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Narrative Review

Update on Brain Tumors: New Developments in Neuro-oncologic Diagnosis and Treatment, and Impact on Rehabilitation Strategies

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Abstract

Brain tumors can be a source of functional impairment to patients due to neurologic sequelae associated with the tumor itself as well as treatment side effects. As a result, many of these patients may require rehabilitation services. Surgery, chemotherapy, and radiation therapy have been longstanding, primary treatment modalities in the management of brain tumors, though these treatments continue to evolve given new developments in research and technology. A better understanding of the diagnostic workup and current treatment standards helps the physiatrist and rehabilitation team identify rehabilitation services needed, recognize potential side-effects from anticipated or concurrent treatments, and coordinate care with referral sources. The purpose of this article is to review these new advances in diagnosis and treatment of patients with brain tumors, as well as discuss the rehabilitation implications for this population, including factors such as rehabilitation approach, timing of concomitant treatment, cost management, and coordination of care.

Introduction

In 2014, there will be an estimated 23,400 new cases of primary brain tumors, representing 1.4% of all malignancies [1]. Brain metastases occur in a larger numbers of survivors, comprising 16%-20% of lung cancer patients, 5% of breast cancer patients, and 1%-2% of colorectal cancer patients [2,3]. Brain tumors can be a source of significant functional impairment due to neurologic sequelae, with the potential for many of these patients to require rehabilitation services. A better understanding of the diagnosis, prognostic indicators, and treatment options is essential for physiatrists to better provide rehabilitation services for these patients. The purpose of this article is to review new advances in diagnosis, imaging modalities, and treatment regimens, as well as the rehabilitation implications for this population.

Literature Selection

Reference texts and a literature search identified studies relevant to brain tumors in adults, utilizing the PubMed Database (National Center for Biotechnology Information via Pubmed.gov). The following search terms were used: brain tumors and genetic mutations, brain tumors and chemotherapy, brain tumors and radiation therapy, brain tumor vaccine, brain tumor imaging, radiation therapy side effects, brain tumor and rehabilitation, brain tumor and functional outcome.

Initial search results were limited to English-language studies. Case reports and case series were excluded except where limited studies were available. The references in the selected articles were used to identify additional relevant sources. The 3 authors reviewed the papers to determine eligibility.

Pathologic Diagnosis

Metastatic brain tumors are classified based on the primary tumor type, whereas primary brain tumors are generally classified and graded based on histology as per the World Health Organization (WHO) classification system. This system provides the basic structure and language for objective assessment that can be communicated across oncology and other medical fields, and can provide direction to the appropriate treatment and possible enrollment in clinical trials. A review of the WHO classification system, which has undergone several revisions, is covered in detail in multiple other articles

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and is out the scope of this article [4,5]. There are several notable histologic, molecular, and genetic factors that will aid in physiatrist assessment. Malignancies generally develop with inactivation of tumor suppressor genes, activation of oncogenes, and loss of ability to repair and initiate apoptosis.

p53

p53 Is a tumor suppressor gene found on chromosome 17. It is a key component in the body's intrinsic mechanism for repair and apoptosis. Mutations of p53 are present in numerous malignancies and are considered to be an early change in tumorgenesis. These mutations are reported to occur in up to 88% of low-grade astrocytomas but only 13% of oligodendrogliomas [6]. In regard to glioblastoma multiforme (GBM), there is a high incidence of p53 mutations in secondary glioblastomas, meaning tumors progressed from low-grade tumors, versus a much lower incidence in primary glioblastomas, tumors that were WHO grade IV upon presentation [7]. However, this mutation has not been found to be a clear predictor of survival in low-grade astrocytomas [6,8].

Ki-67

Ki-67 is a nuclear protein that is absent in the resting cell but is seen in all active phases of the cell cycle. In normal tissue, the protein is absent to minimally present; in malignant tissue, however, it is present in increasing numbers. As a result, the Ki-67 percentage has prognostic importance. Higher Ki-67 percentage typically correlates with poorer prognosis, but the specific significant value varies between tumor types. A Ki-67 percentage of greater than 5.0% has been shown to be associated with reduced survival in patients with anaplastic glioma [9].

Endothelial Growth Factor Receptor

Endothelial growth factor receptor (EGFR) is a cell membrane receptor that, when activated, stimulates intracellular tyrosine kinase activity and triggers cell division. Mutations of EGFR can lead to uncontrolled cell cycle division [10]. In regard to brain tumors, EGFR mutations often result in the development of primary glioblastomas, with EGFR mutations noted in up to 60% of cases, in contrast to approximately 10% of secondary glioblastomas [7,11]. EGFR mutations have been shown to be associated with poor prognosis in primary brain tumors [9,12]. In contrast, EGFR mutations in non—small cell lung adenocarcinoma often present in patients without a smoking history and indicate a better prognosis [13].

1p/19q Deletion

The loss of chromosome arms 1p/19q has been noted preferentially in oligodendrogliomas [14]. Although the biologic importance of these chromosomes is unclear, the 1p/19q deletion has been associated with improved response to treatment and improved survival [15,16].

Methylguanine-DNA Methyltransferase

Methylguanine-DNA methyltransferase (MGMT) is part of the body's DNA repair mechanisms, specifically focused on removing alkylation of the O6 position of guanine. The primary mutation seen in GBM is promoter hypermethylation, leading to silencing of MGMT gene transcription and subsequently impairing the repair process in the tumor cells [17]. Identification of this promoter methylation is indicative of a favorable prognostic factor and response to chemotherapy [18].

Isocitrate Dehydrogenase 1 Gene and Isocitrate Dehydrogenase 2 Gene

Isocitrate dehydrogenase 1 gene (IDH1) and isocitrate dehydrogenase 2 gene (IDH2) are enzymes that catalyze the oxidative decarboxylation of isocitrate outside of the citric acid cycle. The normal process creates α-ketoglutarate; mutations result in the enzymes instead producing D-2-hydroxyglutarate, which is thought to act as a stimulus for malignant changes [19,20]. IDH mutations are significantly more common in secondary glioblastomas as compared to primary glioblastomas [21,22]. The presence of a mutation has important prognostic implications for both anaplastic astrocytoma and glioblastomas. It has been shown that glioblastomas with IDH1 mutations actually have a more favorable prognosis than anaplastic astrocytomas without IDH1 mutations [21,23].

In summary, the identification of genetic mutations and specific tumor markers allows oncologists to better understand the pathophysiology of brain tumors, improve prognostication, and administer focused treatment choices. Table 1 highlights key information in relation to primary brain tumors. Physiatrists can also use this information to better guide patients, their families, and the clinical team.

Diagnostic Functional Imaging

Radiographic imaging of primary and metastatic brain tumors is no longer solely for the purpose of identifying structural abnormalities; the use of current neuroimaging techniques now allows a more thorough evaluation, including diagnosis, grading, and monitoring of brain tumors [24].