Original Article

Hyperbaric Oxygen Treatment Improved Neurophysiologic Performance in Brain Tumor Patients After Neurosurgery and Radiotherapy

A Preliminary Report

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BACKGROUND: Cognitive performance often is impaired permanently in long-term brain tumor survivors after neurosurgery and radiotherapy. Hyperbaric oxygen treatment (HBOT) stimulates neovascularization of hypoperfused tissue and may result in improved functionality of damaged tissue. In this pilot study, clinical neurophysiologic tests were used to assess the effect of HBOT on brain performance. **METHODS:** Ten long-term brain tumor survivors received HBOT for severe cognitive deficits after neurosurgery and radiosurgery. Patients were tested before HBOT and at 6 weeks and 4 months after HBOT. The tests comprised a quantitative electroencephalographic (EEG) examination, the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) for memory performance, and 2 cognitive tests, the number connection test (NCT) and the continuous reaction time test (CRTT). Late event-related components (LERCs) of averaged evoked EEG responses to a visual odd-ball stimulus were analyzed from whole-head activity maps. For comparison, a control group of healthy individuals (no HBOT) also were investigated. **RESULTS:** After HBOT, the amplitude of the LERC with the longest latency, P3b (involved in object interpretation) was improved significantly ($P = .02$). The amplitudes of the N200 (occipital, negative) and the intermediate P3a (centroparietal, positive), LERCs with shorter latencies, and of a small, positive, occipital visual component did not change. Neither latencies nor reaction times changed after HBOT. However, P3a and P3b (parietal, positive) latencies were longer in survivors than in healthy individuals. The NCT produced inconclusive results, but the IQCODE revealed an improvement. When outcomes of the NCT, CRTT, IQCODE, and P3b amplitudes were evaluated in common tests, HBOT appeared to provide substantial improvement ($P<.006$). **CONCLUSIONS:** On the basis of the current results, the authors concluded tentatively that HBOT improves neurophysiologic performance in long-term brain tumor survivors. ***Cancer* 2011;117:3434–44.** *© 2011 American Cancer Society.*

KEYWORDS: radiation damage, cognition, hyperbaric oxygen treatment, electroencephalography, evoked potential mapping..

Brain damage with *cognitive* dysfunction is a feared complication after neurosurgery and radiotherapy (RT) of a brain tumor, and virtually no medical interventions have produced significant or lasting improvement.[1] The incidence and severity of cognitive deficits is related to tumor volume and site, the extent of surgery, radiation volume, total dose, fractionation dose, and radiation technique.[2-7]

Complaints of brain damage vary among these patients. Diminished cognitive performance reportedly is be the most prominent.[8-10] Principally, progressively reduced short-term and working memory and attention underperformance are frequently reported.

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The anatomic substrate of radiation toxicity is microvascular failure.[11] In particular, cognitive impairment from radiation involves damage of the hippocampus.[12] It is believed that the suboptimal microcirculation in the vicinity of the tumor area causes neuronal dysfunction and cell death. In addition, damage to white matter can occur.[13,14] It also is believed that demyelination results in increased propagation time of action potentials (as with multiple sclerosis), resulting in delayed cortical processing. Recording and analyzing electroencephalographic (EEG) responses is a well known and widely accepted method in clinical neurophysiology for establishing dysfunction in the cerebral processing of sensory and cognitive information.

Compared with the extensive literature on radiation damage in brain tumor patients, studies on the mechanisms of cognitive disturbances from neurosurgery are remarkably scarce. However, in addition to direct damage from the dissection of normal brain, hypoxia during and after surgery and irreversible disturbance of the microvascular environment probably contribute to long-term cognitive sequelae.

It is known that hyperbaric oxygen treatment (HBOT) induces neoangiogenesis in irradiated tissue in animal models,[15] and it also has been indicated in clinical studies.[16,17] HBOT is an accepted and effective treatment for hypovascular radiation damage, such as radiation ulcers and cystitis.[18,19] However, the effect of HBOT on chronic brain damage after neurosurgery and RT in adult patients with brain tumors rarely has been investigated.[18] Possible mechanisms of HBOT include the mobilization of endothelial progenitor cells by the induction of bone marrow nitric oxide and by the increase of vascular endothelial and fibroblast growth factors.[20-22]

Hulshof et al[10] studied 6 brain tumor survivors with late brain damage who underwent HBOT at least 1 to 5 years after RT. Those patients were subjected to neuropsychological tests, which yielded variable results. Because only 1 patient improved, it could not be concluded that HBOT generally was successful. This may have been because of the long interval between RT and HBOT (up to approximately 10 years). Another concern is that the patients generally were in poor condition (tumors up to grade 3), which may have resulted in less sensitivity for HBOT and less stable day-to-day performance than what could be achieved in healthier individuals.

A review discussing tissue and organ-type damage after RT concluded that there is no evidence for a benefit from HBOT for neural tissue.[18] However, in children, it was demonstrated that HBOT initially decreased various types of neurologic symptoms of RT damage to brain tissue.[23] Those neurologic improvements after HBOT may have been caused by easier action potential generation by the somatic axon hillock, by faster action potential propagation because of better myelination, and/or by better synaptic transmission.

In the current, small study, we investigated the effect of HBOT in brain tumor patients who had chronic brain damage after RT preceded by neurosurgery. To decrease the influence of daily variability in cognitive performance, the main method of investigation was an EEG approach of recording evoked potentials (EPs) to visual stimulation combined with a limited neuropsychological cognitive examination.

MATERIALS AND METHODS

Participants

Ten patients received HBOT for moderate-to-severe complaints of cognitive impairment after neurosurgery and RT for a brain tumor. Table 1 presents the main characteristics of the patients with regard to age, sex, details of the brain tumor and pre-HBOT disorders and complaints, the time between RT and HBOT, and the number of HBOT sessions. Three patients were examined with extensive neuropsychological testing by our Department of Neurology. We concluded that Patient 1 suffered from slight mental slowness, Patient 2 had an amnestic syndrome, and Patient 8 suffered from mental inflexibility with verbal memory disorders. General neurologic assessment indicated that nearly all patients suffered from chronic fatigue 1 month or more after RT, and 3 of them (Patients 4, 6 and 7) manifested motor complaints. All patients used antiepileptic drugs.

The tumors were highly varied with respect to their histologic type, location, history, and preceding treatment. Figure 1 provides an example from Patient 4, who had a meningioma of the right frontocentral cortex (cerebral falx) before RT, 3 years after extirpation. She suffered from chronic fatigue, reduced short-term memory (also for speech), and impaired locomotion and control of her arm and hand (both left).

All patients were in a stable clinical condition and had normal sleep during the night before the examination. Patients were instructed not to use alcoholic drinks or nonprescribed drugs on the day of testing, on the day before HBOT, and on the days during HBOT. All

Table 1. Patient Characteristics, Previous Treatments, Disorders Before Hyperbaric Oxygen Treatment (HBOT), HBOT Data, Subjective Response, and Current Status

	Patient Characteristics				Treatment Before HBOT		Disorders and Complaints Before HBOT			HBOT Data		Subjective Response and Current Status		
Patient No.	Age, y	Sex	Tumor Histology	Location	Surgery	Radiation Dose, Gy	Chronic Fatigue	Memory Capabilities	General Mental Performance	Sensory or Motor Function	Interval Radiotherapy-HBOT, y	No. of Sessions	Clinical Response After HBOT	Survival After HBOT, y	Current Status as of Jan. 22, 2010
1	32.9	Man	Atypical meningioma	Left frontotemporal	GTR	26 (Pediatric dose); 30×1.8	+	Slightly impaired, slow	Rather impaired	Impaired	0.23	30	Improved	5.9	Alive and worse
2	41.8	Man	Anaplastic oligodendroglioma	Midbrain	Bx	33×1.8	+	Severely impaired	Impaired	Normal	10	40	Not improved	3.7	Alive and stable
3	49.5	Man	Non-Hodgkin lymphoma	Right occipital	Bx	20×2	+	Impaired	Impaired	Normal	5.9	31	Marginally improved	6.2	Alive and well
4	51.1	Woman	Meningioma "en plaque"	Extensive surface right frontoparietal	STR	30×1.8	+	Impaired	Impaired	Impaired	0.3	45	Much and durably improvement	10.1	Alive and stable
5	51.5	Woman	Glioblastoma	Left parietofrontal	GTR	4×7	++	Slightly impaired	Rather impaired	Impaired	12	29	Transient improvement	9.6	Alive and very well
6	55.0	Woman	Solitary brain metastasis (primary: lung)	Right occipital	GTR	12×2.5 Plus 4×6 boost	+	Severely impaired	Impaired	Impaired	0.6	29	Much and durably improved	6.4	Alive and stable
7	57.5	Woman	Non-Hodgkin lymphoma	Left parietal	Bx	20×2 Plus 5×2 boost	+	Impaired	Severely impaired	Severely impaired	8	40	Transient strong improvement	12.0	Alive and stable
8	58.2	Man	Oligodendroglioma	Right frontal	STR plus Chemo	30×18	+	Impaired	Rather impaired	Normal	0.3	30	Not improved	6.3	Alive and stable
9	59.0	Man	Solitary brain metastasis (primary: kidney)	Right frontotemporal	GTR	12×2.5 Plus 4×6 boost	++	Nearly normal	Impaired	Normal	0.3	52	Transient improvement	1.0	Dead
10	75.0	Man	Solitary metastasis of unknown primary	Left occipital	GTR	12×2.5 Plus 4×6 boost	+	Impaired	Impaired	Impaired	1	30	Transient improvement	1.5	Dead

Gy indicates grays; GTR, gross total resection; Bx: biopsy; STR subtotal resection; Chemo, chemotherapy.

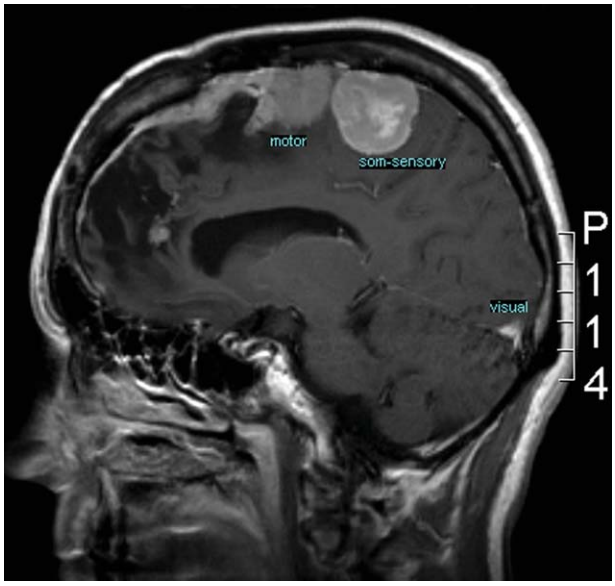

Figure 1. This is a T1-weighted magnetic resonance image (sagittal view) with gadolinium contrast from Patient 4, who had severe cognitive problems after she underwent repeated neurosurgical resections and received definitive radiotherapy for a meningioma "en plaque." Som-sensory indicates somatosensory.

participants had normal binocular vision, and, if necessary, they received optical correction.

Twenty-three age-matched and sex-matched, healthy control individuals from a previous EEG study were used for comparison.[24] Ten matched healthy individuals were used for the other tests.

HBOT was not offered as an experimental treatment. Because no invasive evaluative tests were used for HBOT, neither a signed, formal, written consent nor insurance warranty was required. The neurophysiologic part of the study was approved by the hospital medical ethical committee in accordance with the Declaration of Helsinki and Dutch law. All patients received an information letter describing the study objective and conditions and stating that the evaluative tests would be used for study purposes only.

Hyperbaric Oxygen Therapy

Patients were subjected to HBOT sessions 5 times weekly for 6 to 8 weeks. After pressurizing to 2.5 bar, the breathing gas was delivered by a mask that was fit gas-tight to the patient's face. Three 20-minute blocks of oxygen breathing were separated by 5 minutes of air breathing. The pace of pressurizing and depressurizing was 0.1 bar per minute. None of the patients had an epileptic seizure during the HBOT sessions or for the remainder of the same day.

EEG Examination and Cognitive Tests

The EEG was performed by whole-head, multielectrode EEG mapping, which allowed the evaluation of basic cognitive performance by a visually related simple memory task. To examine the effect of HBOT more extensively, the patients also were subjected to a number connection test (NCT) and a continuous reaction time test (CRTT), and they had to answer a questionnaire about memory performance (the Informant Questionnaire on Cognitive Decline in the Elderly [IQCODE]).

One week before the start of the HBOT sessions, the patients were subjected to an EEG examination, the NCT, the CRTT, and questionnaire. The second and third test sessions took place 6 weeks and 4 months after the cessation of HBOT. The sequence within the session was NCT, EEG, CRTT, and questionnaire.

NCT

The NCT was developed to test visual-sensorimotor integrity in patients with hepatic encephalopathy, and it has been tested often in combination with EEG examination of late event-related components (LERCs).[25] The NCT measures the time needed to connect, in numerical order, a series of randomly placed, encircled numbers from 1 to 25. To ensure reliable results, 4 modifications of the test were performed with intervals of 30 seconds preceding the EEG examination. For each patient, the 4 test times were averaged. An improvement of cognition is supposed to be reflected by a shortening of the performance time.

CRTT

The CRTT is used to measure sustained attention, ie, the ability to attend and respond immediately to sensory stimuli repeated for many minutes. Participants had to press a button as fast as possible after presentation of a bright fixation spot (10-archminute [′] × 10′ visual angle) that appeared on a dark screen for 0.1 seconds. The spot appeared with randomized intervals from 1 to 3 seconds. The spot was presented in 2 series of 40, and the statistics from the 80 reaction times were calculated. A computer registered the time from brightening the spot to pressing of the button. Reaction times were measured with 4-msec resolution from the start of the appearance. An improvement in cognition is supposed to result in a shortening of the reaction time.[26]

IQCODE questionnaire

The IQCODE questionnaire (Dutch version) consists of 16 questions that test cognition, especially memory performance.[27] In this questionnaire, the patient is asked to compare the current performance of some aspect of cognition described in the question with the performance some time ago, eg, before HBOT and 6 weeks after HBOT. The ordinal scale of the score, which ranges from −2 to +2 (5 possible scores), was used as a numeric scale to allow parametric statistics.

EEG measurements

The EEG-evoked responses examined the basic neurophysiologic performance of the brain by using a visually-related, simple memory task. This is done by recording the evoked responses to a visual so-called odd-ball stimulus.[24,28] These responses are superimposed on the (much larger) spontaneous EEG. To elucidate the response, the stimulus is presented repetitively to construct an average response. The odd-ball stimulus is an infrequently occurring visual stimulus (the event) in a series of periodically presented, frequently occurring visual stimuli. The EEG response to the odd-ball stimulus comprises the LERCs.[29] The third and most important LERC is the P3b component (parietal, positive), which is task-related and is associated with cognitive contextual integration and oriental attention.[28] The first and second LERCs are N200 (occipital, negative) and P3a (centroparietal, positive).

During the EEG recordings, the participants watched a black-and-white television monitor (mean luminance, 200 cd/m^2) at a viewing distance of 160 cm. A checkerboard with a small fixation point in the middle and with 12′ checks at 10% contrast was presented as the frequent stimulus, which appeared for 40 msec and disappeared for 660 msec. At the low contrast of 10%, the LERCs of the odd-ball response are much larger (3-4 times) than the sensory part of this response that comprises the small, positive, occipital visual component (CI). Also, the response to the frequent stimulus has amplitudes smaller than the LERCs of the oddball response. Figure 2 presents a frequent stimulus followed by an odd-ball stimulus. Statistically, each sixth presentation of the frequent stimulus was displaced randomly by the odd-ball stimulus, which was a checkerboard with 150′ checks at 10% contrast (Fig. 2, right). This procedure resulted in approximately 60 odd-ball responses and 300 responses to the frequent stimulus per recording of approximately 250 seconds. The patient was asked to count silently the number of odd-ball stimuli during the recording.

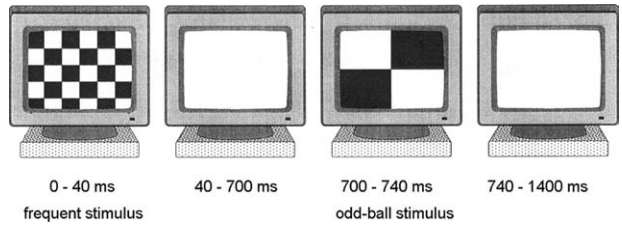

Figure 2. The stimulus configuration is illustrated. In this particular sequence of stimuli, the frequent stimulus is followed by the odd-ball stimulus. The indicated times (in milliseconds [ms]) are the points of time when the respective display is switched on and off with the time starting arbitrarily at 0 ms. The stimuli are presented every 700 ms. The mean luminance of the screen is constant.

The EEG was recorded with a 64-electrode cap (Electrode-Cap International Inc., Eaton, Ohio), and the analysis regularly was based on 64 tinned-copper electrodes. The raw signals were band-pass filtered between 0.5 Hz and 40 Hz and were sampled at 250 Hz. More details about data acquisition and averaging are published elsewhere.[24,30]

The P3b component may comprise subcomponents. Therefore, with an off-line analysis, the raw recordings were digitally phase-free filtered with a first-order, low-pass filter at 8 Hz. In this way, the P3b subcomponents were merged, such that 1 peak was left. The responses to the frequent stimulus and the odd-ball stimulus were averaged separately.

For the construction of circular (2-dimensional topographic) maps, standard electrode positions were applied. The center of the map represented the vertex, and the border of the map was 94°.

Maps at each time sample were constructed by spatially filtering of the responses over the head with 36 spherical harmonics. For details see previous reports.[24,30] Examples of maps are provided in Figure 3.

The odd-ball LERCs were preceded by a small, positive, occipital visual component (CI). In healthy adults, the CI latency is approximately 90 msec. The identification procedure of the components was the same as that for the EPs of healthy (adult) individuals used in earlier studies[24,30] and was done with criteria based on latencies, amplitudes, and map positions of the response components. The LERCs have the following characteristics: N200, a negative component located occipitally, has a normal peak latency of approximately 185 msec and often is extreme at both the left and right lobes. P3a, a positive component, has a peak latency at approximately 260 msec

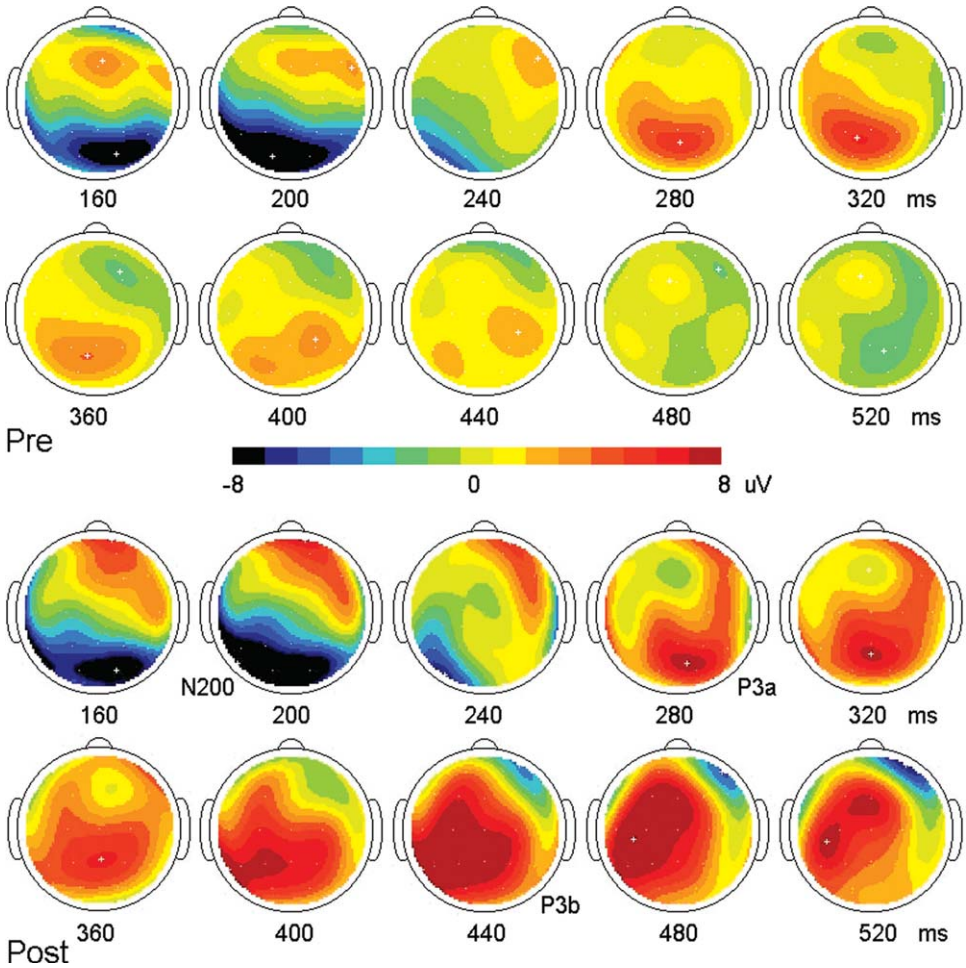

Figure 3. These are electroencephalographic (EEG) maps of 2 responses to a visual odd-ball stimulus from Patient 4 (*Top*) before (Pre) hyperbaric oxygen treatment (HBOT) and (*Bottom*) after (Post) HBOT. The times indicated below the maps are relative to the start of the odd-ball stimulus. (*Bottom*) In the post-HBOT results (obtained 4 months after the completion of HBOT), the late event-related components are clearly distinguishable as predominantly left cortical activity in blue (N200 [occipital, negative]) and in red to orange (P3a [centroparietal, positive] and P3b [parietal, positive]). The post-HBOT images look like maps from a healthy individual, except that the latencies of P3a and P3b are increased. (*Top*) Compared with the post-treatment EEG maps, the pretreatment maps reveal large areas of pathologic inactivity, indicated in blue-green to medium orange (ie, the noise level) in the time range of P3b. The root mean square noise level was (*Top*) 0.91 microvolts (μV) before HBOT and (*Bottom*) 1.05 μV after HBOT.

and has 1 maximum close to the midline between the electrode positions FNz and Oz. P3b also is positive and has a peak latency of approximately 385 msec and a maximum close to the midline between positions Cz and Oz (eg, see Schellart and Reits[24]).

The series of maps with 4-msec resolution were used to identify the major components in the response. Each component was characterized quantitatively by its latency, ie, the instant of time for which 1 of the sequential maps had the highest amplitude. Enhancement of the surmised pre-HBOT-diminished EP components and shortening of their pre-HBOT-increased latencies were considered improvements. We hypothesized that HBOT would result in shorter performance times (NCT), shorter reaction times (CRTT), positive IQCODE scores, increased amplitudes, and shorter latencies of the LERCs and in an unchanged CI.

Data Analysis

Samples did not deviate from the normal distribution, so that both a repeated-measures analysis of variance (rmANOVA) and the Student *t* test could be applied. Two-sided *P* values $< .05$ were regarded as significant. For ratios from 2 measures (post-HBOT/pre-HBOT), the logarithm of the ratios (NCT and CRTT times; EEG amplitudes) were used.

To evaluate the test results as a whole, the 2 individual outcomes (6 weeks log[post-HBOT/pre-HBOT] ratio and 4 months log[post-HBOT/pre-HBOT] ratio) were averaged per test for each patient (NCT, CRTT, and P3b amplitude). Because the 2 obtained scores (per patient) of IQCODE used the pre-HBOT condition and the 6 weeks post-HBOT condition as references, respectively, the averaged score for both was equal to the first score plus half of the second score. The IQCODE scores were expressed as a fraction of the maximal score of 32.

The average of the 6-week and 4-month results allowed a semiquantitative analysis and a numeric analysis. In the semiquantitative analysis, the mean ± standard deviation (SD) values from each test were calculated, and the change per test was expressed in SD units. A value between −0.5 and +0.5 SD was considered no change and was denoted as 0. An improvement, denoted by +, had class limits of 0.5 SD and 1.5 SD; and a strong improvement (++) was >1.5 SD. A worsening has limits of −1.5 SD (<−−) and −0.5 SD (<−). Finally, the relative total score per patient was determined by adding the obtained pluses and minuses scores from all 4 tests.

In the numeric analysis, the (pairwise) averaged outcomes of the NCT, the CRTT, the IQCODE, and the odd-ball test were subjected to a Student *t* test for each type of test. Also, the outcomes of the 4 tests were analyzed together with a *t* test. In this common test, the 4 tests predominantly were weighted by their means. For such a combined test, the Hotteling correction on the number of degrees of freedom (here, ideally, 4×10^{-1}) was obligatory. This correction is based on the correlation coefficient (R) of 2 parameters and amounts to $1/(1 + |R|)^{0.5}$. The 6 correction factors (6 correlation coefficients of the 4 sets) are multiplicative. The Hotteling correction was applied irrespective of the P value of R.

RESULTS

Participants

Patients 1, 8, and 9 underwent the tests before RT. After RT, their test results indicated a decline in neurophysiology and cognition.

After HBOT, Patient 4, who suffered from cognitive problems before RT (as did other patients), reported that cognitive functioning improved well above pre-RT levels. A substantial improvement was confirmed by neurophysiologic testing. The motor disorders also improved considerably (clinical observation). The durable improvements lasted up to the recent evaluation, which was 9.5 years after RT, when this patient had no signs of tumor progression.

Patient 6 also had considerable and durable cognitive (and motor) improvements. Patient 5 (who underwent HBOT 4 years previously) had only a transient improvement.

Before HBOT, Patient 7 was unable to count the number of odd-balls or to walk, even with walking aids. After HBOT, she could count the odd-balls reasonably well and was able to walk with a walking stick.

Patient 9 died after 1 year because of a secondary lung cancer. Patient 10 died 1.5 years after HBOT because of age-related cardiovascular disease. All other patients remained alive at the time of this writing, between 3.7 years and 12 years (mean, 7.6 years; median, 6.5 years; SD, 2.7 years) after their last HBOT session (Table 1, Survival After HBOT). Table 1 summarizes the subjective HBOT results and current status of the patients.

NCT

Six weeks after HBOT, the NCT results reflected a tendency toward shortening the mean performance time from 88 seconds (median, 61 seconds; SD, 26 seconds; range, 25-360 seconds) to 71 seconds (median, 54 seconds; SD, 16 seconds; range, 24-330 seconds). The mean ± SD log(post-HBOT/pre-HBOT ratio) was -0.059 ± 0.081 ($P = .05$). Four months after HBOT, there was another decrease (mean, 64 seconds), but this did not differ from the 6 weeks post-HBOT results. An rmANOVA resulted in $P = .15$. On average, the performance time of patients was 2 times that of healthy individuals (mean ± SD, 31.8 ± 5.0 seconds).

CRTT

The patient reaction times ranged from 224 msec to 746 msec (median, 284 msec), which was much longer than the times in healthy adults (236 ± 11 msec). Reaction times 6 weeks and 4 months post-HBOT, compared with the times pre-HBOT, decreased with an average of 10% (nonsignificant).

IQCODE Questionnaire

Six weeks after HBOT, the IQCODE scores reflected an improvement in cognition (mean score, 5.5; median score, 4; SD, 4.6; n = 9). This improvement was highly significant ($P = .007$). No further improvement was observed at the assessment 4 months after HBOT (mean score, 3.5; median score, 3.0; SD, 8.0; $P = .30$). An rmANOVA yielded $P = .010$.

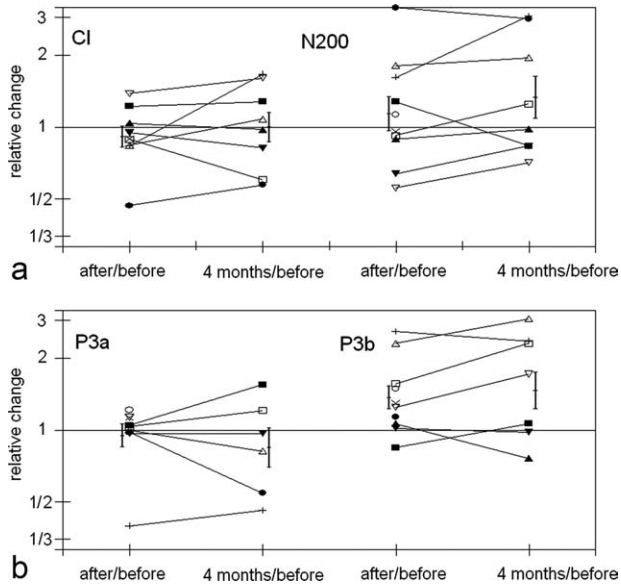

Figure 4. These graphs illustrate the amplitude ratios of 4 late event-related components of averaged evoked electroencephalographic responses to a visual odd-ball stimulus after versus before hyperbaric oxygen treatment (HBOT) (after/before) and 4 months after versus before HBOT (4 months after/before). (a) Relative changes in responses to a small, positive, occipital visual component (CI) and to the N200 (occipital, negative) component are illustrated for all 10 patients. (b) Relative changes in responses to components P3a (centroparietal, positive) and P3b (parietal, positive) are illustrated for all 10 patients. Patients 1 through 10 are represented by solid squares, open squares, solid upward arrowheads, open upward arrowheads, solid circles, open circles, solid downward arrowheads, open downward arrowheads, capital X, and plus, respectively. Also indicated are the mean values (bars indicate 2 times the standard error).

Evoked EEG Potentials

The amplitudes of the components in the response to the frequent stimuli were very small because of the low contrast used and are not discussed further. Amplitudes and latencies of the LERCs revealed high interindividual variability in both the patients and the controls. The sensory CI and the cognitive N200 values did not differ between patients and healthy individuals. However, among the patients, the P3b latency was 60 ± 39 msec longer pre-HBOT (15%; $P = .0003$; n = 10) and 63 ± 71 msec longer post-HBOT (16%; $P = .0006$; n = 10). This also applied to the P3a latency (pre-HBOT: 67 ± 36 msec: 26%; $P = .0001$; n = 9; post-HBOT: 86 ± 25 msec: 33%; $P = 10^{-7}$; n = 9). The P3a and P3b amplitudes of the patients did not differ from those of healthy individuals.

From the measured amplitudes, the logarithm for the amplitude ratio of each response component after HBOT versus before HBOT (after/before) was calculated, and the log ratios of 4 months after/before HBOT also were calculated. Figure 4a illustrates the outcomes for CI and N200 in individual participants and their means, indicated by the thick vertical bars (mean ± standard error of the mean). Amplitudes 6 weeks and 4 months after HBOT were not changed. The same was observed for P3a (Fig. 4b). Comparing the P3b amplitudes 6 weeks and 4 months after HBOT with those obtained before HBOT, the increase in amplitude was substantial; ie, 37% (log[post-HBOT/pre-HBOT] is 0.14 ± 0.15 ($P = .020$; n = 10)), and 47% (log[post-HBOT/pre-HBOT] is 0.17 ± 0.24 ($P = .067$; n = 8)), respectively. An rmANOVA resulted in $P = .0046$. At both 6 weeks and 4 months after HBOT, the latencies of all 4 response components had not changed compared with those before HBOT.

Combining the Test Results

Numerical analysis of the outcomes (Table 2) revealed that the NCT and IQCODE results and the P3b amplitude improved significantly, whereas the CRTT results revealed no improvement (Table 2). Together, the grand

Table 2. Quantitative Mean Relative Change After Hyperbaric Oxygen Treatment per Patient Averaged Over 6 Weeks and 4 Months

Test No.	Test Name	Mean±SD	No. of Patients	*P* (*t* test)
1	Averaged log-ratio NCT	0.047±0.059	9	.0452
2	Averaged log-ratio CRTT	0.042±0.122	9	.3279
3	Averaged log-ratio P3b	0.149±0.167	10	.0200
4	Averaged fraction IQCODE	0.042±0.040	9	.0138
Grand mean for all 4 tests		0.072±0.117	37[a]	.0013

SD indicates standard deviation; NCT, number connection test; CRTT, continuous reaction time test; P3b, the third late event-related component of averaged evoked electroencephalographic responses to a visual odd-ball stimulus (associated with cognitive, contextual integration and oriental attention); IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly.

[a] After Hotteling correction, n=19.7.

Table 3. Qualitative Relative Change After Hyperbaric Oxygen Treatment per Patient Averaged Over Outcomes at 6 Weeks and at 4 Months[a]

	Patient No.									
Measure.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
NCT	+	0	++	+	0	+		0	+	0
IQCODE	+	0	+	++		+	++	−	0	++
CRTT	0	0	−	+	0	++		0	0	0
P3b amplitude	0	+	+	++	0	0	+	0	++	++
Relative total score[a]	2	1	3	6	0	4	3	−1	3	4

NCT indicates number connection test; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; CRTT, continuous reaction time test; P3b, the third late event-related component of averaged evoked electroencephalographic responses to a visual odd-ball stimulus (associated with cognitive, contextual integration and oriental attention).
[a] A plus sign indicates 1, and a minus sign indicates −1.

mean of the NCT, CRTT, and IQCODE results and the P3b amplitudes demonstrated a highly significant improvement after HBOT ($P = .0013$) (Table 2). It should be noted that the IQCODE results were expressed as a fraction and not as the log-ratio. Therefore, combined testing must be conservative. This requirement was fulfilled, because the mean IQCODE results were comparatively low, resulting in a limited influence on the significance of the grand mean. The much more conservative sign test with Hotteling correction (16 times >0 and 4 times <0) yields $P = .0032$.

The outcomes of the 4 tests were not related (the 6 correlation coefficients, all being <0.5 were not significant). This may have been caused by the small number of patients. Moreover, it is likely because the NCT, CRTT, and IQCODE and the odd-ball test address the performance of different domains of cognition.

Table 3 provides results from the semiquantitative analysis: A result of "−" occurred 2 times, "+" occurred 11 times, "−−" did not occur, "++" occurred 8 times, and "0" occurred 16 times. The lowest obtained score of the 4 tests together (total score) was −1. The next lowest score, 0, occurred once. The remaining 8 patients had positive total scores, with +6 as the highest score. The total scores deviated from zero ($P = .0059$). When an overall improvement was defined as a total score ≥ 2 with at least 2 items that rated as at least "+," then neurophysiologic performance and cognition improved in 7 of 10 brain tumor patients after they received HBOT for cognitive problems after neurosurgery and additional RT.

DISCUSSION

In this pilot study, a standard cognitive neurophysiologic test and 3 established cognitive tests were combined to assess the effect of HBOT on brain performance in patients who had long-term cognitive problems after neurosurgery and RT. After HBOT, the most important EEG parameter to quantify cognition, the P3b amplitude, improved significantly. The outcomes of the IQCODE questionnaire suggest a lasting improvement; however, subjective bias cannot be ruled out.

For the NCT, the mean ± standard error intrasession learning effect in patients was −8% ± 3%. Because of this small effect, the approximately 3-month intervals, and the absence of any effect in healthy controls, we assumed that the patients' intersession learning effect was absent. The CRTT had no learning effects.

Results from the NCT and the CRTT were positive or inconclusive. However, in a combined analysis of these 2 tests, the questionnaire, and the changes in P3b amplitude, HBOT appeared to result in a substantial improvement.

The extent of improvement varied from small to substantial, and the extent of duration ranged from transient to long-lasting improvement after HBOT. In general, no further improvement was observed after a longer follow-up. Patient 2 and Patient 8 had no improvement, in accordance with the clinical responses observed after HBOT (see Table 1).

The EEG study indicated that, compared with healthy controls, the propagation velocity along the pathway of P3b and P3a is reduced in patients, which also has been observed, for instance, among patients with dioxin intoxication.[30] HBOT does not appear to restore the propagation velocity, and this is in agreement with the unchanged reaction times. Because the enhanced latencies are likely to rely in the first place on reduced propagation speeds, it is reasonable to assume that HBOT does not repair myelinization damage. The increased P3b amplitude suggests that improved neurophysiologic functioning can be explained by a lower threshold of generation of action potentials and better synaptic performance.

It appears plausible that the success of HBOT will diminish with age and time since neurosurgery and RT, because cerebral neoangiogenesis to support the functional plasticity of the brain decreases with age and time.[31] In the current study, although there was no evidence for an aging effect, the number of patients was too small to draw definite conclusions. Similar considerations apply for the supposed benefit of a short period between tumor treatment and HBOT.

A remarkable finding of the current study was the relatively favorable survival of the patients with brain

tumors, who survived for an average of almost 8 years after HBOT despite unfavorable histology. Although this finding is intriguing, we have no further explanation other than that we selected patients whose performance status was at least good enough for testing, HBOT, and retesting. Despite the small number of patients with brain tumors who had chronic cognitive complaints and the patients' highly variable characteristics, we cautiously conclude that HBOT generally improves both neurophysiologic functioning and cognition.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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