Late neurocognitive sequelae in patients with WHO grade I meningioma

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ABSTRACT

Background: Information on neurocognitive outcome following treatment of benign meningiomas is virtually lacking. This is remarkable considering that survival in these patients is the most favourable of all intracranial tumours. The aim of the present study was therefore to document the extent and nature of neurocognitive deficits in patients with World Health Organization (WHO) grade I meningioma after treatment.

Methods: 89 patients with WHO grade I meningioma who underwent surgery with or without adjuvant radiotherapy were individually matched to 89 healthy controls for age, sex and educational level. Neurocognitive functioning of patients was assessed at least 1 year following treatment and compared with that of healthy controls using the Student's t test. Additionally, associations between tumour characteristics (size, lateralisation and localisation), treatment characteristics (radiotherapy) and epilepsy burden (based on seizure frequency and antiepileptic drug use) and neurocognitive functioning were investigated.

Results: Compared with healthy controls, patients with meningioma showed significant impairments in executive functioning ($p<0.001$), verbal memory ($p<0.001$), information processing capacity ($p = 0.001$), psychomotor speed ($p = 0.001$) and working memory ($p = 0.006$). Patients with skull base meningiomas performed significantly lower on three out of six neurocognitive domains compared with convexity meningiomas. Left-sided as opposed to right-sided meningiomas were related to verbal memory deficits. A higher epilepsy burden was significantly associated with lower executive functioning which primarily could be attributed to antiepileptic drug use. No significant associations were established between neurocognitive status and radiotherapy or tumour volume.

Conclusions: Meningioma patients are characterised by long term deficits in neurocognitive functioning that can partly be attributed to the use of antiepileptic drugs and tumour location but not to the use of radiotherapy.

Meningiomas are primary brain tumours that arise from the meningeal coverings of the brain. With an annual incidence of 6 per 100 000 population, they account for 13–26% of all primary intracranial tumours.[1 2] Ninety per cent of the meningiomas are benign World Health Organization (WHO) grade I tumours.[2] Patients commonly present with epileptic seizures or focal neurological deficits related to local brain or cranial nerve compression, ranging from visual disturbances or hearing loss to extremity weakness.[3 4]

Initial treatment consists of surgical resection. Radiotherapy yields a favourable prognosis, specifically for WHO grade II and III tumours revealing atypia or anaplasia, and also reduces the risk of local recurrence of grade I tumours after subtotal resection. However, the clinical value and optimal timing of radiotherapy after (in)complete surgery or recurrence of WHO grade I meningiomas remain subject to debate.[5–8]

Although radiotherapy is thought to significantly contribute to long term neurocognitive deficits in meningioma patients,[9–11] it is unclear to what extent these deficits are caused, in addition to the tumour itself, by surgery or by other treatment related factors. In patients with low grade gliomas the use of antiepileptic drugs (AED) was found to be associated with significantly reduced neurocognitive functioning.[12] For other types of primary brain tumours it is known that neurocognitive deficits can be attributed to a combination of tumour and medical treatment related factors.[13]

The primary aim of this study was to determine the extent and nature of neurocognitive deficits of patients with WHO grade I meningiomas. Secondly, we examined the effects of tumour characteristics (size, lateralisation and localisation), treatment characteristics (surgery, radiotherapy) and epilepsy burden (based on seizure frequency and AED use) on neurocognitive functioning in patients with meningioma after treatment. Detailed information on the effect of available treatment options on the frequency and severity of neurocognitive deficits in meningioma patients will offer support in the choice and timing of treatment.

METHODS

Patients and healthy controls

In this multicentre cross sectional study, we assessed all consecutive adult patients with WHO grade I meningioma between 1999 and 2005 without clinical or radiological signs of tumour recurrence for at least 1 year after treatment. Patients had to be treated with surgery, with or without adjuvant conventional external beam conformal radiotherapy. They were recruited from the VU University Medical Centre and the Academic Medical Centre, Amsterdam, The Netherlands. The medical ethics committee of both centres approved the study protocol.

Eligibility of patients was checked with the general practitioner and by patient chart review. Excluded from the study were patients with atypical or malignant meningioma (WHO grade II or III) or who had one of the following medical conditions that may interfere with normal

Table 1 Neuropsychological tests used for assessment of neurocognitive functioning

Test name	Description
Letter–Digit Modalities Test[21]	Measures psychomotor speed that is relatively unaffected by a decline in intellectual ability
Rey's Auditory Verbal Learning Test[22]	Examines verbal learning capacity and consolidation of verbal information into long term memory
Working Memory Test[22]	Measures the speed of memory retrieval processes
Digit Span[23]	Measures short term memory and working memory
Category Verbal Fluency Test[22]	A measure of executive functioning and semantic memory
Stroop Color Word Test[22]	Examines information processing speed, selective attention and mental control
Concept Shifting Test[24]	Measures attention, visual searching, mental processing speed and the ability to mentally control simultaneous stimulus patterns

neurocognitive functioning: tumours elsewhere in the CNS, cerebrovascular pathology, congenital CNS malformations, multiple sclerosis, Parkinson's disease, organic psychosis, dementia or schizophrenia. Also, patients had to have sufficient proficiency of the Dutch language to be able to carry out the neurocognitive tests.

Healthy controls providing normative data for the neurocognitive tests were selected from the Maastricht Aging Study[14] which is a large cross sectional study on the biomedical and psychological determinants of cognitive aging of 2000 healthy individuals aged 24–81 years. Patients and healthy controls were individually matched with respect to sex, age and educational level. Educational level was assessed by a Dutch scoring system[15] consisting of an 8 point scale, ranging from unfinished primary education (level 1) to university level (level 8).

The treating physician invited the patients by letter to participate in the study. If patients agreed to participate, an appointment was made for a neurocognitive assessment. Prior to formal testing, patients completed a questionnaire concerning sociodemographic data and health related quality of life[16] (these data will be addressed in a separate paper).

Clinical data obtained at study entry included tumour characteristics (histology, lateralisation, volume) and treatment history (radiotherapy total dose and fraction dose, epilepsy and AED use). All clinical data were derived from the medical records.

Study measures

Neurological functioning and performance status

Neurological functioning was scored with the Neurological Functioning Scale developed by Order and colleagues.[17] Scores range from 1 to 4, with higher scores indicating better neurological functioning. Performance status was assessed by means of the Karnofsky Performance Status scale (KPS).[18] The KPS is an overall indicator of the patient's level of physical functioning used frequently in clinical research in oncology. KPS scores range from 0 (lowest level) to 100 (highest level). The capacity to carry out activities of daily living was assessed by means of the Barthel Activities of Daily Living Index[19] consisting of 10 items assessing continence of the bowels and bladder, grooming, toilet use, feeding, transfer, mobility, dressing, climbing stairs and bathing. Higher scores indicate higher levels of functional independence (range 10–20). An inventory of brain tumour related health problems was made with the Brain Cancer Module (BCM20).[20] The BCM20 is a questionnaire containing 20 items grouped into four scales (future uncertainty, visual disorder, communication deficit and motor dysfunction) and seven single items (headache, seizure, drowsiness, hair loss, itching, weakness of both legs and difficulty controlling bladder function).

Neurocognitive functioning

Because the origin and severity of neurocognitive impairments in meningioma patients might vary greatly, a wide range of neurocognitive functions were assessed by means of a standardised test battery (see table 1).[21–24] Trained psychometricians, supervised by a board certified neuropsychologist (MK), administered the standardised neurocognitive test battery either at home or at the hospital.

To accomplish data reduction, individual neurocognitive test scores were converted into z scores using the means and SDs of the matched healthy controls as a reference. Subsequently, z scores were transformed into the following six neurocognitive domains: (1) information processing capacity, (2) psychomotor speed, (3) attentional functioning, (4) verbal memory, (5) working memory and (6) executive functioning. Construction of these neurocognitive domains was based on a principal component analysis using Varimax rotation with Kaiser normalisation performed on the z scores of healthy controls.[12] The outcome of the principal component analysis was confirmation of the neurocognitive domains conventionally used in neuropsychological practice.

Because of the variety in seizure history and AED use, patients were assigned to one of six levels on a single ordinal scale, with higher levels representing a higher epilepsy burden: level 1, epilepsy free; level 2, epilepsy, seizure free in the year before testing without AEDs; level 3, epilepsy, seizure free in the previous year with AED monotherapy; level 4, epilepsy, seizure free in the previous year with AED polytherapy; level 5, epilepsy, less than six seizures in the previous year and on AED monotherapy or polytherapy; and level 6, epilepsy, more than six seizures in the previous year with AED monotherapy or polytherapy.[12] Preoperative CT and/or MRI tumour volume was calculated using the equation: $^4/_3\pi \times (\frac{1}{2}x \times \frac{1}{2}y \times \frac{1}{2}z)$.

Statistical analysis

Using SPSS 11.0, Student two tailed t tests for independent samples were employed to test for differences in neurocognitive functioning between patients and controls. Associations between brain tumour related health problems (BCM20), radiotherapy (yes/no), epilepsy burden (level 1–6) and tumour volume on the one hand and neurocognitive domain test scores on the other, were explored by correlational and multiple regression analyses. Student t tests were performed to determine associations between neurocognitive functioning and tumour lateralisation and localisation. Where relevant, corrections for age, educational level and sex were made. Statistical significance was set at $p<0.05$.

RESULTS

Sociodemographic and clinical characteristics

Of the 123 patients who met the inclusion criteria, 34 patients were excluded; 16 patients could not be traced and 14 patients declined participation as they expected testing to be too burdensome. Three patients had insufficient proficiency of the Dutch language and one patient had severely impaired hearing. Thus 89 eligible patients remained to be studied.

Table 2 Sociodemographic and clinical characteristics of the study group

Variables	Meningioma patients (n = 89)	Healthy controls (n = 89)	p Value*
Characteristics			
Age (years) (mean (SD))	58.6 (12.1)	58.3 (13.3)	0.876
Sex (male) (n (%))	23 (26)	23 (26)	1.000
Educational level (years) mean (SD)	3.8 (2.2)	3.7 (2.1)	0.859
Dexterity			
Right-handed (n (%))	83 (93)	–	–
Left-handed (n (%))	2 (2)	–	–
Ambidextrous (n (%))	4 (5)	–	–
Premorbid intelligence			
Dutch Adult Reading Test (mean (SD))	94.4 (15.7)	–	–
Treatment			
Time since treatment (years) (mean (SD))	3.4 (2.0)	–	–
Surgery only (n (%))	67 (75)	–	–
Surgery and radiotherapy (n (%))	22 (25)	–	–
Use of AEDs (n (%))	23 (26)	–	–
Valproic acid	8	–	–
Phenytoin	5	–	–
Oxcarbazepine	3	–	–
Levetiracetam	2	–	–
Carbamazepine	2	–	–
Clonazepam	1	–	–
Topiramate	1	–	–
Gabapentin	1	–	–
Epilepsy burden†			
Level 1 (n)	56	–	–
Level 2 (n)	10	–	–
Level 3 (n)	10	–	–
Level 4 (n).	2	–	–
Level 5 (n)	8	–	–
Level 6 (n)	3	–	–
Tumour lateralisation			
Left-sided (n (%))	37 (42)	–	–
Right-sided (n (%))	25 (28)	–	–
Bilateral (n (%))	27 (30)	–	–
Tumour localisation			
Convexity (n)	45	–	–
Tentorium/falx (n)	18	–	–
Skull base (n)	40	–	–
Orbita (n)	3	–	–
Olfactorius (n)	6	–	–
Tumour size and number			
Volume (ml) (mean (SD))	46.1 (51.8)	–	–
Area (cm^2) (mean (SD))	13.0 (1.0)	–	–
No of tumours (mean (SD))	1.1 (0.6)	–	–
Functional/performance status			
Karnofsky (mean (SD))	81.1 (18.2)	–	–
Barthel (mean (SD))	18.0 (2.8)	–	–
Order me	1.2	–	–

*Student's t test.
†Patient groups with higher levels representing a higher epilepsy burden; level 1, epilepsy free; level 2, epilepsy, seizure free in the year prior to testing without AED; level 3, epilepsy, seizure free in the previous year with antiepileptic (AED) monotherapy; level 4, epilepsy, seizure free in the previous year with AED polytherapy; level 5, epilepsy, less then six seizures in the previous year on mono, or polytherapy; level 6, more than six seizures in the previous year and on AED mono or polytherapy.

As a consequence of the matching procedure, patients and healthy controls did not differ significantly in age, sex or educational level (table 2). The average time since treatment at the moment of neuropsychological testing was 3.4 years. All 89 patients were treated with surgery; complete tumour resection was achieved in 49 and incomplete resection in 40 patients. Twenty-two patients received adjuvant conformal radiotherapy with fraction doses of 1.8–2.0 Gγ, with total doses ranging from 50 to 54 Gγ. Irradiated patients had meningiomas of the skull base (n = 12), tentorium (n = 3), convexity (n = 2), n opticus (n = 1) or at both skull base and tentorium or convexity (n = 4). Thirty patients had epileptic seizures prior to surgery. Of these, 22 patients became seizure free following surgery with (n = 12) or without (n = 10) AEDs, seven patients reported no change in epilepsy burden after surgery despite AEDs and four patients reported worsening or onset of seizures postoperatively. At the moment of neuropsychological testing, 23 patients were using AEDs.

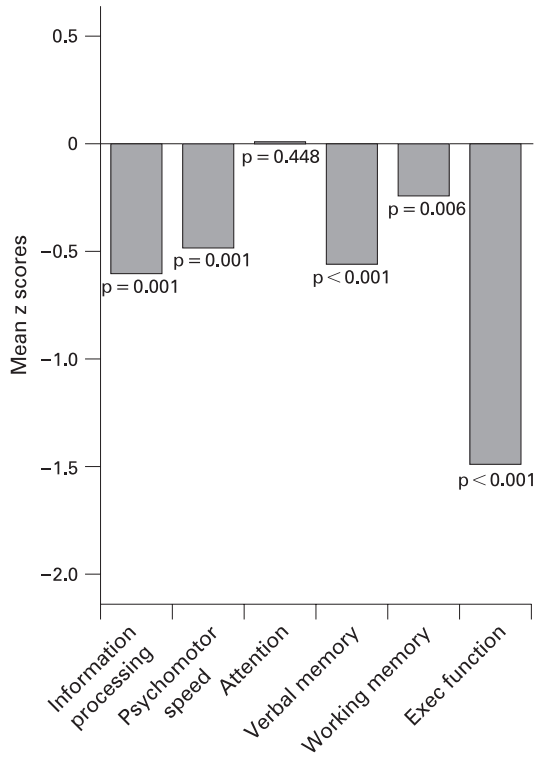

Figure 1 Mean z scores on the neurocognitive domains of patients with meningioma relative to that of age, sex and education matched healthy controls, represented by the "0" line. Lower scores indicate a lower performance. p Values are based on t test comparisons.

The Neurological Functional Scale was not indicative of serious neurological impairment (mean 1.2 (SD 0.4)). Barthel scores (mean 18.0 (SD 2.8)) were also not indicative of serious limitations in patient's ability to perform daily life activities. The KPS scale, however, showed that the group of meningioma patients attained suboptimal levels of physical functioning after treatment (mean 81.1 (SD 18.2)).

Neurocognitive functioning of meningioma patients

Neurocognitive outcome of meningioma patients relative to that of healthy controls is shown in fig 1. Neurocognitive deficits of patients were most pronounced in executive functioning as their mean z score was found to be 1.5 SD below that of the healthy control group, a cut-off that is usually held as indicative of neurocognitive impairment ($p<0.001$, 95% confidence interval (CI) −1.890 to –1.364). Compared with healthy controls, patients with meningioma also had limitations in verbal memory ($p<0.001$, 95% CI −0.977 to −0.439), information processing capacity ($p = 0.001$, 95% CI −2.034 to −0.532), psychomotor speed ($p = 0.001$, 95% CI −1.134 to 0.264) and working memory ($p = 0.006$, 95% CI −0.706 to −0.085). Attentional functioning was not found to be significantly impaired ($p = 0.448$, 95% CI −0.328 to 0.319).

Neurocognitive functioning related to treatment modalities, tumour characteristics and brain tumour related health problems (BCM20)

Regression analyses (table 3) showed a higher epilepsy burden to be significantly related to lower executive functioning. Additional analyses using Student t tests revealed that patients using AEDs (ie, groups 3, 4, 5 and 6) had significantly lower executive functioning ($p = 0.035$) and psychomotor speed ($p = 0.024$) than patients not using AEDs (ie, groups 1 and 2). However, no differences in neurocognitive functioning were found between patients with (ie, groups 5 and 6) or without (ie, groups 1, 2, 3, and 4) epileptic seizures.

Patients who reported more communication deficits, as evidenced by BCM20 scores, had a lower executive and attentional functioning. Increased feelings of drowsiness were also associated with lower information processing capacity and psychomotor speed. Analysis using the Student's t test showed that patients using AEDs reported significantly more feelings of drowsiness than patients not using AEDs ($p = 0.013$). However, feelings of drowsiness could not be attributed uniquely to AED use as AED use remained a significant predictor of executive functioning ($\beta = -0.233$) even after correcting for feelings of drowsiness in a regression model.

Additional analysis was performed to investigate whether the observed neurocognitive deficits among the 89 meningioma patients were mainly due to AED use. After exclusion of patients using AEDs, neurocognitive functioning of patients with meningioma not using AEDs ($n = 67$) remained significantly lower in all neurocognitive domains except for attentional functioning relative to healthy controls (executive functioning $p<0.001$; verbal memory $p<0.001$; information processing $p = 0.004$; working memory $p = 0.021$; psychomotor speed $p = 0.050$).

Table 3 Associations between neurocognitive functioning on the one hand and tumour volume, radiotherapy, epilepsy burden and brain tumour related health problems on the other

Neurocognitive domain	Tumour volume	Radiotherapy	Epilepsy burden	Drowsiness*	Communication deficits*
Executive functioning	β = −0.076; p = 0.579	β = 0.050; p = 0.592	**β = −0.251; p = 0.006**	β = −0.168; p = 0.058	**β = −0.335; p<0.001**
Verbal memory	β = 0.004; p = 0.979	β = −0.021; p = 0.811	β = −0.094; p = 0.293	β = 0.034; p = 0.746	β = −0.101; p = 0.300
Information processing	β = 0.013; p = 0.927	β = −0.001; p = 0.991	β = −0.116; p = 0.241	**β = −0.318; p = 0.002**	β = −0.052; p = 0.596
Psychomotor speed	β = −0.042; p = 0.779	β = 0.085; p = 0.395	β = −0.163; p = 0.105	**β = −0.438; p<0.001**	β = −0.087; p = 0.336
Working memory	β = −0.070; p = 0.618	β = −0.110; p = 0.244	β = −0.068; p = 0.474	β = −0.128; p = 0.191	β = −0.046; p = 0.638
Attention	β = 0.053; p = 0.698	β = 0.040; p = 0.685	β = −0.120; p = 0.221	β = −0.171; p = 0.083	**β = −0.203, p = 0.037**

Significant associations ($p<0.05$) are shown in bold type.
*BCM20 scale, brain tumour related health problems scale.
β, standardised coefficient.

Student t tests showed tumour lateralisation and localisation to be related to neurocognitive functioning. Patients with left-sided meningiomas performed significantly worse on verbal memory tasks than right-sided meningiomas ($p = 0.042$). Moreover, patients with skull base meningiomas ($n = 24$) had significantly lower performance in the domains of verbal memory ($p = 0.007$), information processing ($p = 0.033$) and psychomotor speed ($p = 0.040$) compared with meningiomas located on the convexity ($n = 28$). In order to examine whether dexterity affected neurocognitive outcome, we excluded left-handed and ambidextrous patients and found that statistical analyses yielded identical outcomes (data not shown). As sample sizes of the different tumour locations were too small for additional regression analysis, associations between neurocognitive functioning and radiotherapy or tumour volume could not be established.

No significant associations were found on group level between neurocognitive functioning on the one hand and radiotherapy and tumour volume on the other.

DISCUSSION

Thus far, only a few studies have been published on the incidence and cause of neurocognitive deficits in patients with meningiomas. In 2000, Tucha *et al* observed memory and language impairments prior to surgery in a group of brain tumour patients with predominantly meningiomas.[25] A subsequent study of Tucha *et al* among patients with exclusively frontal meningiomas reported prior to and following surgery both preoperative and postoperative serious impairment in verbal fluency tasks which can be considered as an indication of compromised executive functioning.[26] The aforementioned findings are in accordance with the deficits in verbal memory and executive functioning of meningioma patients observed in the present study.

Although patients with meningioma performed significantly poorer than healthy controls on all neurocognitive domains, the domain of executive functioning was most profoundly impaired. Disturbance of executive functioning may have considerable impact on a person's everyday life functioning as executive functioning is involved in neurocognitive processes such as organising, planning and decision making.[27] It is usually considered to be linked to frontal lobe activity, although neuroimaging studies showed executive functioning to be dependent on other brain regions as well,[28] and thereby possibly more vulnerable to neurocognitive compromise than other neurocognitive domains.

We found lower executive functioning to be associated with a higher epilepsy burden, which primarily can be attributed to AED use and not to epileptic seizures per se. A previous study on low grade glioma patients also demonstrated AED use to have a deleterious effect on executive functioning.[12] Post hoc analyses also showed that AED use is associated with feelings of drowsiness. It is save to assume that the reductions in attentiveness associated with AED use might give rise to deficits in executive functioning of meningioma patients. The present study only investigated the effects of older types of AED; newer types of AED might have less detrimental effects on neurocognitive functioning.[29]

Neurocognitive impairment of meningioma patients, however, cannot solely be attributed to the use of AEDs as neurocognitive functioning among meningioma patients not using AEDs is still compromised compared with healthy controls.

Tumour location was found to be related to neurocognitive functioning. Verbal memory deficits in left-sided meningioma patients are to be expected as the left hemisphere is dominant for language in the majority of people. Dexterity is unlikely to be a confounding variable of neurocognitive functioning as exclusion of left-handed and ambidextrous patients yielded the same neurocognitive outcomes. The above mentioned finding is in accordance with the more severe neurocognitive disability of patients with low grade glioma in the dominant hemisphere compared with non-dominant low grade gliomas.[30] Patients with skull base meningiomas were found to have worse neurocognitive functioning than those with convexity meningiomas, especially concerning more basic neurocognitive functions such as information processing speed and psychomotor speed. Skull base meningiomas may be more prone to neurocognitive damage because of the inherent more difficult surgery.[31]

No statistically significant associations were found between adjuvant radiotherapy and neurocognitive functioning. In a recently published study on a subset of the present study, in which surgically treated patients were individually matched to patients who underwent adjuvant radiotherapy after surgery, we also found no indication that radiotherapy is detrimental to an already impaired neurocognitive functioning.[32]

Evidently, this study has its limitations. Since a pretreatment assessment is lacking, a comprehensive differentiation between tumour and treatment related factors (ie, effects of surgery) cannot be made. A prospective study including pre-surgery assessment of neurocognitive function is planned to start shortly.

In conclusion, this study demonstrates that patients with meningioma have extensive long term neurocognitive deficits following treatment with or without adjuvant radiotherapy. Our results indicate that the influence of radiotherapy on neurocognition is negligible whereas the use of AEDs negatively affects neurocognitive functioning.

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