

Symptoms in Neuro-Oncology
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SIGNIFICANCE OF THE TOPIC

Primary central nervous system (CNS) tumors, although rare, are a devastating diagnosis associated with high rates of morbidity and mortality. Although they account for only 2% of all cancers diagnosed in the United States, they are the fourth leading cause of cancer death in young males and may be increasing in frequency in elderly U.S. citizens at an alarming rate (CBTRUS, 2001). Patients diagnosed with these tumors often are also suffering from neurologic effects, such as seizures, poor cognition, and muscle weakness (Armstrong & Gilbert, 1996). These deficits alone often render persons incapable of caring for themselves or participating in usual activities. Little research has been conducted about the occurrence of symptoms, the distress associated with symptoms, or quality of life (QOL) in persons with CNS tumors (Strang & Strang, 2001). Even less is known about how symptoms are experienced by members of various ethnic groups with CNS tumors. These factors contribute to the continuation of care based on tradition and not on science.

INTEGRATIVE AND SYSTEMATIC REVIEW

As stated above, primary CNS tumors are relatively rare and, in general, have a poor prognosis. Evaluation of the occurrence of symptoms and their management have been limited by small sample size and the age of the data used in the analysis. Most studies which have been performed are descriptive in nature and often performed as an adjunct to evaluation of a treatment modality. The primary discipline who has completed these studies are physicians. Recently, neuropsychologists have also published on symptom assessment and management (Sheibel, Meyers, and Levin, 1996; Sherer, Meyers, and Bergloff, 1997). Nursing publications have been primarily review articles, with only a few exceptions (i.e., Lovely, Miakowski, &

Dodd, 1999). The overall scope of literature that does exist can be divided into epidemiological studies; tumor-related physical symptoms; psychological symptoms; treatment-induced symptoms.

Epidemiology: CNS tumors are a heterogeneous group of neoplasms that vary widely by morphologic features, site of origin, genetic alterations, growth potential, extent of invasiveness, tendency for progression and recurrence, and treatment response (Gurney & Kadan-Lottick, 2001; Percy, Van Holten, & Muir, 1990). In the year 2000, the Central Brain Tumor Registry of the United States (CBTRUS) reported that the incidence of CNS tumors was 11.3 cases per 100,000 person-years. An estimated 35,519 new cases of primary benign or malignant brain tumors are expected to be diagnosed in 2001 (CBTRUS, 2001).

Benign tumors of the brain constitute about 40% of all primary brain tumors and include such histologic types as meningiomas, acoustic neuromas, and low grade forms of tumors primarily thought of as malignant, including, astrocytomas, ependymomas, and oligodendrogliomas. A benign tumor is composed of slow-growing cells, but can be life threatening when located in vital areas. In addition, benign tumors often dedifferentiate to a more malignant type; median survival duration is less than 7 years for certain histologic types. Primary malignant tumors are usually invasive and composed of fast growing cells. The most common type of primary malignant tumor in adults is glioblastoma multiforme. Primary tumors, whether benign or malignant, rarely spread outside of the CNS. Therefore, most symptoms tend to be neurologic in origin

National incidence by ethnicity is reported only for Caucasians and African Americans. Caucasians have higher overall rates for all CNS tumor types. A review of rates among various ethnic groups in 5 continents indicated that some ethnic groups, such as New Zealand Maoris,

New Zealand Pacific Polynesian islanders, and Jews living in Israel and the United States, have higher incidences than Caucasians living in the same geographical areas (Muir et al, 1987). This is the only published study reporting ethnic variations in CNS tumor rates. No study has been undertaken to evaluate differences in the experiences or occurrence of symptoms associated with primary brain tumors in diverse ethnic populations.

. The five-year relative survival rates following diagnosis of a primary malignant brain tumor are 31.3% for males and 30.2% for females (Ries et al., 2000). This represents only a modest improvement from the 22.5% for those with tumors diagnosed between 1974 and 1976, despite a concerted effort at developing new treatment approaches. Initial research indicates the importance of symptom control in persons with other types of cancer in relation to QOL, tolerance of treatment, and disease progression. Pain has been shown to adversely affect wound healing, immune suppression, and progression of metastatic disease (Page & Ben-Eliyahu, 1997; Kiecolt-Glaser, Page, Marucha, MacCallum, & Glaser, 1998; & Ben-Eliyahu, Page, & Shakar, 1999). This highlights the importance that symptom assessment and control may have in patients whose tumors cannot be well controlled, such as those with primary brain tumors.

Symptoms in CNS Tumors: The health status of individuals with a primary CNS tumor varies with the patient's age, health prior to diagnosis, tumor location and type, and treatment course. The healthiest individuals whose tumors are located within quiescent areas of the brain, with no comorbid factors, face a chronic illness, with continued follow-up needed for the rest of their lives. For the most devastated patients, inability to communicate and to control bodily functions may ensue.

Patients who have metastatic brain tumors (those that originate in other parts of the body) often experience symptoms related to the primary site of cancer and other metastatic sites

(Armstrong & Gilbert, 2000). In general, primary brain tumors do not metastasize outside of the CNS; therefore, symptoms that occur are neurologic in origin. Brain is made up of highly specialized tissues that control all of our body functions (Rabbitt & Page, 1998). The tumor and associated edema either invade or compress the brain tissues, resulting in either generalized symptoms of increased intracranial pressure or specific symptoms based on tumor location within the brain. Early symptoms include headaches, seizures, nonspecific cognitive or personality changes, or focal neurologic signs (Frankel & German, 1958; Gehan & Walker, 1977; Greenberg, Chandler, & Sandler, 1999) Headaches are the first symptom in 35% of those diagnosed with a brain tumor and occur at some point in the disease trajectory in 70% (McKeran & Thomas, 1980; Rabbitt & Page, 1998). One-third of patients experience a seizure as a first symptom and 50-70% of patients experience a seizure at some point in their disease (McKeran & Thomas, 1980). In approximately 50% of patients who experience one or more seizures, the seizure is generalized. Approximately 15-20% of patients also experience some difficulty with cognition (McKeran & Thomas, 1980). Fobair Mackworth, Varghese, & Prados (1990) reported that, in 1988, all but 18% of patients with a brain tumor treated at the University of San Francisco Brain Tumor Center were prevented from returning to work full-time after diagnosis, as a consequence of symptoms.

Although the above information is often cited, a review of original sources reveal that, with the exception of the recent study by Fobair and colleagues, this data is based on patient samples from the early 1960's to 1970's. The data was primarily collected in a retrospective fashion, from physician completed history and physical exams. In addition to the difficulty with the age of the data and retrospective nature, much of the data was collected prior to the widespread use of MRI's. This may be important, as a recent review indicated that the use of MRI may lead to

earlier diagnosis which may impact symptom presentation (Radhakrishnan, Mokri, Parisi, O'Fallon, Sunku, & Kurland, 1995).

Symptoms seldom occur in isolation. Recently published studies by physicians in the general oncology patient population, indicated that persons with solid tumors reported an average of 11-13 symptoms, which occurred concurrently (Chang, Hwang, Feuerman, & Kasimis, 2000; Portenoy, et al., 1994). Mukand and colleagues (2001) evaluated the extent of neurologic deficits in patients' with primary brain tumors who were admitted to their inpatient rehabilitation unit. They found 74.5% of the patients had three or more concurrent neurologic deficits, and 39.2% had 5 or more deficits. The most common deficits were impaired cognition (80%), followed by weakness (78%), visual-perceptual sensory loss (38%), and bowel and bladder dysfunction (37%). Less common symptoms were cranial nerve palsy, dysarthria, dysphagia, aphasia, and diplopia. Although this is a select population, it highlights that brain tumor patients may have more than one symptom occurring simultaneously.

The importance of the multiplicative nature of symptoms has been reported by both nursing and physician researchers in other disease states. According to Lenz and colleagues (1997), the concurrence of multiple symptoms is likely to result in an experience that is multiplicative rather than additive. Symptoms may act as a catalyst for the occurrence of other symptoms and the distress associated them. For example, pain has been reported to be disproportionately more severe when both fatigue and nausea are experienced at the same time (DeVito, 1990). No published study has evaluated the distress associated with symptoms in persons diagnosed with a primary brain tumor.

The occurrence of symptoms can also influence functional health status. It has been demonstrated in several disease states other than cancer that patients who have multiple

symptoms or more severe symptoms have a lower functional health status, lower cognitive functioning, less effective role performance, and lower physical performance capabilities (Fawcett, Tulman, & Myers, 1988; Graydon, Ross, & Webster, 1995; Milligan, Parks, & Lenz, 1991; & Pugh, & Milligan, 1995). In patients with cancer, symptom-related distress has been found to significantly and independently predict change in patient functioning (Given, Given, Azzouz, & Stommel, 2001; & Sarna, 1998). Recently, the occurrence of multiple symptoms in patients with prostate cancer was shown to predict treatment failures and poor therapeutic outcomes. (Clark & Talcott, 2001). Only two studies, both performed by neuropsychologists and rehabilitation physicians, have evaluated symptoms and functional status in persons with primary brain tumors. Sherer, Meyers, and Bergloff (1997) evaluated the efficacy of postacute brain injury rehabilitation in patients with primary brain tumors and reported that 50% of the patients had improved independence after rehabilitation. Both this study and the one by Mukand and colleagues (2001) reported that a majority of the patients returned home and cared for themselves. However, nearly one-third of the patients in both studies required readmission to an acute care hospital for symptom management. This highlights the effect that symptoms can have on functional status. In addition, it points out the importance of identifying symptoms and the need for assessment and management approaches in the primary brain tumor population.

Psychological Symptoms: Research on a variety of symptoms and disease states other than brain tumor patients, has established that the mental states of anxiety and depression contribute to the occurrence, timing, distress, and quality of symptoms that occur (Dales, Spitzer, Schechter, & Suissa, 1989; Leidy, 1990; Pugh, 1990; Pugh & Milligan, 1995). In addition to the neurologic symptoms already described, patients with primary CNS tumors are at risk for interference with emotional and social well-being. Besides the emotional impact of the cancer

diagnosis, patients often experience changes in body image, either as a result of the tumor, the surgery, or the effect of steroids on body-fat distribution. Depression and alterations in usual behavioral patterns can occur. Changes in role function and ability to maintain employment and independence in basic activities can also occur. Although such changes often are reported in clinical papers and in small studies of patients admitted to rehabilitation units, no systematic study evaluating their occurrence has been reported (Armstrong & Gilbert, 1996; Bell, O'Dell, Barr, & Yablon, 1998; O'Dell, Barr, K., Spanier, D., & Warnick, 1998; Rabbitt & Page, 1998).

Two recent interdisciplinary studies used a phenomenological approach to further evaluate QOL after diagnosis of a primary brain tumor (Salander, Bergenheim, & Henriksson, 2000; Strang & Strang, 2001). Salander and colleagues interviewed 28 patients with malignant gliomas at several points during their disease trajectory. They reported that in slightly more than a third of the patients, life-continuity was lost, so they experienced only "time of disease". The two thirds who reported experiencing "time of everyday life" had been able to return to work or to study on at least a part-time basis. Most reported that this loss of "time of everyday life" was most affected by the occurrence of symptoms and the inability to carry out daily activities. Strang and Strang recently explored to what extent patients with brain tumors and their next of kin were able to cope with, understand, and create meaning in their situation and whether these concepts were related to Antonovsky's concept of sense of coherence (SOC). Antonovsky's view is that individuals with a strong SOC have the ability to perceive stressors as manageable, meaningful, and comprehensible (Wolff & Ratner, 1999). This study reported that comprehensibility was to a large extent constructed by the patient's own thoughts and theories, despite an insecure situation. "Manageability" was achieved by active information-seeking strategies, by social support, and by coping, including positive reinterpretation of the situation.

“Meaningfulness” was central for QOL and was created by close relationships as well as by work. Strang and Strang concluded that SOC explained how exposed persons handle their situation and integrated essential parts of comprehensibility and manageability and of finding meaning in one’s life. The ability to find meaning may then affect the distress associated with symptoms as they occur.

Treatment- Related Symptoms: Symptoms associated with therapy have been well described and include worsening of existing physical and psychological symptoms and/or development of new symptoms (Lee, Nauert, & Glass, 1986; Maire, Coudin, Guerin, & Caudry, 1987; Scheibel, Meyers, & Levin, 1996). The most common therapy for all types of primary CNS tumors is radiotherapy to the brain. Transient side effects associated with radiation include acute effects of nausea, hair loss, tinnitus and hearing loss, focal skin reactions, and worsening of existing neurologic symptoms (Dropcho, 1991). Faithful (1991) followed patients for 6 weeks after radiation therapy and described a somnolence syndrome that occurred during this period. The somnolence was associated with reports of sleepiness, sensory changes, and arm and leg weakness. In addition, long- term effects on memory and cognition, characterized by progressive dementia, motor slowing, and gait impairment, have been reported (Kiebert et al, 1998). Intellectual dysfunction has been reported in all adults, is discernible 4 to 6 months after treatment, and is more pronounced 2-3 years after treatment (Strohl, 1998). Other effects, such as short-term effects on attention and memory, have been reported (Archibald et al, 1994; Armstrong et al, 1993). However, these studies evaluated patients only after radiotherapy, with no baseline assessment performed. A recent study by Lilja et al (2001) of patients with primary brain tumor treated with external- beam radiotherapy reported that the deficits seen after radiotherapy were present before treatment, and most likely were related to the effects of the tumor within the brain.

This indicates the need for a standardized assessment technique to fully evaluate patients with primary CNS tumor longitudinally along the disease trajectory.

Because primary brain tumors do not metastasize to other organs of the body and because chemotherapy has limited effectiveness, these tumors have required a different treatment approach than other solid tumors, including the use of focal therapies. As a result, symptoms commonly associated with other cancers and their treatment either have not been reported or are not well described in patients with a primary CNS tumor (Armstrong & Gilbert, 1996). For example, weight loss and anorexia, common symptoms of many cancer diagnoses and a component of symptom distress scales (Cleeland et al, 2000), often do not exist in patients with CNS tumors because of the common use of corticosteroids in this patient population. In fact, these patients often experience weight gain. Other side effects associated with steroid use often seen in this patient population are not commonly found with other malignancies. For example, Dropcho & Soong (1991) reported a 10.6% incidence of steroid myopathy among 216 patients with brain tumors. The resulting proximal weakness can limit activities of daily living, hamper transfers, and affect swallowing and can significantly impair functional status in patients with primary brain tumors.

GAPS

In summary, little research has been completed on the assessment of symptoms in patients with primary brain tumors and how these relate to patients' QOL. Most studies are descriptive in nature. Symptom distress has not been addressed in this patient population, and the differences among ethnic groups in terms of symptom distress and QOL have not been explored.

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