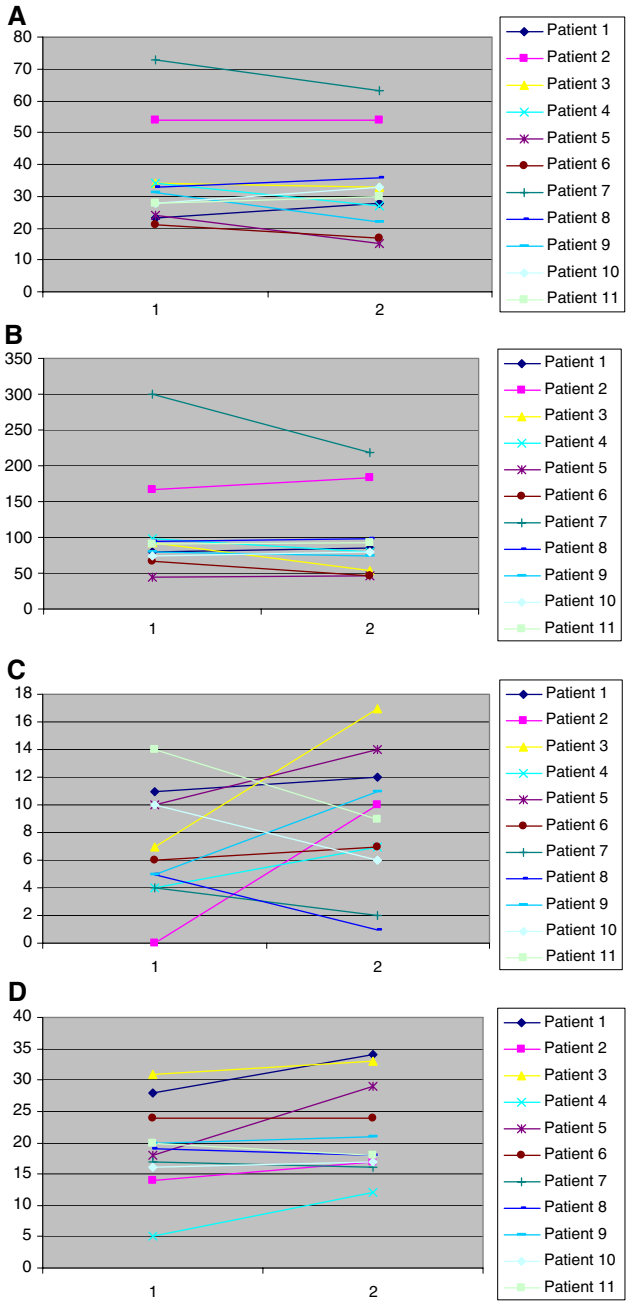

Fig. 1 Individual patients' performances in the neurocognitive tests at baseline (*1*) and after 10 weeks of group training (*2*). **A:** Trail Making Test A: measures the time in seconds patients use to connect in sequential order 25 numbers randomly distributed on a page. **b**: Trail Making Test B: measures the time in seconds patients need to connect numeric alphabetic pairs (e.g. 1-A-2-B-3-C…) randomly distributed on a test page. **c**: Controlled Oral Verbal Association (COWA): Patients are asked to say aloud as many words as possible beginning with a given letter within 1 min. This challenge is done three times with three different letters within 3 min. **d**: Hopkins Verbal Learning Test: patients hear a list of 12 words and are asked to recall as many as possible, repeated three times

patients continued their studies and three of the patients re-started working, one part time as air traffic controller, the two others as clerks. So, at least for some time, these patients were able to regain a "normal life pattern" despite their burden as glioblastoma patients.

This pilot study demonstrates that the efforts spent in neurocognitive training of patients with HGG, even glioblastomas, is not invariably futile and that further endeavours in patient empowerment might be worthwhile. Although the situation is indeed different, the concept is comparable with the situation of muscular training for patients with cardiac diseases several years ago, when one was used to thinking that muscular training would overstrain and therefore be detrimental to those patients. Meanwhile, individually fitted adequate training has become one of the most efficacious therapies in cardiologic rehabilitation. Hopefully, a comparable positive result will become achievable for patients with malignant gliomas.

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