Cognition in patients with newly diagnosed brain metastasis: profiles and implications

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Abstract Cognitive impairment is a common symptom in patients with brain metastasis, and significant cognitive dysfunction is prevalent in a majority of patients who are still able to engage in basic self-care activities. In the current study, the neurocognitive performance of 32 patients with brain metastasis and 32 demographically-matched controls was examined using a battery of standardized neuropsychological tests, with the goal of comprehensively examining the cognitive functioning of newly diagnosed brain metastasis patients. The cognition of all patients was assessed within 1 week of beginning treatment for brain metastasis. Results indicated impairments in verbal memory, attention, executive functioning, and language in relation to healthy controls. Performance in

relation to appropriate normative groups was also examined. Overall, cognitive deficits were prevalent and memory was the most common impairment. Given that cognitive dysfunction was present in this cohort of patients with largely minimal functional impairment, these results have implications for patients, caregivers and health care providers treating patients with brain metastasis.

Keywords Cognition · Memory · Brain metastasis · Malignant brain tumor

Introduction

Current estimates place the incidence of brain metastases (BM) from solid tumors in the United States at 170,000 new cases a year, and approximately 10–30 % of adult cancer patients will develop BM [1]. Incidence rates are, however, increasing because of an aging population and medical advances that contribute to cancer patients living longer [1]. The most common location of BM is in the cerebral hemispheres (70 %), but metastasis to the cerebellum (15 %) and brainstem (<5 %) also occur [2, 3]. Significant morbidity and mortality is associated with BM with an overall median survival time of 7 months [4].

Metastatic brain tumors can cause substantial cognitive disability, but the extent and type of cognitive dysfunction often varies from patient to patient because of differential tumor volume and location [5]. Moreover, adverse effects of treatment are commonly associated with impairments in executive functioning, memory, sustained attention, and other cognitive abilities [6]. BM patients may also experience psychiatric symptoms, particularly depression and anxiety [8] and these factors can affect cognition as well. Finally, BM patients with more pronounced cognitive

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impairments are likely to experience functional difficulties and associated decreased quality of life [6, 7].

Approximately 90 % of BM patients enrolled in a randomized Phase III treatment study displayed impairment on at least one neurocognitive test [9, 10]. Impairment was prevalent at baseline and primary impairments in memory, executive functioning, and fine motor control were noted. In a smaller study, at least 70 % of patients exhibited impairments to verbal memory and a majority of patients were impaired in motor speed and dexterity [11]. Deficits in processing speed and executive functioning were less pronounced—18 and 36 %, respectively.

Although the neurocognitive function of BM samples has previously been described [7, 9–11], a detailed description of the neurocognitive profile of the cohort is not available in the literature and patient samples have not been evaluated relative to demographically-matched healthy controls. For example, cognition has been examined in relation to quality of life [7], but a detailed analysis of cognition was not conducted. Moreover, although rates of cognitive dysfunction on a number of neuropsychological tests has been reported, the primary focus of these studies was to examine cognition in relation to clinical correlates and survival [9, 10] and to assess the feasibility of using a brief neuropsychological battery in this patient group [11]. The current study was conducted to comprehensively examine the profile of cognitive deficits associated with BM in a sample of patients largely able to engage in self-care activities. Commonly used neuropsychological tests measuring a wide range of abilities including frontal/executive functioning, verbal memory (immediate and delayed recall, retention, and recognition memory), processing speed, verbal fluency, and fine motor control and dexterity were utilized. Commensurate with previous studies [9, 11], it was hypothesized that memory function would be most impaired, and that most of the sample would display impairments on multiple cognitive tests.

Methods

Participants

Thirty-two newly diagnosed (i.e., first diagnosis and first treatment) BM patients were recruited from the Departments of Radiation Oncology or Neurosurgery at the University of Alabama at Birmingham (UAB) between the dates of August 2011 and October 2013. All diagnoses were made by a radiation oncologist and the primary tumors were verified histologically. Inclusion criteria were as follows: age 19 years or older; presence of a supratentorial lesion; and absence of pre-existing psychiatric neurologic, or medical illness. Participants were assessed

within a week of starting radiation therapy. This study was approved by the institutional review board at UAB. Written informed consent was obtained from either the patient or legal representative prior to data collection.

The following treatments for BM were used: conventional surgery; single fraction radiosurgery with Gamma Knife or LINAC technology (15 Gy–24 Gy) for tumors ≤ 4 cm; hypofractionated focal radiation with LINAC for tumors >3 –4 cm (5–6 Gy $\times$ 5 fractions for 25–30 Gy total); and whole brain radiation therapy (WBRT) (with LINAC technology) (30 Gy in 10 fractions to 37.5 Gy in 15 fractions). Off-study guidelines for radiosurgical treatment at UAB followed maximum tolerated doses outlined in RTOG 9005 [12]. A majority of patients had previously received chemotherapy but no patient was actively receiving chemotherapy treatments at the time of study evaluation.

In total, 32 healthy controls were recruited from the community and were individually matched to patients on age and education. Neuropsychological evaluations of controls were conducted to ensure the absence of medical and psychiatric conditions that could impair cognition. Controls were screened over the telephone prior to the study visit for any pre-existing health, psychiatric, or cognitive problems that could affect cognition.

Measures

The Hopkins Verbal Learning Test—Revised (HVLT-R) [13] is a measure of verbal learning and memory, in which subjects learn 12 words over three learning trials. After a 25-min delay, free recall of the list is queried, as is recognition. Normative data corrected for age from the test manual (corrected for age) were used, with higher scores indicating better memory.

The Digit Span subtest from the Wechsler Adult Intelligence Scale—Third Edition (WAIS-III; [14]) is a measure of attention and concentration, in which subjects repeat orally presented digit strings, forwards and backwards. Normative data from the test manual (corrected for age) were used.

The Digit Symbol subtest from the WAIS-III is a measure of processing speed and divided attention in which subjects have 120 s to correctly match number and symbol pairs using a key at the top of the page. Normative data from the test manual (corrected for age) were used.

To evaluate phonemic verbal fluency, patients were given 1 min apiece to name as many words as possible that begin with the letters “C,” “F,” and “L.” To evaluate semantic verbal fluency, patients were given 1 min to name as many animals—beginning with any letter—as possible. Normative data corrected for age and education were used [15].

The Trail Making Test (TMT) Parts A and B from the Halstead–Reitan Neuropsychological Battery are measures of processing speed and executive functioning/set-shifting, respectively. For TMTA, the patient was asked to draw a line connecting the numbers 1–25 in numerical order. For TMTB, the patient was required to switch between numbers and letters (i.e., 1 to A, A to 2, 2 to B). For both tasks, raw score is equal to the number of seconds to completion. Normative data were corrected for age, gender, and education [16].

The Grooved Pegboard Test is a measure of fine motor ability and manual dexterity. The patient is required to rotate a key to match a slot. The pegboard contains 25 slots and a key must be placed into each slot before the patient can move on to the next slot. The score is the total number of seconds to complete the task for both the dominant and nondominant hands. Normative data corrected for age were used [16].

Depression symptoms were assessed with the Beck Depression Inventory—Second edition (BDI-II) [17]. The BDI-II contains 21 questions scored on a Likert scale of 0–3, with higher scores indicating greater depressive symptoms.

Karnofsky Performance Status scale was used as a measure of functional status [18]. A score of 100 indicates no complaints or evidence of disease. A score of 90 indicates minor disease symptoms and the ability to carry on normal activity. A score of 80 indicates obvious disease symptoms and the ability to engage in normal activities with effort. A score of 70 indicates obvious disease symptoms and the ability to independently care for self but lacking the ability to participate in active work. A score of 60 indicates the requirement of occasional assistance but the ability to care for most personal needs. A score of 50 indicates considerable assistance and frequent medical care (see Table 1).

Data analyses

In total, five analyses were conducted. First, a series of independent *t*-tests were conducted to determine if BM patients and normal controls differed in age, education, and neurocognitive performances. Second, a Chi square test was conducted to determine if BM patients and normal controls differed in gender and racial distribution. Third, to characterize the neurocognitive profiles in BM, descriptive statistics including means, standard deviations, and cumulative frequencies were calculated for neuropsychological measures. Fourth, the prevalence of cognitive impairment was determined on each of the different cognitive measures. For each cognitive measure's total score (and any relevant subscales), the percentage of participants falling into the mildly impaired (i.e., ≤ 5 th percentile) range was calculated. Finally, to further characterize the pattern of memory performance, a series of paired-samples *t*-tests were utilized:

Table 1 Functional status and primary tumor location

	Number (%)
Karnofsky score	
100	2 (6.5)
90	11 (35.5)
80	6 (19.4)
70	8 (25.8)
60	3 (9.7)
50	1 (3.2)
Primary tumor location	
Lung	15 (46.8)
Melanoma	7 (21.8)
Breast	6 (18.7)
Renal	1 (3.1)
Head and neck	1 (3.1)
Gynecological	1 (3.1)
Colon	1 (3.1)

Number of patients with percentage in parentheses. Karnofsky score missing for one patient

- (1) HVLT-R Trial 3 versus Delayed Recall to look for evidence of rapid forgetting.
- (2) HVLT-R Delayed Recall versus Delayed Recognition to look for evidence of a retrieval deficit.

Due to the number of comparisons, a conservative alpha of 0.01 was used for all analyses.

Results

Sample characteristics

Sample demographics can be found in Table 2. BM patients and healthy controls did not differ significantly in age, education, gender, or ethnicity. Primary tumor locations can be found in Table 1. In total, 21 patients had undergone chemotherapy treatments in the past, but none were receiving chemotherapy at the time of their study assessment. Seven patients underwent surgical resection prior to testing. Twenty-six patients were within a week of starting brain radiation treatment (11 whole brain and 15 focal) at the time of the study assessment. The remaining six patients were assessed prior to any radiation treatment for BM. Half of the patients ($n = 16$) had two or fewer brain lesions and half ($n = 16$) had three or more. Tumors were located in the left hemisphere for 6 patients, in the right hemisphere for 10 patients, and in both hemispheres for 16 patients. All patients had supratentorial tumors. Median Karnofsky Performance Status score for BM patients was 80 (range = 50–100, mean = 79.4, $SD = 10.2$).

Table 2 Demographic characteristics of sample

	Range	Controls n = 32	Brain metastases patients n = 32	<i>p</i> [†]
Age	31–84	57.2 (10.4)	58.3 (12.6)	0.691
Gender, n (%)				0.209
Female		15.0 (46.9)	20.0 (62.5)	
Male		17.0 (53.1)	12.0 (37.5)	
Race, n (%)				0.354
African American		5.0 (15.6)	2.0 (6.3)	
Caucasian		27.0 (84.4)	29.0 (90.6)	
Asian-American		0.0 (0)	1.0 (3.1)	
Education	9–20	14.3 (2.0)	13.8 (2.8)	0.447

Except for gender and race, values are mean (SD)

[†] *p* value for omnibus test of group differences (age, education) or Pearson's Chi square test (gender, race). Race analyzed white compared to other using Fisher's exact test

Overall neurocognitive performance and self-reported depressive symptoms

Performance of healthy controls and BM patients on neuropsychological measures are listed in Table 3. With the exception of TMTA and Digit Symbol, BM patients performed significantly worse than healthy controls on all administered neuropsychological measures. The number of patients impaired at the 5th percentile or lower on 0, 1, 2 or 3 or more neuropsychological measures are in Table 4. Less than 20 % of BM patients were completely cognitively intact (i.e., no impairments on any test). Over 80 % of the patients were impaired on one or more cognitive measures, over 75 % were impaired on two measures, and over half (56 %) were impaired on three or more measures.

Scores on a self-report measure of depressive symptoms were significantly higher for BM patients than for healthy controls ($t[42.8] = -3.835, p < 0.001, d = 1.15$). Number of self-reported depressive symptoms (BDI-II total score) was not significantly correlated with any cognitive test result: WAIS-III Digit Span ($r = 0.099, p = 0.707$), Animal Fluency ($r = 0.030, p = 0.908$), Phonemic Fluency ($r = 0.179, p = 0.491$), HVLT-R Total Recall ($r = 0.107, p = 0.682$), Trails A ($r = 0.319, p = 0.212$), Trails B ($r = -0.064, p = 0.807$), and WAIS-III Digit Symbol Coding ($r = 0.030, p = 0.908$).

Hopkins Verbal Learning Test—Revised

Compared with age-corrected normative data, the mean score for HVLT-R Total Recall was at approximately the 9th percentile (Table 3), with over 80 % of the patient

group falling at or below the 5th percentile. Performance on Delayed Recall tended to be somewhat better (22nd percentile). However, 50 % of patients exhibited impairment at or below the 5th percentile. Although 28 % of patients exhibited impaired retention, mean retention (38th percentile) was in the average range. Recognition memory performance fell in the 32nd percentile, with 40 % of patients exhibiting impairment at or below the 5th percentile.

Since learning and memory have not been well characterized in BM, a series of paired-samples *t* tests examined various scores on the HVLT-R. First, using age-corrected scores, BM patients did not differ significantly on Immediate Recall compared with Delayed recall ($t[31] = -1.192, p = 0.243, d = 0.01$). Second, performance was significantly poorer on Delayed Recall than on Delayed Recognition Discrimination ($t[31] = -3.127, p = 0.004, d = 0.48$).

Discussion

Consistent with prior studies [6, 9–11], cognitive impairment was frequent in this cohort of newly diagnosed patients with BM. With the exception of processing speed, patients with BM were impaired in relation to controls across all evaluated cognitive domains including attention, memory, language, and executive functioning. Over 80 % of this cohort exhibited some level of cognitive impairment, and this estimate closely matches those noted in an earlier study of cognition in BM [9].

When specific cognitive domains are examined, the average BM patient exhibited a neurocognitive pattern dominated by memory impairment. Between half and over three-quarters of this cohort were at least mildly impaired on two measures of verbal memory: HVLT-R Immediate Recall (50 % impaired) and HVLT-R Delayed Recall (80 % impaired). However, although less frequent and severe, impairments in language, executive functioning, and fine motor ability were also prominent. In contrast, impairments to attention were minimal, despite the patient group performing worse than health controls on a task of basic attention.

Although memory functioning has been previously reported in a large cohort of BM patients [9, 10], our results present a fuller characterization of encoding, storage, and retrieval in these patients. First, compared with age-matched peers, learning and memory for verbal information tended to fall in the low average range. Second, despite the low average performance of this cohort, a majority of patients exhibited at least mild impairment (i.e., ≤ 5 th percentile) on at least one aspect of learning and memory. Third, patients with a “subcortical” memory pattern are

Table 3 Neurocognitive performance

Measure	Controls	BM patients	% BM patients impaired at 5th percentile	<i>t</i>	<i>df</i>	<i>p</i> *
Attention						
Digit span	18.1 (3.3)	14.9 (3.8) 42.6 (27.9)	4.0	3.009	38.1	0.005
Expressive language						
Animal fluency	18.8 (3.8)	15.0 (4.6) 25.0 (24.2)	21.4	3.001	39.2	0.005
Phonemic fluency	41.5 (10.4)	27.4 (14.5) 24.8 (29.0)	46.4	3.832	42.1	<0.001
Memory						
HVLT-R immediate	25.8 (4.3)	18.3 (6.7) 9.0 (17.3)	80.0	4.746	44.5	<0.001
HVLT-R delayed	N/A	5.8 (3.7) 22.4 (29.0)	50.0	N/A	N/A	N/A
HVLT-R retention	N/A	72.8 (38.4) 37.7 (34.3)	27.6	N/A	N/A	N/A
HVLT-R recognition	11.0 (1.1)	8.9 (3.2) 32.9 (31.4)	40.0	3.473	35.2	0.001
Executive function						
Trails A	26.4 (7.7)	44.5 (34.3) 41.7 (29.4)	15.4	−2.679	31.5	0.012
Trails B	66.3 (31.0)	152.8 (100.1) 26.5 (26.8)	30.8	−4.249	34.7	<0.001
Digit symbol	69.5 (16.6)	54.4 (20.1) 36.8 (32.9)	13.6	2.627	38.0	0.012
Motor						
Grooved pegboard	N/A	95.0 (46.1)	33.3	N/A	N/A	N/A
Dominant hand		20.6 (24.6)				
Grooved pegboard	N/A	97.8 (40.0)	27.3	N/A	N/A	N/A
Nondominant hand		19.9 (22.0)				
Depression						
BDI	4.0 (4.0)	9.0 (4.7)	N/A	−3.835	42.8	<0.001
	N/A	N/A				

* *p* value for independent *t* test. For BM patients, the top row is raw scores and the bottom row is normatively corrected percentiles (mean with standard deviation in parentheses)
BM brain metastasis, *HVLT-R* Hopkins Verbal Learning Test—Revised, *BDI* Beck Depression Inventory, *N/A* not available

expected to present with retrieval deficits [19]. In this sample of BM patients, a significant dissociation between delayed recall and recognition discrimination indicates that some level of retrieval deficit is present. Thus, the memory profile based upon this sample's average performance more resembled a “subcortical” than a “cortical” pattern [20]. Fourth, it has been previously hypothesized that retrieval deficits are associated with frontal activity [21] and that frontal processes may be disrupted even in patients without a frontal lesion [11]. Thus, our findings further support the notion that memory deficits in BM are a function of striatofrontal dysfunction.

The typical patient in our sample presented with significantly poorer attention, language, and executive functioning than healthy controls. Similarly, a large number of

patients were impaired at or below the 5th percentile in language (46 %), executive functioning (31 %), and fine motor dexterity (33 %). In regards to language functioning, normatively corrected average percentiles were strikingly similar for performances on semantic and phonemic fluencies. However, more than twice as many patients were impaired at or below the 5th percentile on phonemic than semantic fluency. This pattern is interesting given that phonemic fluency may be more dependent on frontal processes than semantic fluency and less common in cortical dementias such as Alzheimer's disease [22]. In combination with the finding that at least some level of retrieval deficit is present in this sample of BM patients, the pattern of performances on verbal fluency measures further supports the position that striatofrontal dysfunction is related

Table 4 Frequency of total number of impaired measures by patient (n = 32)

Number of tests impaired	Number of patients impaired at 5th percentile	Percentage (%) of patients impaired at 5th percentile
0	6	18.8
1	1	3.1
2	7	21.9
3+	18	56.2

to many of the cognitive symptoms observed in this cohort. Despite simple attention being impaired in relation to healthy controls, only a small number of patients demonstrated impairment at or below the 5th percentile. Although not significantly impaired in relation to controls, approximately 15 % of patients exhibited impaired processing speed. Finally, this cohort of BM patients had significantly more depressive symptoms than demographically-matched healthy controls and about 20 % of patients were at least mildly depressed according to BDI-2 scores. However, although depression can be associated with reduced cognitive ability [23], depression was not related to cognitive test performance. This result indicates that depression may not be a primary contributor to cognitive dysfunction in BM.

There are several limitations and future directions to be considered. First, participants were only recruited from a single university based medical center, thereby, limiting generalizability of the current findings to the entire BM population. Second, patients in this study had heterogeneous primary cancers. Future studies might investigate whether there are cognitive differences between different etiological groups. Third, the performance of a sample of patients with BM on common neurocognitive measures was examined in the current study. It is expected, however, that moderators of cognitive functioning likely exist in this group. For example, mood can affect attention, learning and memory and other domains. Thus, although a brief self-report depression measure was administered, mood and other potential moderators should be better examined in this cohort in future studies. Fourth, although studying cognition in various patient samples yields a better characterization of functioning, studying how cognitive impairments affect activities of daily living would enhance this characterization. In other words, do patients with BM with impaired cognition also have difficulties with managing medications and finances or driving? By analyzing these questions, a relevant link between objective cognitive assessment and the relation to real-life function can be made. Fifth, the current study examined average performance in a sample of BM patients. However, BM patients represent a heterogeneous group with numerous disease factors (e.g., lesion location, lesion size, lesion type, etc.)

that can lead to different cognitive limitations. Future studies should examine these factors in isolation, so a better characterization of cognitive dysfunction in BM can be attained. Finally, future studies enrolling larger, multi-institutional, more homogeneous samples of participants with BM are needed to cross validate the current results.

These findings not only have implications for the well-being of the patient but also have implications for the well-being of the caregiver. This sample of BM patients presented with significant memory deficits. Thus, education regarding compensatory strategies (e.g., use of memory notebooks, poster boards or dry erase boards, alarms or cellphone reminders, and lists) is recommended based on the current results. Finally, given that patient cognition is associated with caregiver burden [24], caregivers should be routinely screened for burden and referred to mental health professionals when appropriate.

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Conflict of interest The authors report no conflicts of interest.

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