Symptom Clusters in Patients With Newly-Diagnosed Brain Tumors

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Abstract: A symptom cluster comprises three or more concurrent symptoms. There is a paucity of symptom cluster research in cancer patients. Data from a previously conducted clinical trial were analyzed to search for symptom clusters. This phase III, placebo-controlled, double-blind, prospective, randomized clinical trial of 66 patients assessed the effect of prophylactic d-threo-methylphenidate (d-MPH) on quality of life (QOL) in newly diagnosed brain tumor patients receiving brain radiation therapy. Patients received 5–15 mg of d-MPH or placebo twice daily starting on week 1 of radiation therapy and continuing for 8 weeks post radiotherapy. QOL data were collected at baseline; the end of radiation therapy; and 4, 8, and 12 weeks following radiation therapy using the Functional Assessment of Cancer Therapy (FACT), the FACT-Brain subscale, and the Center for Epidemiologic Studies Depression Scale. Exploratory factor analysis, multidimensional scaling (MDS), and cluster analysis were used to search for symptom clusters. The trial failed to show a treatment effect; patients receiving d-MPH or placebo were analyzed together to search for clusters. Two symptom clusters were identified using exploratory factor analysis—a language cluster including difficulty reading, writing, and finding the right words and a mood cluster including feelings of sadness, anxiety, and depressed mood; these clusters were supported by MDS and cluster analysis. Our results suggest that interventions that target both cognitive function and mood should be considered in this patient population. Further research on symptom clusters in brain tumor patients is needed.

Brain malignancies are a significant source of morbidity and mortality. In the United States each year, approximately 18,500 primary brain and nervous system tumors are diagnosed, and some 12,760 deaths related to these cancers occur.[1] Brain metastases are even more common—their estimated annual incidence in the United States is 170,000.[2] In fact, 20%–40% of all cancer patients develop brain metastases at some point[3]; non-small cell lung cancer, small cell lung cancer, breast cancer, and melanoma are the most common sources of metastases to the brain.[4]

The 5-year survival rates for primary brain tumors range from 20%–50%, depending primarily upon the specific type of tumor and the age of the patient.[5] The median survival time for patients with brain metastases after they undergo a typical 2-week course of radiation therapy (30 Gy in 10 fractions) is 4.2 months.[6] However, if their brain metastases are left untreated, patients have a median survival of only about 4 weeks.[7]

Brain tumors, whether metastatic or primary, significantly affect neurocognitive function and quality of life (QOL) and often make the performance of normal activities at work and home difficult. The common global effects of brain tumors are fatigue; drowsiness; apathy; depression; anxiety; and decreased motivation, concentration, and short-term memory.[8–10]

Damage to the central nervous system (CNS) in brain tumor patients is mediated both by the presence of the tumor and by the aggressive therapies used to slow the growth of, or eliminate, the tumor. Surgery, radiation therapy, chemotherapy, and immunotherapy are all potentially damaging to the CNS. Other drugs that commonly are used to treat tumor and/or treatment-associated sequelae (eg, steroids, antiepileptics, analgesics, antiemetics) also may negatively affect the CNS.[11]

Most cancer patients experience multiple concurrent symptoms, yet the majority of symptom research focuses on single symptoms. Future studies must better define these concurrent symptoms and guide the management of individuals who experience multiple related symptoms.[12]

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Symptom clusters are defined as three or more concurrent symptoms that are related to one another.[12] To qualify as a cluster, these symptoms must not merely occur simultaneously; if simultaneous occurrence was the only criterion, then clusters would simply be groups of the most frequently encountered symptoms. Exploratory factor analysis, multidimensional scaling, Pearson correlations, cluster analysis, and other statistical methods may be used to search for symptom clusters to ensure that individual symptoms are related and are not merely coexistent. Identification of true symptom clusters could lead to a better understanding of the symptomatology of brain tumors and yield treatments targeting multiple symptoms.[12–16] Few studies have examined properly defined symptoms that cluster in cancer patients.[15]

Investigators from our institution recently reported on the efficacy of d-threo-methylphenidate (d-MPH) in irradiated primary and metastatic brain tumor patients.[17] This report concerns an analysis of QOL data obtained from the patients who participated in the d-MPH trial to identify symptom clusters. It includes information on the prevalence of self-reported symptoms in these patients before and after a course of radiation therapy to provide a better understanding of the types of symptoms experienced by patients with CNS malignancies.

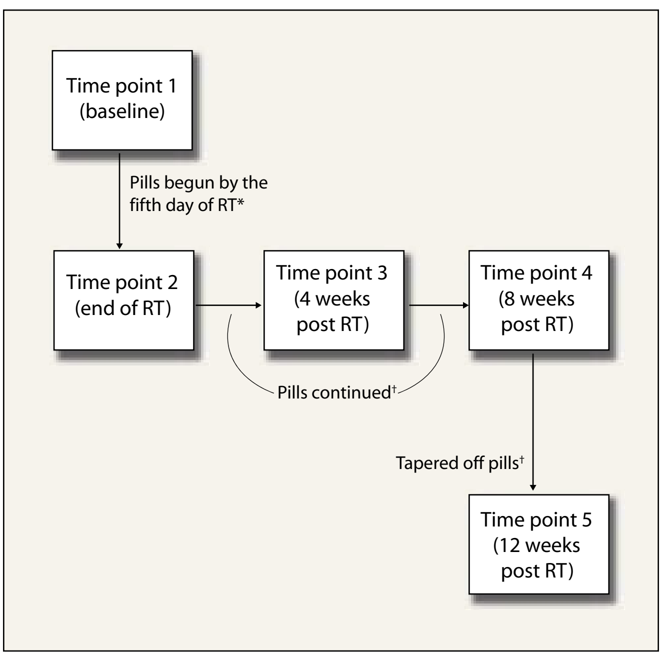

Figure 1 Treatment Schema

*The period between time points 1 and 2 varied among patients depending on the length of therapy required for each clinical situation.

†The pills were either d-threo-methylphenidate or placebo, depending on the arm of the trial to which the patient was randomize. The search for symptom clusters uses only data collected during the first two time points of the trial.

Abbreviations: RT = radiation therapy

Methods

PATIENT ENROLLMENT AND ELIGIBILITY

After providing informed consent, 68 patients with either brain metastases or a histologically confirmed primary brain tumor were enrolled in a phase III, double-blind, randomized clinical trial of the effect of d-MPH on cognitive functioning and QOL following radiation therapy through the Comprehensive Cancer Center of Wake Forest University protocol 97600. Two patients who dropped out of the study before receiving therapy are not included in this sample. Patients were enrolled at either Wake Forest University or at one of the institutions participating in its Community Clinical Oncology Program Research Base.

Eligibility criteria included age of at least 18 years; diagnosis of metastatic or primary brain tumor; planned course of partial or whole-brain radiation therapy (total dose ≥ 2500 cGy in ≥ 10 fractions of 180–300 cGy/fraction; no craniospinal irradiation); Karnofsky performance score of at least 70; life expectancy of 3 months or more; hemoglobin level of at least 10.0 g/dL; white blood cell count of at least 1,500 cells/mm^3; platelet count of 75,000 cells/mm^3 or more; no prior brain or spinal cord radiation (radiotherapy to other sites allowed); no history or current use of medication for attention deficit disorder, anxiety disorder, or schizophrenia; no history of or current substance abuse; no current use of antidepressants; no family history of or active Tourette's syndrome; no history of or active glaucoma; and no hypertension or other cardiovascular disease requiring antihypertensives and/or other cardiac medications. Patients may have received previous chemotherapy; they also were allowed to receive chemotherapy concomitantly with brain irradiation.

This article focuses solely on the presence of symptom clusters in patients enrolled in the above trial at baseline before the initiation of radiation therapy (time point 1) and at the end of radiation therapy (time point 2). All patients (eg, those receiving placebo or drug) were included in one sample population to detect symptom clusters. (For an explanation and justification for the combination of the two groups, see "Sample Generation and Time Points Used to Search for Possible Symptom Clusters" below.)

TREATMENT

Patients were assigned randomly to receive either d-MPH or a matching placebo. The starting dose was 5 mg of d-MPH or placebo twice daily, which had to be started by the fifth radiation treatment. After 5–7 days, the dose was increased to 10 mg of d-MPH or placebo twice daily and, after 10–14 days, to 15 mg of d-MPH or placebo twice daily. If the patient experienced any side effects during the dose escalation, the dose was reduced to 5–10 mg/day, as tolerated. Patients took the drug or placebo during brain irradiation therapy and for 8 weeks following radiation therapy and then were tapered off the drug from weeks 9–12 post radiation. QOL and neurocognitive measures were evaluated at five time points: time point 1, time point 2, and at 4, 8, and 12 weeks post radiotherapy (Figure 1).

MEASURES

The Functional Assessment of Cancer Therapy (FACT) is a validated scale used to measure QOL in all types of cancer patients. It consists of 27 questions in four domains: physical well-being (GP), social/family well-being (GS), emotional well-being (GE), and functional well-being (GF). The FACT uses a scale of 0–4 to ask respondents "how true each statement has been for you during the past 7 days." The scale is labeled the following way on the form that the patient completes: "not at all" (0), "a little bit" (1), "somewhat" (2), "quite a bit" (3), and "very much" (4).[18]

The FACT also has a validated brain subscale (FACT-Br), which includes an additional 18 items that cover symptoms specific to brain tumor patients[19]; it uses the same 0–4 scale used on the general version of the FACT.

The Center for Epidemiologic Studies Depression Scale (CESD)[20] was used to measure depressive symptom severity. This scale contains 20 items; individuals designate how often they have experienced each of the symptoms over the previous week. The scale for responses is 0–3 and includes the following frequencies: "rarely or none of the time (less than 1 day)"(0), "some or a little of the time (1–2 days)" (1), "occasionally or a moderate amount of the time (3–4 days)" (2), and "most or all of the time (5–7 days)" (3). A cutoff score of 16 or more indicates an increased likelihood of clinically significant depression. Some somatic symptoms of cancer overlap with depressive symptoms, but this cutoff score has been shown to be reasonable in cancer patients.[21,22] For the purposes of this study, patients with total CESD scores of at least 16 were not defined as being clinically depressed; rather, they were considered to have a depressed mood.

STATISTICAL METHODS

Symptom cluster structure was explored using four different methods: Pearson correlations, multidimensional scaling (MDS), exploratory factor analysis, and cluster analysis.[23] It was necessary to narrow the number of variables (symptoms) used to detect symptom clusters, because a ratio of the number of variables:sample size that is less than 1:5 is the recommended minimum[24] for performing factor analysis. Therefore, only the most prevalent symptoms were included in the search for symptom clusters. A symptom prevalence of 20% at baseline was chosen, because it provided a reasonable amount of symptoms to use in the search for clusters.

Exploratory factor analysis attempts to determine the underlying structure and unobserved variables or factors among a set of observed variables. It involves grouping data into factors that are characteristic of these variables. Factor loadings then quantify how much each variable fits into a given factor; variables that load heavily into the same factor are correlated together. The method of maximum likelihood and the varimax rotation were used to obtain the factor analysis results presented in the text and tables.

Pearson correlation was used to quantify the relationship between each individual variable (symptom) and every other variable. MDS uses the correlation matrices from Pearson correlations to generate a visual map of how variables relate to one another. A cluster of symptoms would theoretically appear close together on the MDS-generated figure.

Cluster analysis sorts variables into groupings with other variables that are similar in profile. The clusters generated are suggestive of symptom cluster structure. Cluster analysis also may be used to generate diagrams that are helpful for visualizing the clustering of symptoms. With regard to our cluster analysis, hierarchical variable clustering using centroid components as implemented in SAS PROC VARCLUS (SAS/STAT, Cary, NC) was used to determine which variables clustered together. SAS PROC TREE (SAS/STAT, Cary, NC) was used to plot the resulting cluster analysis results.

By examining all of these statistical methods as a whole, one can suggest symptoms that are clustering together in a given patient sample. Additionally, the prevalence of each symptom at time points 1 and 2 was reported using simple percentages of the respondents.

PREVALENCE OF INDIVIDUAL SELF-REPORTED SYMPTOMS

Items representing symptoms from the FACT, the FACT-Br subscale, and the total CESD score were selected for analysis. Some items from the FACT and its brain subscale are negatively worded, and others are positively worded; the positively worded items were reverse scaled. A symptom was considered to be present if it had a rating of 3-4 on the FACT or FACT-Br subscale. Depressed mood was considered to be present if the total CESD score was 16 or more. Severity scores for various items were used in the search for symptom clusters.

These items and their prevalence at time points 1 and 2 are listed in Table 1. Items on the FACT and the FACT-Br were excluded from the search for symptom clusters if they did not directly represent a symptom (eg, "I have trouble meeting the needs of my family," "I am able to work"). However, these items appear in Table 1, along with the percentage of patients experiencing each symptom or condition.

SAMPLE GENERATION AND TIME POINTS USED TO SEARCH FOR POSSIBLE SYMPTOM CLUSTERS

The search for symptom clusters only used data from the first two time points (Figure 1), because the sample size declined greatly over time. Sixty-six patients were evaluated at time point 1, and 55, 43, 32, and 20 patients remained at time points 2, 3, 4, and 5, respectively.

Patients from both the d-MPH and placebo groups were combined into one sample for this part of the analysis because there were no statistically significant differences between the

Table 1

Prevalences of Individual Symptoms in Patients With Brain Tumors

ITEM DESCRIPTION	ITEM	BASELINE*	END RT†
Can't drive vehicle	BR18	63%	57%
Can't work	GF1	43%	56%
Frustrated	**BR4**	41%	41%
Don't feel independent	BR7	37%	43%
CESD total score ≥ 16	**CESD**	36%	38%
Not content with current quality of life	GF7	35%	29%
Trouble meeting the needs of my family	GP3	31%	24%
Not enjoying things I do for fun	GF6	31%	33%
Lack of energy	**GP1**	30%	38%
Worry condition will worsen	GE6	30%	12%
Bothered by decreased contribution to family	BR12	30%	33%
Not sleeping well	**GF5**	27%	25%
Can't read like before	**BR16**	26%	26%
Not satisfied with sex life	GS7	25%	44%
Trouble with eyesight	**BR6**	25%	16%
Work isn't fulfilling	GF2	24%	40%
Can't remember new things	**BR3**	24%	24%
Feel nervous	**GE4**	22%	15%
Can't write like before	**BR17**	22%	20%
Can't find the right words	**BR8**	21%	10%
Difficult thought expression	BR9	19%	22%
Bothered by personality change	BR10	19%	6%
Feel sad	**GE1**	18%	10%
Afraid of seizures	BR5	18%	18%
Can't put thoughts into action	BR15	17%	14%
Worry about dying	GE5	16%	6%
Can't make decisions	BR11	16%	25%
Pain	GP4	15%	10%
Can't concentrate	**BR1**	14%	18%
Not enjoying life	GF3	13%	12%
Have had seizures	BR2	13%	6%
Trouble with hearing	NTX6	13%	16%
Not satisfied with my coping with illness	GE2	11%	10%
Haven't accepted illness	GF4	11%	10%
Can't put thoughts together	BR13	11%	14%
Must spend time in bed	GP7	10%	12%
Need help caring for myself	BR14	10%	10%
Losing hope	GE3	8%	6%
Nausea	GP2	6%	13%
Feel ill	GP6	6%	12%
Don't feel close to friends	GS1	6%	2%
Don't get emotional support from family	GS2	6%	0%
Bothered by side effects of treatment	GP5	5%	23%
Don't get support from friends	GS3	5%	2%
Family hasn't accepted my illness	GS4	3%	2%
Not satisfied with family communication about illness	GS5	3%	2%
Don't feel close to partner	GS6	3%	4%

The item column contains the system of coding used on the FACT to designate each individual statement for which patients are asked to respond (ie, BR17, GS1). Those items used in the search for symptom clusters are printed in **bold** type. Please refer to the "Methods" section for information on how the presence of a symptom was defined and how items were selected for inclusion in the search for symptom clusters.

*At baseline (time point 1), 62–63 patients responded to each item.

†At the end of RT (time point 2), 49–52 patients responded to each item.

Abbreviations: RT = radiotherapy; CESD = Center for Epidemiologic Studies Depression Scale; BR = Functional Assessment of Cancer Therapy (FACT) brain subscale; GF = FACT functional well-being; GS = FACT social/family well-being; GP = FACT physical well-being; GE = FACT emotional well-being ; NTX = FACT neurotoxicity.

drug and placebo group with regard to the FACT total score, the FACT-Br score, or the CESD total score ($P > 0.05$ for all).[17] In addition, differences between the drug and placebo groups with regard to the symptoms used in the search for clusters were compared at time point 2 to assess the validity of combining drug and placebo groups ($P > 0.05$ for all comparisons). None of the patients had received d-MPH or placebo at time point 1.

Results

DEMOGRAPHICS

As previously noted, the sample at time point 1 consisted of 66 patients (mean age, 54.5 years; median, 53.8 years; range, 28–79 years) and included 35 males (53%), 55 Caucasians (83%), and 11 African-Americans (17%). In all, 32 patients had a primary brain tumor, and 34 had brain metastases; 41 patients were treated at Wake Forest University Comprehensive Cancer Center, and 25 were treated at member facilities of its research base.

SYMPTOM CLUSTERS

The most prevalent self-reported symptoms (eg, those present in > 20% of patients at baseline using the FACT, the FACT-Br, and the total CESD score) were used to search for possible symptom cluster structure. Items included were GP1 (lack of energy), GF5 (not sleeping well), GE4 (feel nervous), BR3 (can't remember new things), BR4 (frustrated), BR6 (trouble with eyesight), BR8 (can't find the right words), BR16 (can't read like before), BR17 (can't write like before), and the total CESD score. Two additional items were also included because they became highly prevalent when symptom presence was defined using 2, 3, or 4 (instead of 3 or 4). The two additional items included were BR1 (can't concentrate) and GE1 (feel sad), which brought the total number of symptoms used to search for clusters to 12.

Table 2

Factor Analysis at Baseline (Time Point 1)

ITEM	SYMPTOM	FACTOR 1	FACTOR 2	FACTOR 3	CLUSTER
GP1	Lack of energy	0.139	0.330	0.191	None
GE1	Feel sad	0.041	**0.797**	0.155	Mood
GE4	Feel nervous	0.027	**0.691**	0.035	Mood
GF5	Not sleeping well	0.078	0.038	0.342	None
BR1	Can't concentrate	0.161	0.011	**0.987**	None
BR3	Can't remember new things	0.012	0.072	0.332	None
BR4	Frustrated	0.287	0.351	0.170	None
BR6	Trouble with eyesight	0.090	0.055	0.157	None
BR8	Can't find the right words	**0.432**	0.231	0.054	Language
BR16	Can't read like before	**0.756**	0.115	0.365	Language
BR17	Can't write like before	**0.911**	0.073	0.229	Language
CESD	Depressed mood	0.331	**0.631**	0.018	Mood

The above grid shows the three-factor solution generated at baseline (n = 58). Symptoms that load heavily into the same factor (in **bold** type) are related to one another.

Abbreviations: GP = Functional Assessment of Cancer Therapy (FACT) physical well-being subscale; GE = FACT emotional well-being; GF = FACT functional well-being; BR = FACT brain subscale; CESD = Center for Epidemiologic Studies Depression Scale

Patients who responded to all 12 of these items were selected for the analyses (time point 1, 58 patients; time point 2, 48 patients). Those who dropped out after time point 1 were similar to those who remained in the sample at time point 2 with regard to each of the 12 symptoms, the total FACT score, the total FACT-Br score, and the total CESD score ($P > 0.05$).

The exploratory factor analysis yielded a three-factor solution based on a scree plot. The factor analysis results at time point 1 are shown in Table 2, and the factor analysis results at time point 2 are shown in Table 3.

At time point 1, the factor structure suggested two symptom clusters: language (factor 1) and mood (factor 2). The language cluster included items BR8 (can't find the right words), BR16 (can't read like before), and BR17 (can't write like before); the mood cluster was made up of items GE1 (feel sad), GE4 (feel anxious), and the CESD total score (depressed mood). The third factor had only one symptom, BR1 (can't concentrate); however, a symptom cluster is defined by multiple symptoms. Therefore, the baseline factor analysis data suggested a cluster of language-related symptoms and a cluster of mood symptoms. An MDS-generated illustration (Figure 2) and a cluster analysis-generated illustration (Figure 3) supported the presence of these two clusters at time point 1 and provided a means of visualizing the cluster structure.

At time point 2, there was a factor structure consistent with the symptom clusters found at time point 1. The language symptoms loaded heavily together on factor 1, and the mood symptoms loaded on factor 2. This strengthened the possible existence of a language cluster and a mood cluster in

Table 3

Factor Analysis at the End of Radiation Therapy (Time Point 2)

ITEM	SYMPTOM	FACTOR 1	FACTOR 2	FACTOR 3	CLUSTER
GP1	Lack of energy	0.267	0.342	**0.468**	Symptom pair
GE1	Feel sad	0.169	**0.581**	0.270	Mood
GE4	Feel nervous	0.148	**0.933**	0.195	Mood
GF5	Not sleeping well	0.094	0.147	0.394	None
BR1	Can't concentrate	0.096	0.012	**0.995**	Symptom pair
BR3	Can't remember new things	0.311	0.079	0.389	None
BR4	Frustrated	0.229	0.370	0.182	None
BR6	Trouble with eyesight	0.019	**0.477**	0.031	None*
BR8	Can't find the right words	**0.483**	0.223	0.047	Language
BR16	Can't read like before	**0.809**	0.185	0.299	Language
BR17	Can't write like before	**0.820**	0.095	0.182	Language
CESD	Depressed mood	0.264	**0.659**	0.143	Mood

The above grid shows the three-factor solution generated at the end of radiation therapy (n = 48). Symptoms that load heavily into the same factor (in **bold** type) are related to one another.

*BR6 was not associated with the mood cluster at both time points, it was not considered to be a member of that symptom cluster.

Abbreviations: GP = Functional Assessment of Cancer Therapy (FACT) physical well-being; GE = FACT emotional well-being; GF = FACT functional well-being; BR = FACT brain subscale; CESD = Center for Epidemiologic Studies Depression Scale

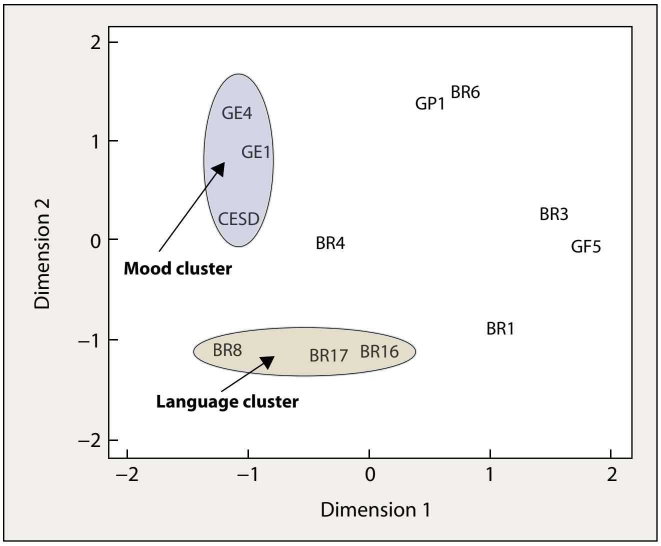

Figure 2 Multidimensional Scaling of Symptoms at Baseline (Time Point 1)

Symptoms that appear closely together are related. The language and mood clusters identified using factor analysis (Table 2) are labeled.

Abbreviations: GE1 = feel sad; GE4 = feel nervous; GF5 = not sleeping well; GP1 = lack of energy; BR1 = can't concentrate; BR3 = can't remember new things; BR4 = frustrated; BR6 = trouble with eyesight; BR8 = can't find the right words; BR16 = can't read like before; BR17 = can't write like before; CESD = depressed mood

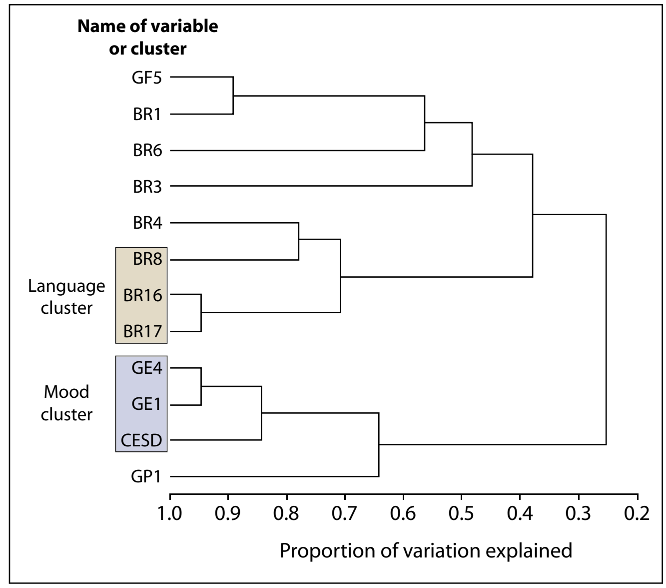

Figure 3 Cluster Analysis-Generated Illustration of Symptom Clusters at Baseline (Time Point 1)

Moving from right to left, symptoms are split into progressively smaller groups of the symptoms to which they are related at time point 1. The farther to the left symptoms remain grouped, the more highly correlated they are to one another. The language and mood clusters identified using factor analysis (Table 2) are labeled.

Abbreviations: GF5 = not sleeping well; BR1 = can't concentrate; BR6 = trouble with eyesight; BR3 = can't remember new things; BR4 = frustrated; BR8 = can't find the right words; BR16 = can't read like before; BR17 = can't write like before; GE1 = feel sad; GE4 = feel nervous; CESD = depressed mood; GP1 = lack of energy

this patient sample. The mood symptoms were accompanied by the symptom coded by BR6 (trouble with eyesight) at time point 2, which did not occur at time point 1. This change likely was an artifact of the small sample size; because BR6 was not associated with the mood cluster at both time points, it was not considered to be a member of that symptom cluster. The third factor once again included BR1 (can't concentrate), but this time it also included GP1 (lack of energy). Because BR1 and GP1 did not cluster at both time points, they did not appear to have as robust of a relationship as did the symptoms present in the language cluster and the mood cluster. In addition, symptom clusters should include three or more related symptoms. Thus, BR1 and GP1 did not meet criteria for a symptom cluster; instead, they comprised a symptom pair. An MDS-generated illustration (Figure 4) and a cluster analysis-generated illustration (Figure 5) supported the presence of the language and mood clusters at time point 2 and provided a means of visualizing the cluster structure.

Discussion

In performing this analysis, investigators searched for possible symptom clusters in a group of primary and metastatic brain tumor patients receiving radiation therapy. Identifying symptom clusters should lead to a better understanding of the symptoms of CNS tumors and their treatment-associated sequelae. The results from the exploratory factor analyses (Tables 2 and 3), multidimensional scaling (Figures 2 and 4), and cluster analyses (Figures 3 and 5) indicated that two symptom clusters were consistent over time: language and mood. The language cluster included problems with finding the right words, reading, and writing, and the mood cluster included feelings of sadness, anxiety, and depressed mood.

The results demonstrated that language difficulty and mood dysfunction are prominent problems in brain tumor patients; this is consistent with the current literature and with our clinical experience. Cognitive dysfunction, including language difficulty, results from the tumor itself, surgery, and treatment with radiotherapy, chemotherapy, steroids, and antiepileptics.[25,26] Altered mood, including depression and anxiety, is another common symptom of brain tumors and their treatment.[10,27,28]

The symptom clusters identified in this study were found in data not originally collected for this specific purpose; therefore, the results generated have some limitations. The small sample size necessitates replication on larger, more diverse samples. Choosing selected symptoms based on prevalence limited the clusters that could have emerged; use of additional or different symptoms might have identified different clusters. Given the exploratory nature of this study and the lack of similar studies, these results provide interesting goals for future studies.

Few, if any, studies have searched for symptom clusters in brain tumor patients. Symptom cluster research as a whole

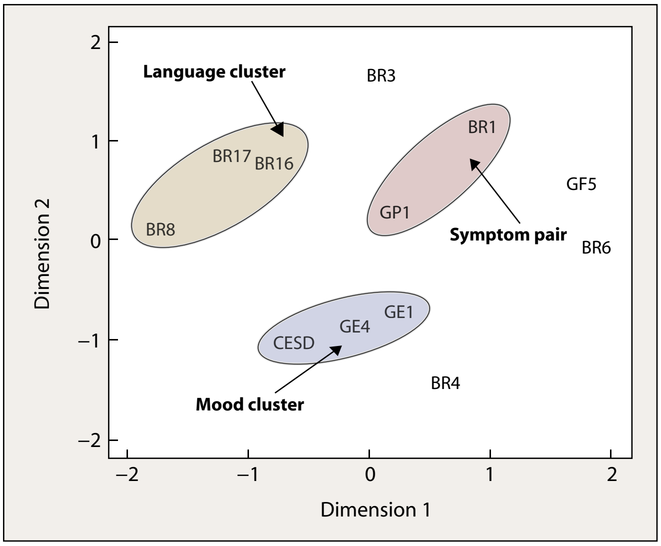

Figure 4 Multidimensional Scaling of Symptoms at the End of Radiation Therapy (Time Point 2)

Symptoms that appear closely together are related. The language cluster, the mood cluster, and a symptom pair identified using factor analysis (Table 3) are labeled.

Abbreviations: BR3 = can't remember new things; BR8 = can't find the right words; BR16 = can't read like before; BR17 = can't write like before; GP1 = lack of energy; BR1 = can't concentrate; CESD = depressed mood; GE1 = feel sad; GE4 = feel nervous; GF5 = not sleeping well; BR6 = trouble with eyesight; BR4 = frustrated

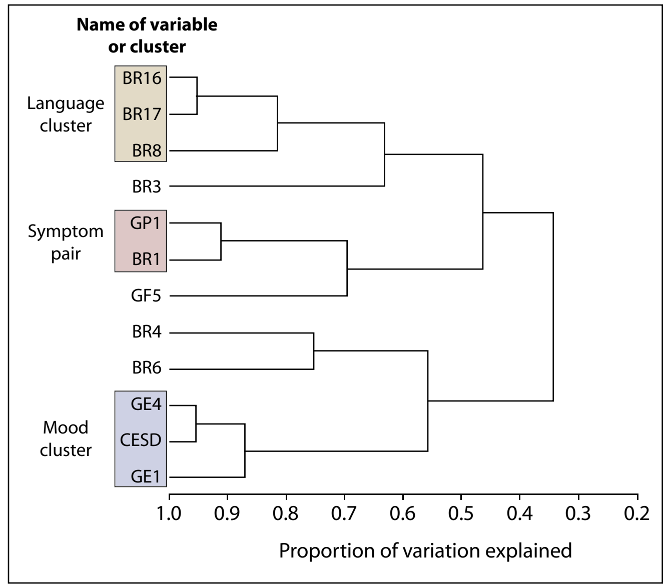

Figure 5 Cluster Analysis-Generated Illustration of Symptom Clusters at the End of Radiation Therapy (Time Point 2)

Moving from right to left, symptoms are split into progressively smaller groups of the symptoms to which they are related at the end of radiation therapy (time point 2). The farther to the left symptoms remain grouped, the more highly correlated they are to one another. The language cluster, the mood cluster, and a symptom pair identified using factor analysis (Table 3) are labeled.

Abbreviations: BR16 = can't read like before; BR17 = can't write like before; BR8 = can't find the right words; BR3 = can't remember new things; GP1 = lack of energy; BR1 = can't concentrate; GF5 = not sleeping well; BR4 = frustrated; BR6 = trouble with eyesight; GE4 = feel nervous; CESD = depressed mood; GE1 = feel sad

is a relatively new area that has developed some momentum in recent years.[12–16] Future studies may include larger patient samples, examine the evolution of clusters over time, compare clusters among different groups (eg, primary and metastatic brain tumor patients), and observe the influence of different therapeutic interventions on particular clusters. The number of patients in this sample was too small for the aforementioned analyses, but future studies should attempt to address these and other topics.

The identification of more concrete symptom clusters in primary and metastatic brain tumor patients will help investigators and clinicians to understand the symptomatology of primary and metastatic brain tumors better. Symptom clusters also may provide a target for interventions. It would be especially useful to know which specific intervention is most effective at addressing QOL issues in patients who manifest each particular symptom cluster. For example, the subset of patients who manifest the language cluster might benefit from drugs that target cognitive function (eg, donepezil [Aricept]), whereas those without that cluster may not. In addition, patients who exhibit the mood cluster could respond to antidepressants or anxiolytics. Further research of symptom clusters in brain tumor patients is needed to better define the presence of exact clusters in this population and to determine whether knowledge of these clusters can be useful in the clinical setting.

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