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Neurocognitive impairment, neurobehavioral symptoms, fatigue, sleep disturbance, and depressive symptoms in patients with newly diagnosed glioblastoma

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Abstract

Background. In addition to poor survival rates, individuals with glioblastoma (GBM) are at risk of neurocognitive impairment due to multiple factors. This study aimed to characterize neurocognitive impairment, neurobehavioral symptoms, fatigue, sleep disturbance, and depressive symptoms in newly diagnosed GBM patients; and to examine whether neurobehavioral symptoms, fatigue, sleep, and depressive symptoms influence neurocognitive performance.

Methods. This study was part of a prospective, inception cohort, single-arm exercise intervention in which GBM patients underwent a neuropsychological assessment shortly after diagnosis (median 4 weeks; ie, baseline) and 3, 6, 12, and 18 months later, or until tumor progression. Here, we present baseline data. Forty-five GBM patients (mean age = 55 years) completed objective neurocognitive tests, and self-report measures of neurobehavioral symptoms, fatigue, sleep disturbance, and depressive symptoms.

Results. Compared to normative samples, GBM patients scored significantly lower on all neurocognitive tests, with 34 (76%) patients exhibiting neurocognitive impairment. Specifically, 53% exhibited impairment in memory retention, 51% in executive function, 42% in immediate recall, 41% in verbal fluency, and 24% in attention. There were high rates of clinically elevated sleep disturbance (70%), fatigue (57%), depressive symptoms (16%), and neurobehavioral symptoms (27%). A multivariate regression analysis revealed that depressive symptoms are significantly associated with neurocognitive impairment.

Conclusions. GBM patients are vulnerable to adverse outcomes including neurocognitive impairment, neurobehavioral symptoms, fatigue, sleep disturbance, and depressive symptoms shortly after diagnosis, prior to completing chemoradiation. Those with increased depressive symptoms are more likely to demonstrate neurocognitive impairment, highlighting the need for early identification and treatment of depression in this population.

Keywords

brain tumor | depressive symptoms | fatigue | neurocognition | sleep

Glioblastoma (GBM) is the most common form of central nervous system malignancy in adults, with an incidence rate of 4.1 per 100 000 per year.[1] Standard treatment includes surgical resection followed by radiotherapy with concurrent and adjuvant temozolomide. Even with advances in medical treatment, GBM continues to rank among the most lethal human cancers; the median survival rate is 14.6 months and overall survival is 10% at 5 years.[2,3] Many patients struggle with neurocognitive impairment, neurobehavioral changes, fatigue, sleep disturbance, and depressive symptoms during the course of disease related to the tumor and cancer treatments. Thus, in addition to research investigating the mechanisms underlying GBM progression and survival, there is increased emphasis on maintaining the quality of life in these patients.

The impact of the disease and medical treatments on the brain makes neurocognitive and neurobehavioral impairment common morbidity in GBM patients. Up to 89% of GBM patients experience neurocognitive impairment at the time of diagnosis,[4,5] although precise estimates have not been reported as these studies contain mixed brain tumor samples and use brief computerized tests measuring broad neurocognitive functions. In addition, surgery and radiotherapy potentially contribute to further neurocognitive decline.[6–8] Neurocognitive impairment is associated with disease burden, poorer survival rates, radiologic progression, and deterioration in GBM patients' functional independence.[9–11] Neurocognitive impairment has been shown to contribute to lower quality of life in many neurological diseases, including brain tumors.[12,13] Identifying modifiable factors that impact neurocognition in this population may provide targets for intervention to maintain quality of life.

Fatigue is among the most common and distressing symptoms for those with primary brain tumors.[14,15] The estimated frequency of fatigue in primary brain tumors ranges from 40% to 80%.[16–18] Fatigue correlates with other symptoms, including depression, sleep disturbance, and neurocognitive performance in heterogeneous samples of primary brain tumor patients.[17,19,20] Only one study has investigated fatigue in GBM (n = 65), suggesting that these patients experience significantly more fatigue post-surgery compared to healthy age and sex-matched controls.[18]

Sleep disturbance is also common in cancer patients,[21,22] with rates ranging from 30% to 93%,[23,24] though most studies focus on patients with breast and lung cancer. Sleep disturbance seldom occurs in isolation, with most patients reporting multiple concurrent symptoms, particularly fatigue.[19] While strongly correlated, sleep disturbance and fatigue are distinct constructs. Although sleep disturbance is common, it has received little attention compared to other symptoms, particularly in individuals with high-grade brain tumors.

Individuals with brain tumors are also prone to experiencing elevated depressive symptoms after diagnosis.[25–28] These patients are more vulnerable to psychological distress than other cancer populations due to factors including tumor location, functional sequelae of the disease, and other treatment side effects.[29] Rates of depressive symptoms range from 25% to 93% (for a review, see Mugge et al.[27]). The wide range is likely related to heterogeneity in brain tumor histopathology, variance in the time since diagnosis and time since surgery, and differences in the measurement of psychological symptoms. However, higher tumor grade and being newly diagnosed are associated with the most frequent depressive symptoms,[30] indicating that individuals with newly diagnosed GBM may be at heightened risk.

The evidence reviewed above suggests that neurobehavioral symptoms, fatigue, sleep disturbance, and depressive symptoms are particularly relevant to consider in the context of patients with GBM. It is unclear how these factors influence neurocognition. The present study aims to characterize neurocognitive impairment, neurobehavioral symptoms, fatigue, sleep disturbance, and depressive symptoms in patients with newly diagnosed GBM, and determine how these factors influence neurocognition. If these variables are associated with neurocognitive impairment, strategies that improve these symptoms might alleviate neurocognitive concerns and help GBM patients maintain quality of life over the course of the disease.

Methods

Participants and Procedure

Ethical approval was obtained from the University Health Network Research Ethics Board, and written informed consent was obtained from all patients prior to enrollment. The present study was part of a prospective, inception cohort, single-arm exercise intervention study (clinicaltrials.gov identifier: NCT03390569) in which GBM patients underwent a standardized assessment of physical and neurocognitive functioning, mood, fatigue, and quality of life, prior to completing chemoradiation (ie, baseline) and 3, 6, 12, and 18 months later, or until tumor progression. Participants were recruited from the neuro-oncology clinic at the Princess Margaret Cancer Center, Toronto, Canada. Patients were eligible for participation if they: Were ≥18 years of age, had a confirmed, histological diagnosis of GBM (according to WHO 2016 criteria[31]), were scheduled to be treated with chemoradiation, good performance status as measured by the Eastern Cooperative Oncology Group (ECOG)[32] (ie, ECOG 0-2); ability to communicate in English; and clearance for exercise participation by a treating oncologist. Participants were excluded from participating in this study if they had brain metastases secondary to a noncentral nervous system cancer diagnosis, or if they had psychiatric or neurological disorders that could interfere with participation. Here, we present baseline data from this exercise intervention study.

Measures

Multiple measures were used to operationally define our variables of interest and are described in detail below. Clinical characteristics were extracted from a review of electronic medical records.

Neurocognitive outcomes.— Neurocognitive testing was conducted by a trained research coordinator supervised

by a neuropsychologist (K.E.). The Wechsler Test of Adult Reading (WTAR), was used as a proxy for premorbid intellectual functioning.[33] The following tests, which measure verbal learning and memory retention, executive function, and speeded lexical fluency were selected based on recommendations from the International Cognitive and Cancer Task Force (ICCTF)[34]: Hopkins Verbal Learning Test-Revised (HVLT-R) Total (immediate recall), Delayed (delayed memory), Retention (percentage of learned words remembered at delayed recall),[35] Trail Making Test Parts A (attention and speed) and B (executive function),[36] and the Controlled Oral Word Association of the Multilingual Aphasia Examination (verbal fluency).[37]

Neurobehavioral function. — The Frontal Systems Behavior Scale[38] is a 46-item self-report measure designed to measure behavior disturbances related to frontal system dysfunction in 3 domains: Apathy, disinhibition, and executive dysfunction. Each item is rated both before illness and at the present time (ie, after illness/diagnosis). Higher scores indicate greater frontal systems dysfunction. *T*-scores ≥65 are considered clinically significant.

Fatigue. — The Fatigue Symptom Inventory (FSI)[39] is a 14-item self-report measure designed to assess fatigue severity, fatigue frequency, perceived interference associated with fatigue, and the daily pattern of fatigue. High scores indicate greater levels of fatigue. A score of ≥3 on the average fatigue severity scale is the recommended cutoff for discriminating cases with and without clinically meaningful fatigue.[40]

Sleep. — The Pittsburgh Sleep Quality Index (PSQI)[41] is a 19-item self-report questionnaire for evaluating sleep quality over the previous month. The 19 questions are combined into 7 clinically derived component scores, each weighted equally from 0 to 3. The component scores are added to obtain a global score ranging from 0 to 21. Higher scores indicate worse sleep quality. Consistent with recent literature examining the factor structure of the PSQI,[42] of these 7 component scores were collapsed into 3 factors: Sleep Efficiency, Perceived Sleep Quality, and Daily Disturbances. A score of ≥5 on the global score is the recommended cutoff for discriminating cases with and without sleep impairment.[41]

Depressive symptoms. — The Hospital Anxiety and Depression Scale (HADS)[43] is a 14-item self-report measure, with 7 items measuring depressive symptoms (range = 0–21). High scores on this scale indicate greater levels of depressive symptoms. A score of ≥7 is the recommended cutoff in glioma and medically ill populations, as this score represents an optimal trade-off between sensitivity and specificity.[44,45]

Statistical Analyses

Neurocognitive test scores were converted to demographically corrected *z*-scores (mean = 0, standard deviation = 1) using published normative data, stratified by patient age, sex, and level of education when appropriate. A deficit score of 0 (no impairment, *z*-score >−1.5), 1 (impairment, *z*-score ≤−1.5 and >−2.0), or 2 (severe impairment, *z*-score≤−2.0) was derived. In accordance with recommendations from the ICCTF,[34] deficit scores were then averaged to determine Global Deficit Scores (GDS), which weights the number and severity of below-average scores in a test battery. Frequency of neurocognitive impairment was defined as the number of patients with two or more neurocognitive test scores at or below a *z*-score of −1.5 and/or the number of patients with a single test score at or below a *z*-score of −2.0.[34] FrSBe scores were converted to demographically corrected *T*-scores.

We performed two-tailed independent one-sample *t*-tests to explore whether GBM patients differed from age- (and when available education and sex-) equivalent population norms on each of the neurocognitive tests. To gain insight into individual test performances, the number of patients scoring in the impaired range (ie, *z*-score ≤−1.5) on each neurocognitive test and above clinical cutoffs on neurobehavioral symptoms, fatigue, sleep, and depressive symptoms measures was counted.

To identify factors that contribute to neurocognitive impairment, linear univariate regression analyses were conducted, with the primary endpoint being neurocognitive impairment (GDS). This included demographic (age, sex, and education) and disease (tumor laterality, Isocitrate Dehydrogenase [IDH] status) factors, neurobehavioral symptoms (apathy, disinhibition, and executive dysfunction), fatigue, sleep disturbance, and depressive symptoms. Continuous independent variables (eg, fatigue, sleep, and depressive symptoms) were centered around their mean.[46] Categorical independent variables (eg, tumor laterality, sex, and IDH status) were effect-coded before being added to the regression model. MGMT methylation status was unavailable for 38% of participants (see Table 1) and therefore excluded from analyses.

All factors univariately associated with neurocognitive performance (*P*-value ≤.1) were included in the backward linear multivariate analysis. Before conducting the regression analysis, assumptions were tested (eg, normality distributions). Associations between variables were derived using Pearson correlation coefficients. Statistical significance was defined as *P*-value <.05. *P*-values are two-sided. Results are considered exploratory and corrections for multiple comparisons were not performed.[47,48] All analyses were performed using SPSS version 26 and R version 1.2.5042.

Results

Demographic and Clinical Characteristics

The research assistant screened 186 individuals for eligibility between August 2017 and March 2020 when recruitment was terminated due to the Coronavirus Disease 2019 (COVID-19) pandemic. Of the patients screened, 76 (41%) did not meet inclusion criteria, 35 (19%) declined participation, and 21 (11%) were not approached due to RA schedule conflicts. The remaining 54 provided informed consent; 3 of those patients died prior to baseline assessment, 4 did

Table 1. Study Participant Demographic and Medical Characteristics

	Mean (SD)	Range
Age (years)	54.7 (12.5)	22–78
Education (years)	16.2 (3.0)	10–26
	Median	Range
Time between diagnosis and Ax (weeks)	4	1–13
Time between chemoradiation start and Ax (weeks)	1	0–4
Dexamethasone dose per day (mg)	2.5	0–16
	N(%)	
Sex		
Female	12 (26.7)	
Male	33 (73.3)	
Handedness		
Right	38 (84.4)	
Left	3 (6.7)	
Did not report	4 (8.9)	
Antidepressant and/or anxiolytic medication		
Yes	5 (11.1)	
No	35 (66.7)	
Unknown	10 (22.2)	
Premorbid history of depression		
Yes	2 (4.4)	
No	43 (84.4)	
Unknown	5 (11.1)	
Dexamethasone		
Yes	34 (75.5)	
No	7 (15.5)	
Unknown	4 (8.9)	
Extent of surgical resection		
Total	3 (6.7)	
Subtotal	34 (75.6)	
Biopsy	6 (13.3)	
Unknown	2 (4.4)	
IDH Status		
Mutated	10 (22.2)	
Wildtype	30 (66.7)	
Unknown	5 (11.1)	
MGMT promoter methylation		
Methylated	16 (35.6)	
Unmethylated	12 (26.7)	
Unknown	17 (37.8)	
Tumor laterality		
Right	23 (51.1)	
Left	19 (42.2)	
Bilateral	3 (6.7)	
Tumor location		
Frontal	12 (26.7)	
Parietal	11 (24.4)	
Temporal	5 (11.1)	
Temporal-parietal	5 (11.1)	
Frontoparietal	4 (8.9)	
Occipital	2 (4.4)	
Frontotemporal	2 (4.4)	
Thalamus	2 (4.4)	
Intraventricular	1 (2.2)	
Multifocal	1 (2.2)	

Abbreviations: Ax = neuropsychological assessment. IDH = Isocitrate Dehydrogenase; MGMT = 0[6]-methylguanine-DNA methyltransferase.

not return calls to schedule an assessment, and 2 withdrew consent. Demographic and treatment information for the 45 participants who completed the baseline assessment (41% of those eligible) is reported in Table 1. The median time between diagnosis and neuropsychological assessment was 4 weeks (range = 1–13). Premorbid rates of depression were low (4.4%) based on responses to the self-administered comorbidity questionnaire.[49]

Characterization of Neurocognitive Impairment, Neurobehavioral Symptoms, Fatigue, Sleep Disruption, and Depressive Symptoms

A substantial proportion of our sample exhibited neurocognitive impairment, neurobehavioral symptoms, fatigue, sleep disruption, and depressive symptoms (see Table 2). Using ICCTF criteria, 34 (76%) patients exhibited neurocognitive impairment. Specifically, 53% of patients (highest proportion) displayed impairment in memory (HVLT-R Delayed Recall), followed by 51% in executive function (TMT B), and 42% in immediate recall (HVLT-R Total). GBM patients exhibited significantly lower scores on all neurocognitive tests relative to population norms.

With respect to symptoms, only 6% of patients endorsed having clinically significant neurobehavioral symptoms before disease onset, while 26% reported significant neurobehavioral symptoms after disease onset (ie, at the time of their baseline assessments). Specifically, 33% reported clinically significant executive dysfunction, 27% reported clinically significant apathy, and 22% reported clinically significant disinhibition after disease onset. In addition, 57% of patients scored above the cutoff (≥3) for fatigue, 70% scored above the cutoff (≥5) for sleep disturbance, and 16% scored above the cutoff (≥7) for depressive symptoms.

Multivariate Regression

Neurocognitive impairment (GDS) was univariately associated with fatigue, depressive symptoms, apathy, and self-reported executive dysfunction (see Table 3), which

Table 2. Neurocognition, Neurobehavioral Symptoms, Fatigue, Sleep Disturbance, and Depressive Symptoms at Time of Diagnosis

Variable	Measure	Mean (SD)	*N*	Below Cutoff , *n* (%)
Neurocognition	WTAR	107.12 (7.36)	43	—
	HVLT-R Total	−1.43 (0.93)	45	19 (42.22)*
	HVLT-R Delayed Recall	−1.36 (1.11)	45	24 (53.33)*
	HVLT-R Retention	−0.73 (1.38)	45	14 (31.11)*
	COWA	−0.94 (1.33)	42	17 (40.47)*
	TMT A	−1.11 (2.53)	45	11 (24.44)*
	TMT B	−1.51 (1.53)	45	23 (51.11)*
				Above cutoff , n (%)
Neurobehavioral Symptoms	FrSBe Apathy Before	46.93 (10.31)	45	4 (8.89)
	FrSBe Disinhibition Before	47.71 (12.26)	45	3 (6.67)
	FrSBe Executive Dys. Before	49.62 (11.00)	45	4 (8.89)
	FrSBe Total Before	47.84 (10.70)	45	3 (6.67)
	FrSBe Apathy After	54.44 (14.89)	45	12 (26.67)
	FrSBe Disinhibition After	52.62 (15.49)	45	10 (22.22)
	FrSBe Executive Dys. After	56.76 (15.56)	45	15 (33.33)
	FrSBe Total After	55.78 (17.10)	45	12 (26.67)
Fatigue	FSI Severity	3.35 (1.89)	42	24 (57.14)
	FSI Interference	2.43 (2.22)	42	—
	FSI Frequency	3.13 (2.07)	42	—
	FSI Total	2.80 (1.84)	42	—
Sleep	PSQI Sleep Efficiency	2.21 (1.85)	39	—
	PSQI Perceived Sleep Quality	2.63 (2.10)	40	—
	PSQI Daily Disturbances	2.03 (1.13)	38	—
	PSQI Global Score	6.78 (3.45)	40	28 (70.00)
Depressive Symptoms	HADS Depression Scale	4.18 (3.08)	44	7 (15.91)

Notes: A cutoff of $z \leq -1.5$ was used to characterize impairment on individual neurocognitive tests. In addition, the following cutoff scores were used to characterize clinically elevated symptoms: ≥3 for FSI Severity, ≥5 for PSQI Global Score, and (≥7) for HADS Depression Scale.
Abbreviations: WTAR = Wechsler Adult Reading Test Predicted WAIS-IV Full Scale IQ Score; HVLT-R =Hopkins Verbal Learning Test-Revised; COWA = Controlled Oral Word Association; TMT = Trail Making Test; FrSBe = Frontal Systems Behavior Scale; Executive Dys. = Executive Dysfunction; FSI = Fatigue Symptom Inventory; PSQI = The Pittsburgh Sleep Quality Index; HADS = Hospital Anxiety and Depression Scale.
*t-test, $P < .01$.

were subsequently entered in the multivariate analysis. In the backward selection linear multivariate regression analysis, only depressive symptoms remained significantly associated with to neurocognitive impairment (see Table 3), explaining 11.3% of the variance, $F(1, 42) = 5.327$, $P = .026$, AIC = 63.7403, RMSE = 0.4773. Interrelationships between neurocognitive impairment, fatigue, sleep disruption, depressive symptoms, apathy, disinhibition, and self-reported executive dysfunction are presented in (Appendix Table 1). Only depressive symptoms were significantly correlated with neurocognitive impairment ($r = 0.34$, $P = .03$). A graphical representation of the distribution between neurocognitive impairment and depressive symptoms as measured by individual items on the HADS is presented in (Appendix Figure 1). Although cognitively impaired individuals reported greater severity of depressive symptoms overall, the patterns of depressive symptoms were similar in patients with and without cognitive impairment across most HADS items, with the exception of item 10 (lost interest in appearance), where all individuals in the not cognitively impaired group responded with "I take just as much care as ever," and 33% of individuals in the cognitively impaired group endorsed a decreased interest in taking care of physical appearance.

Discussion

In addition to poor survival rates, GBM patients are vulnerable to adverse outcomes including neurocognitive impairment, neurobehavioral symptoms, fatigue, sleep disturbance, and depressive symptoms. Our findings demonstrate that the majority of these individuals experience these symptoms shortly after diagnosis, prior to completing chemoradiation. Our data represent the first

Table 3. Linear Regression Analyses

Variable	Univariate		Multivariate	
	β	*P*	β	*P*
Age	–0.003	0.627		
Sex	0.007	0.937		
Education	–0.026	0.398		
Tumor Laterality	–0.126	0.129		
IDH status	0.041	0.847		
FSI Total	0.067	0.100′	[a]	[a]
PSQI Total	–0.009	0.659		
HADS Depression	0.054	0.026*	0.054	.026*
FrSBe Apathy	0.009	0.100′	[a]	[a]
FrSBe Disinhibition	0.005	0.297		
FrSBe Executive Dysfunction	0.009	.086′	[a]	[a]

Note: Neurocognitive impairment (ie, Global Deficit Score) was the outcome variable in univariate and multivariate regression analyses.
Abbreviations:IDH = Isocitrate Dehydrogenase;FSI = Fatigue Symptom Inventory; PSQI = the Pittsburgh Sleep Quality Index; HADS = Hospital Anxiety and Depression Scale; FrSBe = Frontal Systems Behavior Scale.
′$P \leq .1$;
*<0.05.
[a]Were included in the linear multivariate analysis but removed during backward selection.

standardized assessment of these adverse outcomes in a homogeneous cohort of newly diagnosed GBM patients. The literature has focused on assessing these outcomes in low-grade tumors.[6] The diagnosis and treatment of GBM place a substantial socioeconomic burden on patients and their families, and the time commitment to undergo several hours of neurocognitive testing and complete questionnaires must be carefully weighed against competing demands. Moreover, it is a challenge for patients to complete these tests when feeling unwell. These difficulties, compounded by high dropout rates as a result of early disease progression and death, make the investigation of these outcomes, particularly challenging. Direct comparison with previous studies is therefore hampered by the extant literature. Our findings roughly match the estimates reported in the few existing GBM studies, and the cancer literature more broadly.

Specifically, our sample scored significantly lower than the normative sample on all neurocognitive tests, with 76% exhibiting global neurocognitive impairment. Consistent with other studies conducted with GBM samples (impairment rates on individual neurocognitive tests of up to 55%–60%[10,11]), impairment on individual neurocognitive tests ranged from 24% to 53% in our sample. Our findings related to the proportion of patients with elevated fatigue (57%) also match the 40%–80% reported among individuals with primary brain tumors.[16–18] In addition, 70% of our sample presented with sleep disturbance, consistent with rates reported in other cancer patients of 30%–93%.[23,24] Finally, depressive symptoms estimates in this sample (16%) are consistent with other GBM samples (see Mugge et al.[27] for a review). Given the poor prognosis of GBM, preserving the quality of life in these patients is paramount. We have demonstrated that these patients are vulnerable to adverse outcomes and they are at risk of further decline as they progress through treatment given that surgery and radiotherapy targeting the brain have been shown to induce complications.[6–8] These symptoms may result in the inability to return to work or maintain functional independence including activities of daily living in long-term GBM survivors,[50] thus warranting further investigation.

We also explored whether neurobehavioral symptoms, fatigue, sleep disruption, and depressive symptoms influence neurocognition. Here, depressive symptoms were associated with neurocognitive performance; greater depressive symptoms were associated with higher severity of neurocognitive impairment. Depressive symptoms are known to commonly coexist with GBM and can significantly affect the quality of life of these patients.[27] It has been suggested that untreated depressive symptoms in GBM patients can result in decreased patient survival, and increased depression or burnout in caregivers.[27] Furthermore, these potentially treatable depressive symptoms have been associated with higher healthcare utilization costs in glioma patients and productivity loss in their caregivers.[51] Our findings indicate that depressive symptoms can develop early in the course of the disease and may contribute to neurocognitive impairment, highlighting the need for early identification and treatment in this population. Moreover, to address neurocognitive deficits directly, patients may also benefit from cognitive rehabilitation services which are currently being adapted for patients with brain tumors.[52] It is recognized that the pace associated with the acute treatment of this disease may make it difficult to provide and maintain this type of care. Our data, however, highlight the importance of support and attention for these patients early in the course of the disease,

because they are already struggling with these symptoms that may also be contributing to cognitive decline.

Limitations of this study include limited statistical power related to sample size. Although not statistically ideal, the sample size is relatively large when considering the nature of the disease and prior studies assessing neurocognitive impairment in GBM samples.[6] In addition, although IDH status was not significantly associated with neurocognitive outcome in this sample, IDH and MGMT methylation are important markers for tumor progression in patients with GBM. It would be interesting to determine if these molecular classifications and other factors such as tumor size and location, medications, and extent of resection influence neurocognitive outcomes in this population.[5] Future studies would benefit from further investigation into these medical variables. Moreover, participants in this study were well-educated (mean = 16 years); our results may underestimate the symptoms of those who have less education, fewer resources, and do not receive treatment in a large tertiary cancer center in a major urban area. Participation in this study required patients to exhibit good performance status (ie, ECOG 0–2) and clearance for exercise participation by a treating oncologist. Thus, our results likely underestimate the level of adverse outcomes and disease burden across all individuals with GBM. Nevertheless, our study provides novel information about multiple issues facing newly diagnosed GBM patients from which future investigations can be developed. In those studies, it will also be interesting to characterize outcomes based on the molecular characteristics of these tumors, given the recent changes to classification criteria for this disease.[53]

In summary, many patients with GBM experience neurocognitive impairment, neurobehavioral symptoms, fatigue, sleep disturbance, and depressive symptoms early in the course of their disease. Our findings suggest that those with increased depressive symptoms are more likely to have neurocognitive impairment, underscoring the importance of screening and early intervention for emotional distress in this population. Given that surgery and radiotherapy potentially contribute to further neurocognitive decline,[6–8] finding alternative ways to understand and address the concerns of this vulnerable group should be a priority for future research.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Practice* online.

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Conflicts of Interest Statement

The authors have no conflicts of interest to disclose.

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