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Investigation of the neuropsychological sequelae of brain tumors is extremely complex largely because the neurobehavioral consequences of brain tumors depend upon complex interactions among disease and treatment variables as well as patient characteristics. To illustrate some of these complexities, we present case studies of two patients in whom the behavioral outcome was not easily predictable on the basis of our current understanding of brain-behavior relationships in tumor patients. The case studies do illustrate how neuropsychological evaluation aids in identifying cognitive deficits which have implications for subsequent quality of life. Recommendations for future experiments and statistical analyses of neurobehavioral data of this population are given. (Henry Ford Hosp Med J 1990;38:213-8)

Despite recent advances in imaging technology, surgical techniques, and other treatment modalities, the treatment of patients with brain tumors remains challenging. Indeed, the prognosis for patients with malignant brain tumors is bleak. Similarly, despite dramatic advances in our knowledge of brain-behavior relationships, our understanding of the neurobehavioral effects of brain tumors remains primitive. In part, this is true because such understanding requires us to unravel a complex interaction between disease- and treatment-related variables and patient characteristics.

Cognition, a vital determinant of quality of life, must be an important consideration in the management of brain tumor patients. Accordingly, we must improve our understanding of the neuropsychological sequelae of intracranial neoplasms. To the extent that we are able to evaluate the neurocognitive sequelae of these diseases and their various treatments, we can counsel patients and their families more effectively. Moreover, knowledge of their neuropsychological sequelae should assist neurosurgeons, radiotherapists, oncologists, and other involved professionals managing patients with brain tumors.

The outcome of treated brain tumors has been investigated in considerable detail. Extensive data exist about survival rates, intellectual function, psychiatric status, residual neurological symptoms, and quality of life among these patients (1-8). The cognitive and psychological sequelae of various regimens of radiotherapy, chemotherapy, and surgical intervention have been studied and reported (9-11). Nevertheless, drawing definitive conclusions regarding the neurobehavioral consequences of brain tumors remains difficult, partly because of differences among the studies regarding the selection of subjects and variables. Moreover, investigators have tended to analyze relevant variables in isolation (i.e., univariate rather than multivariate data analyses) and often fail in the complete evaluation of potentially important medical variables.

As with any lesion of the brain, localization of a tumor is essential in the effort to evaluate its behavioral effects. For example, tumors of the left hemisphere are more likely to interfere with language processes than are those which invade the right cerebral hemisphere. There are exceptions to this general rule (12). Similarly, anterior cortical lesions produce deficits in higher order conceptual and/or executive abilities while lesions located posteriorly result in more specific perceptual and cognitive deficits. In the case of malignant tumors, such generalizations may not always apply. For example, cognitive measures known to be sensitive to frontal lobe functioning failed to differentiate between circumscribed tumors in the anterior versus the posterior regions of the brain (13). Current assumptions regarding the focal nature of malignant brain tumors may be misleading. Difficulties understanding the localization variable probably arise because these tests are interpreted to demonstrate gross regional differences (e.g., supratentorial versus infratentorial, intrinsic versus extrinsic) rather than more precise abnormalities produced by tumors at a specific neuroanatomical site (5,13,14).

Interactive or conjoint effects of medical variables also cloud interpretation. For example, many studies of the cognitive effects of chemotherapy and radiation therapy fail to consider the neurohormonal status of the patient (1,15). Possible cognitive effects resulting from radiotherapy-induced necrosis (16), from postsurgical changes in the brain (15), or from sensory deficits (such as visual disturbances following treatment for tumors such as craniopharyngioma) (17) must also be considered in the interactional equation. Secondary effects associated with large

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tumors (e.g., distortion and/or herniation of brain tissue, edema, increased intracranial pressure, hydrocephalus) also affect the patient's neurocognitive status.

The cognitive sequelae of any brain disorder depend on inherent characteristics of the patient, e.g., age, premorbid medical history, and presence of other systemic disease. The "Kennard Principle" proposes that the developing brain has greater plasticity or capacity to recover functions than does the mature brain. The validity of this assumption is questionable in view of contradictory evidence (18-21). Similarly, while the effects of irradiation on the adult brain have been well described, the long-term effects in children remain somewhat obscure. There is evidence that even low doses of radiation can produce changes in the brain which are not apparent until many years later (22,23).

To illustrate some of the factors that are important in determining the neuropsychological sequelae of brain tumors, we are reporting the cases of two patients with cerebral neoplasms, one glioblastoma multiforme and one meningioma.

Case Reports

Case 1

A 50-year-old white male was admitted to the hospital following an episode of severe frontotemporal headache, nausea, vomiting, and mental confusion. Computed tomography (CT) revealed a large left infratemporal lesion with mass effect, midline shift to the right, and surrounding edema (Fig 1, left panel). The left lateral ventricle was obliterated, and there was no hydrocephalus. Brain biopsy revealed glioblastoma multiforme, and the patient underwent left temporal lobectomy.

Postoperatively, his mentation appeared fairly normal although he had mild difficulty with word-finding. There was weakness in the upper right extremity and a homonymous quadrantic visual field defect. Over the next several months the patient received external radiation therapy and monthly chemotherapy (BCNU). Two months following resection he underwent stereotaxic I^{125} interstitial radiation therapy. Postoperative CT approximately two weeks prior to the neuropsychological evaluation revealed the site of the left temporal resection (Fig 1, right panel). The sylvian fissure was clearly visible and the ventricles were of normal size.

Neuropsychological evaluation—Consultation approximately four months following surgery revealed an alert, oriented, and cooperative individual who was attentive throughout the day-long evaluation. His speech was adequate with respect to fluency, articulation, and prosody, and his verbal utterances were logical and coherent. He seemed to comprehend task instructions readily and denied significant changes in his mental status except for some mild word-finding difficulties. He had returned to work on a 4- to 5-hour/day basis and felt that he was performing satisfactorily although he acknowledged some concern over a tendency to fatigue. The patient had 18 years of formal education and was employed in a senior management position with a large multinational corporation.

The neuropsychological test results are presented in Table 1. Psychometric intelligence as measured by the Wechsler Adult Intelligence Scale (Revised) (WAIS-R) rated into the 14th percentile ranking for general language skills (Verbal IQ = 84) and into the 32nd percentile ranking for visual-perceptual, visual-constructional, and visual-reasoning ability (Performance IQ = 93). These results suggest significant deterioration in his overall psychometric intelligence. Indeed, an estimate of his premorbid intelligence, based on a regression formula utilizing

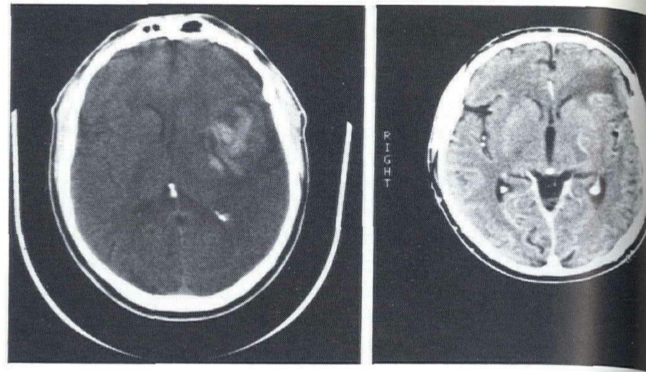

Fig 1—Case 1: Presurgical (left panel) and four months postsurgical (right panel) computed tomography scans.

various demographic factors, yielded a Predicted IQ score of at least 118.

On the Wechsler Memory Scale (Revised) (a global measure of memory functioning) he obtained a General Memory Index of 66 which is more than two standard deviations below that expected for normative age cohorts. Memory Scale subtests revealed markedly deficient performances in the immediate recall of both verbal and visual-spatial information. Particularly noteworthy were his poor performances on delayed recall. There were also disturbances in psycholinguistic and language-related functions. For example, his performance on a consonant sound-symbol matching task (Speech Sounds Perception) was at least mildly impaired, and he experienced marked difficulty in a task requiring him to generate words based on initial letter cues (Controlled Oral Word Association Test). It was also evident that tasks which demanded problem solving and concept formation were rather difficult. He was able to form only four of six concepts in a nonverbal measure involving attribute identification, ability to utilize information feedback, and problem-solving skill (Wisconsin Card Sort task). This was considered a poor performance for a man of his educational and socioeconomic background. Slowness in completing visual-spatial negotiation tasks (Trail Making Test, parts A and B) suggested a lack of flexibility in his thinking. He was extremely slow completing the three trials of the Tactual Performance Test which involves tactually-guided behavior and psychomotor coordination in the absence of vision. Furthermore, his incidental recall of the shapes and spatial locations of the blocks used on this test was impaired. Simple motor and psychomotor functioning appeared to be intact, although he encountered marginal difficulty on several measures of complex tactile perceptual ability (Finger Agnosia and Finger Dysgraphesthesia tasks).

Disturbances in this patient's language functioning were not entirely unexpected as he had undergone a left temporal lobectomy. However, his difficulties with some nonverbal tasks, general lowering of psychometric intelligence, and problems with tasks of a problem-solving nature are not easily explained by the site of his resection. In any case, we doubted that he could continue effectively in his job, a position which required problem solving, flexibility and adaptability in thinking, and some degree of creativity. This judgment proved to be correct, and the patient was placed on medical disability.

Comment—In this patient, the neuropsychological tests suggested more cognitive impairment than was apparent. His presentation on interview suggested that he was much more competent intellectually than was actually the case. Although he reported mild word-finding and memory difficulties, he either denied or was unaware of more pervasive deficits. Comprehensive objective evaluation revealed the extent of his

Table 1
Neuropsychological Test Results: Case 1

Test	Results	Test	Results
Wechsler Adult Intelligence Scale (Revised)		Wisconsin Card Sort (Concepts)	4*
		Tactual Performance Test	
Verbal IQ	84	Right hand	13.07*
Information	5*	Left hand	11.07†
Digit span	7*	Both hands	9.20†
Vocabulary	7*	Memory (number correct)	3*
Arithmetic	6*	Location (number correct)	1†
Comprehension	10	Finger Tapping (number)	
Similarities	6*	Right hand	44.4*
Performance IQ	93	Left hand	42.6*
Picture completion	7*	Grooved Pegboard Test	
Picture arrangement	8	Right hand	60
Block design	7*	Left hand	60
Object assembly	6*	Grip Strength (kilograms)	
Digit symbol	10	Right hand	49.0
Full Scale IQ	87	Left hand	47.5
Predicted IQ	118.07	Finger Agnosia (errors)	
Wechsler Memory Scale (Revised)		Right hand	4*
Verbal memory	77*	Left hand	0
Visual memory	66†	Finger Dysgraphesthesia (errors)	
General memory	66†	Right hand	2
Attention/concentration	88	Left hand	5*
Delayed recall	< 50‡		
Speech Sounds Perception (errors)	11*		
Controlled Oral Word Association (number correct)	16‡		
Judgment of Line Orientation (number correct)	15‡		
Trail Making Test, part A (sec)	34*		
Trail Making Test, part B (sec)	117*		

*Mild impairment.
†Moderate impairment.
‡Marked impairment.

neurocognitive impairment. In order to advise patients and their families about the patient's ability to function in the home, job, and community, the care team must obtain a comprehensive understanding of his cognitive status. In this patient, some of the test results were difficult to explain on the basis of tissue removal from the left temporal region; other areas of the brain were also compromised. Whether this was secondary to edema surrounding the surgical site, a consequence of chemotherapy and/or radiation therapy, the effects of anticonvulsant medications, or some combination of these factors cannot be determined. Rapid growth of glioblastoma multiforme often causes cognitive dysfunction. However, in this patient CT scans did not reveal hydrocephalus. These tumors frequently are multifocal in nature, and additional sites of neoplasms may not be detected by current radiographic techniques (24). In the management of such patients, repeated neuropsychological testing can reveal the changing nature of their deficits.

Case 2

A 52-year-old white female presented with frontal headaches of approximately four hours duration. Preoperative CT revealed the presence of masses in the falx and left frontal areas (Fig 2, left panel). The noncontrast scan revealed extensive calcification of the mass on the falx. With contrast enhancement, the left frontal lesion is illustrated (Fig 2, right panel). Cerebral angiography revealed hyperdense mass lesions adjacent to the left frontal convexity and the left parasagittal region adjacent to the falx. A 50% stenosis of the right internal carotid artery with possible posterior ulceration was observed. Brain biopsy revealed meningotheliomatous and psammomatous meningiomas.

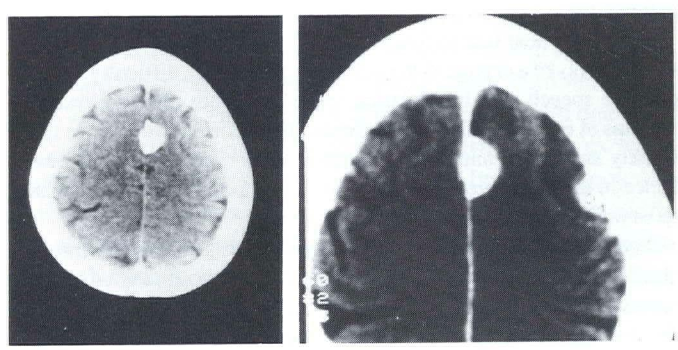

Fig 2—Case 2: Presurgical computed tomography scans. (Enhanced view, right panel.)

Approximately one month later the patient underwent left frontal craniotomy and the two meningiomas were removed. Postoperatively, she experienced mild expressive dysphasia, mild dyspraxia of the upper right extremity, and questionable right-sided neglect. Most of the

Table 2
Neuropsychological Test Results: Case 2

Test	Results	Test	Results
Wechsler Adult Intelligence Scale (Revised)		Wide Range Achievement Test (Revised)	
Verbal IQ	92	Reading SS (centile)	112 (79)
Information	9	Spelling SS (centile)	111 (97)
Digit span	10	Arithmetic SS (centile)	99 (47)
Vocabulary	8	Speech Perception (errors)	3*
Arithmetic	6*	Rhythm (errors)	7
Comprehension	9	Controlled Oral Word Association	41
Similarities	8	Judgment of Line Orientation	23
Performance IQ	85	Finger Tapping	
Picture completion	6*	Right hand	38.4*
Picture arrangement	6*	Left hand	33.6
Block design	6*	Grooved Pegboard Test	
Object assembly	6*	Right hand	63
Digit symbol	7*	Left hand	83†
Full Scale IQ	88	Finger Agnosia (errors)	
Wechsler Memory Scale	9	Right hand	0
% Recall	83%	Left hand	0
Visual reproduction	4	Finger Dysgraphesthesia (errors)	
% recall	75%	Right hand	2
Associate learning	13.5	Left hand	0
Memory quotient	101	Trail Making Test (seconds)	
Buschke Selective Reminding Test		A (errors)	31 (0)
		B (errors)	204 (4)‡
Total	104	Wisconsin Card Sort Test	
T/C	N/A	Concepts	1†
LTS	98*	Errors (perseverative/total)	27/65
CLTR	38‡		

*Mild impairment.
†Moderate impairment.
‡Marked impairment.

neurological deficits had resolved by the time she was discharged from the hospital one week later. Discharge medications included phenytoin, 100 mg, three times daily.

During the next four to five months the patient experienced episodes which involved a change in her perception of herself, difficulty with expressive speech, and brief staring spells that were often followed by feelings of extreme fatigue. These episodes occurred two to three times weekly and lasted nine to ten minutes. EEG revealed a local disturbance in the left central, sylvian, and midtemporal regions interpreted to be potentially epileptiform.

Neuropsychologic evaluation—The patient was evaluated neuropsychologically eight months after brain surgery. She complained of experiencing "sharp resonating-like pains" in her head, as well as episodic "spells" characterized by cognitive and motor "slowing." These spells occurred approximately two to ten times daily and lasted two to three minutes. Otherwise the patient was largely asymptomatic. During the assessment proceedings, she was initially hostile and suspicious. However, with explanation of the test procedures and rationale for testing, she became cooperative and put forth good effort. She seemed to understand examination questions and task directives with ease, and her verbal production displayed intact fluency and prosody. Her mood was slightly tense, and she was somewhat emotionally labile, shifting between bonhomie, tearfulness, and anger.

The neuropsychological tests revealed a level of psychometric intelligence (as measured by the WAIS-R) within the low-average range (Full Scale IQ = 88) (Table 2). No appreciable discrepancy was noted between her verbal and nonverbal intellectual skill competencies (Verbal IQ = 92, Performance IQ = 85). Her performance on standardized intelligence testing was near to our estimates of her premorbid intellectual functioning based on a regression equation using demographic data (Predicted IQ of 95 to 100). As such, she did not appear to exhibit any noteworthy decline in general intelligence. Consonant with the results of intelligence testing, the patient exhibited a Memory Quotient of 101 on the Wechsler Memory Scale. This average level of performance reflects functionally intact auditory-verbal and visual-amnestic capacities.

No evidence existed of any aphasia-like language disturbance. The patient's conversational speech demonstrated normal fluency and prosody, while her performance on rule-governed verbal fluency measures was average. No significant problems were noted on tasks to assess her understanding of the phonological or acoustical structure of language, and her dictionary of functional word knowledge (i.e., verbal lexicon) was average as well. Brief academic achievement testing revealed normally developed word recognition, written spelling, and arithmetic abilities.

A few scattered ability deficits were noted on psychomotor testing, but there was no consistent evidence of any lateralized impairment. Finally, haptic-perceptual examination did not reveal evidence of finger agnosia or dysgraphesthesia.

Within this fairly intact neuropsychological ability repertoire, however, were a number of significantly impaired performance measures of "executive functioning" and/or higher order conceptual reasoning. For example, the patient encountered difficulty in a task involving the ability to abstract and develop concepts with visually presented information (Wisconsin Card Sort task), as well as in a measure of her ability to moderate and modulate her performance under conceptual shifting conditions (Trail Making Test). In general, her performance was "perseverative-like" in quality, and her thinking processes seemed confused and disorganized. This inability to organize thought processes in the context of complex problem-solving and/or strategy-generating situations was likely responsible for her poor performance on the Buschke Selective Reminding Test. This test is dependent on generating an effective mnemonic plan or strategy in order for good performance.

While the patient was viewed as somewhat emotionally labile and behaviorally disinhibited during the examination, more formal objective personality testing (Minnesota Multiphasic Personality Inventory) did not reveal any evidence of significant psychopathology.

Approximately nine months following her initial evaluation, she was seen for brief neuropsychological reassessment. Selected neuropsychological test measures revealed a pattern of performance virtually identical to that seen at the initial evaluation; she encountered considerable difficulty on tasks requiring flexibility in thinking, concept formation, modification of behavior utilizing informational feedback, and problem-solving skill. For example, on the Wisconsin Card Sort Test she was unable to obtain a single concept and incurred a large number of perseverative errors. Similarly, her performance on the Category Test (a measure of nonverbal concept formation and problem-solving skill) yielded a score in the moderately impaired range. On both of these measures, the subject is provided with informational feedback regarding the correctness of response, but the patient was unable to use this information to modify her behavior. She was exceptionally slow when required to negotiate visual-spatial patterns utilizing numerical cues sequentially and numerical and alphabetical cues alternately for orientation and direction (Trail Making Test, parts A and B). The latter result suggests that she experiences difficulty shifting conceptual set. Finally, she again encountered difficulty in her ability to develop an efficient mnemonic strategy within the context of a complex verbal learning paradigm (Buschke Selective Reminding Test). Emotionally, there was evidence of mild disinhibition and labile mood, and the patient tested as being mildly depressed.

Comment—While it is commonly believed that meningiomata are relatively benign and treatable tumors, this case study demonstrates that these tumors can have a significant impact on neurocognitive functioning. Neuropsychologic dysfunction depends on the site of the neoplasm, and the severity of dysfunction can be variable. Rather circumscribed cognitive disruption is evident in the present case, in marked contrast to the generalized neurocognitive disturbance caused by the infiltrative, possibly multicentric glioma in case 1.

The psychometric findings in this case illustrate focal impairment of executive functions (e.g., higher order conceptual reasoning, cognitive flexibility, strategic planning, and problem solving). This constellation of neurocognitive inefficiencies is consistent with the known sites of brain involvement, the frontal and prefrontal cortical regions. The patient had noticed that she could not make decisions as rapidly as she once was able. Even trivial domestic activities were problematic at times, and she had concerns about her ability to drive an automobile.

In addition to her neurocognitive deficiencies, the patient exhibited features of emotional lability and behavioral disinhibition. She felt mildly depressed and had difficulty controlling her emotions. She experienced cerebral seizures, and these "absence-like" spells caused her appreciable distress.

Because of this otherwise relatively benign neoplasm, this woman's neurocognitive, behavioral, and emotional changes proved to be devastating. In large part, this is due to the site of the tumor and to the partial resection of her left frontal lobe.

Although the initial results of psychometric intelligence testing suggested that the patient was relatively intellectually intact, more comprehensive neuropsychological testing revealed significant cognitive impairments. Moreover, neurocognitive deficits are possibly linked to the disruption of her behavior and emotional well-being.

Discussion

Prediction of the cognitive outcome in brain tumor patients is extremely complex. The first case illustrates that the posttreatment cognitive deficits associated with an apparently well-circumscribed tumor were more extensive than was apparent from examination of the mental status. Of course, postoperative edema and radiation therapy undoubtedly contributed to the patient's deterioration. The second case illustrates that removal of relatively benign, noninvasive tumors may also disturb the patient's mental adaptation. In the second case the location of the tumor was important in determining the cognitive and emotional outcome. Both cases illustrate the difficulty in predicting cognitive sequelae of tumors based on analysis of location, histology, and treatment.

While case studies and univariate research designs unquestionably contribute to our understanding of this complex topic, further scientific progress will require a more sophisticated approach. Part of the problem in tumor research stems from the infrequency of certain tumors. The problem of small sample size may be minimized by multivariate analysis of larger samples which are heterogeneous in many respects.

Recent developments in computer-guided stereotaxic biopsy procedures have disclosed a means to reconstruct mass brain lesions by analysis of CT scan data (25). Such reconstruction can reveal the primary area of involvement, as well as secondary tissue damage associated with vascular changes and radiation effects and conditions such as calcification or edema. These data along with knowledge of histology, neurohormonal status, treatment, and the premorbid medical history can be combined into a set of independent variables. By utilizing this data set one could apply multiple regression analysis to determine the extent to which these variables can predict specified behavioral outcome test scores: measures of memory, language, nonverbal skills, and psychomotor functioning. Conversely, one could employ discriminative function analysis (e.g., impaired or not impaired for a particular behavioral measure) for a number of relevant predictor (independent) variables. In addition to increasing our understanding of the behavior associated with specific areas of the brain, such analyses may provide a basis for more precise prediction of the neuropsychological outcome of treated neoplasms.

We have emphasized the intellectual and cognitive sequelae of treated brain tumors and have only alluded to quality of life. We do not disagree with the decision to treat many brain tumors aggressively, but the whole impact of such treatment needs to be more carefully evaluated. One must consider from the patient's perspective whether an increase in longevity (often measured in months) is sufficient reason to warrant treatment which may yield a seriously impoverished quality of life. Neuropsychological evaluation provides important information about the patient's adaptation, but we must also consider the emotional status and daily living skills of such patients. Armed with such information we will be better able to advise patients accurately and wisely.

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