14 Brain Stem Gliomas in Children

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14.1 Epidemiology

Brain tumors are the most common solid tumors and second most common malignancies in children after the leukemias. Approximately 1100–1200 new cases of brain and central nervous system tumors are seen yearly in children under the age of 14 in the United States. Brain stem tumors account for 10%-20% of all brain tumors in children (ABRAMSON et al. 1974; LITTMAN et al. 1980; BLOOM et al. 1990). For the purposes of this chapter, brain stem will be defined as the medulla oblangata and the pons and will exclude the thalamus and midbrain. No sex or racial predominance is noted in brain stem gliomas. The mean age at diagnosis varies from 6.5 to 8.9 years (HALPERIN 1985; FREEMAN and SUSSA 1986; EIFEL et al. 1987; FRIEDEL et al. 1987; STRONK et al. 1987; HALPERIN et al. 1989b; SHRIEVE et al. 1992).

14.2 Clinical presentation

The duration of symptoms prior to diagnosis is highly variable. More than 50% will have a relatively brief duration of symptoms (less than 1 month) before diagnoses, whereas 17% will have symptoms for at least 6 months before diagnosis (HALPERIN 1985; GRIGSBY et al. 1987, 1989; HALPERIN et al. 1989b). Symptoms arise as a result of either obstruction of cerebrospinal flow or local destruction or compression of structure in the region of the brain stem or nerves coursing through the brain stem. The most common presenting symptoms are ataxia (62%-63%), motor disturbances (37%), headaches (42%-61%), and nausea and vomiting (24%-43%). Less common symptoms include dysarthria, personality changes, seizures, and failures to thrive in infants (HALPERIN 1985; EIFEL et al. 1987, 1989; HALPERIN et al. 1989b). Cranial nerve deficits, most commonly involving nerves III–VII, occur in 65% of patients, and abnormal cerebellar testing occurs in 63%. Other less common signs include papilledema, head tilt, and long tract signs.

14.3 Prognostic Factors

A wide array of clinical, pathologic, and radiologic characteristics have been reported to be of prognostic significance. Location of the lesion is the most frequently discussed and has been incorporated into the eligibility criteria of three major cooperative group trials in brain stem gliomas (LEE 1975; GREENBERGER et al. 1977; ALBRIGHT et al. 1986; EDWARDS et al. 1987, 1989; EIFEL et al. 1987; FREEMAN et al. 1987, 1988; HALPERIN et al. 1989a, b). Retrospective reports from Duke and the Joint Center for Radiation Therapy (GREENBERGER et al. 1977; HALPERIN 1985; EIFEL et al. 1987) found that patients with tumors located in the midbrain or thalamus had a superior survival when compared to those with lesions of the pons and medulla after treatment with conventional radiotherapeutic techniques (57%-72% vs 28%-38% 5-year survival). Two special subgroups of brain stem gliomas have been identified that have an improved overall survival and that are often amenable to surgical resection. The first is an exophytic tumor which arises from the dorsum of the brain stem, fills or
partially fills the fourth ventricle, and is isodense or hypodense on CT scan. These tumors are generally associated with a prolonged duration for symptoms prior to diagnosis and accounted for 8% of all brain stem lesions in the Toronto series of 121 patients (Hoffman et al. 1980; Stroink et al. 1987; Sanford et al. 1988). Of 16 of these tumors that were approached with a subtotal resection, 13 were pathologically identified as grade I or II astrocytomas, two as gangliogliomas, and only one as an anaplastic glioma. Fifteen of the 16 patients were alive 8 months to 23 years after therapy. Epstein and Wisoff (1988) described a second subgroup of patients with tumors of the cervicomedullary junction. In his series of 24 resected patients, 16 were found to have benign astrocytomas, four gangliogliomas, and four anaplastic astrocytomas or glioblastoma multiforme after gross total resection, and required no postoperative therapy.

The impact of histologic grade on survival is unclear at present. In most series, only a minority of cases have tissue available for histological diagnosis (17%-64%) (Halperin 1985; Albright et al. 1986; Freeman and Suissa 1986; Eifel et al. 1987; Grigsby et al. 1987, 1989; Packer et al. 1985, 1990b). Such biopsies often reveal low-grade astrocytomas, and their significance has been called into doubt on the basis of sampling error. Most studies fail to show a major impact of grade on survival; however, there are some notable exceptions. One is the review of prognostic factors in the combined series of cases from the Children's Hospitals of Pittsburgh and Philadelphia (Albright et al. 1986). The presence of mitoses in histological specimens had a dramatic inverse effect on survival (15 of 18 with mitoses were dead within 6 months and the longest period of survival was only 2.4 years, whereas 18 of 6 without mitoses were alive at 4 years). In this study, the presence of Rosenthal fibers or calcification was associated with improved survival. The recent evaluation of hyperfractionation for brain stem gliomas in children from the CCG (Children's Cancer Group) (Edwards et al. 1987, 1989) also suggests that there is a correlation between high-grade malignancy and poor survival. Most studies, however, fail to show a significant correlation between biopsy results and survival (Littman et al. 1980; Berger et al. 1983; Stroink et al. 1986).

Computed tomographic characteristics of the lesion have been analyzed with respect to survival. Pediatric tumor that appear clearly focal on CT scan or MR scan have a significantly better prognosis than those that are diffusely infiltrative (90% vs 46% 1-year survival in the CCG study) (Epstein 1985; Stroink et al. 1986; Edwards et al. 1987, 1989; Stroink et al. 1987; Shrieve et al. 1992). Likewise, tumors that display an exophytic pattern tend to fare better than intrinsically expansile lesions. Epstein and Wisoff (1989) reported on 27 cases of diffuse lesions approached surgically, all of which were found to be either anaplastic astrocytomas or glioblastoma multiforme, whereas of six focal lesions, all less than 2.5 cm on MR scan, half were found to be low-grade astrocytomas. The presence of a hypodense lesion prior to enhancement with contrast has been suggested as a poor prognostic factor, as well, and most likely associated with diffuse involvement of the brain stem (Albright et al. 1986).

Clinical characteristics associated with a poor prognosis include rapid progression of symptoms over a 2-month course (Edwards and Prados 1987; Edwards et al. 1987, 1989; Grigsby et al. 1989; Shrieve et al. 1992), the presence of multiple cranial nerve deficits (Albright et al. 1986; Edwards and Prados 1987; Edwards et al. 1987, 1989; Shrieve et al. 1992), or the presence of long tract signs (Albright et al. 1986; Freeman and Suissa et al. 1986). The CCG studies of hyperfractionation have found a highly significant reduction in time to progression and survival for patients whose symptoms began ≤2 months prior to diagnosis (Edwards et al. 1989; Shrieve et al. 1992). Albright et al.'s study (1986) also found a significant decrease in overall survival in patients whose signs had been present for less than 6 months prior to diagnosis. Patients with duration of symptoms ≥6 months have been excluded from the Pediatric Oncology Group (POG) Study unless they have other evidence suggestive of high-grade malignancy (biopsy positive for anaplastic astrocytoma or glioblastoma or multiple cranial nerve signs) (Freeman et al. 1988, 1991). In one series, the 2-year actuarial survival was 71.3% for those without cranial nerve deficits, versus 20.3% for those with cranial nerve deficits (Albright et al. 1986).

Aside from the previously mentioned favorable subtypes (cervicomedullary, exophytic dorsal lesions), the impact of surgery on overall survival has been negligible. A retrospective analysis from the Mallinckrodt Institute of 70 pediatric thalamic and brain stem lesion did not find a benefit of subtotal resection over no surgery (Grigsby et al. 1987), but the majority of studies have not shown any impact with radical surgery for the most brain stem lesions (Greenberger et al. 1977; Epstein 1985; Halperin...