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Brainstem gliomas

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The brainstem, or mesencephalon, is defined as the midbrain, pons, and medulla. Gliomas within the brainstem comprise 10–20% of all pediatric central nervous system (CNS) tumors. In the United States, there are approximately 150–300 annual cases [3, 14]. Brainstem gliomas can occur at any age, although they generally present in childhood, with the mean age of diagnosis at 7 to 9 years [5, 11]. There is no gender predilection.

In the era before modern imaging, all brainstem gliomas were regarded as a single pathological entity, and the prognosis was considered uniformly poor. In 1969, Matson [12] summarized that "regardless of specific histology, brainstem gliomas must be classified as malignant tumors since their location in itself renders them inoperable." Pool was one of the first neurosurgeons to advocate surgery for certain brainstem tumors (BSTs). He operated upon several children and reported a survival of 10 to 25 years [9]. In the early 1980s, several neurosurgeons began reporting favorable surgical outcomes for certain types of brainstem gliomas [4, 6, 7, 10, 13]. Classification systems were then introduced, which attempted to identify those tumors that benefited from surgery. These morphological systems further evolved with the advent of magnetic resonance imaging (MRI), thus helping to predict tumor behavior and determine the best management algorithm for these tumors.

Many classification schemes have been devised for BSTs. The earliest categorizations relied on computed tomography (CT) and surgical observations; however, the more recent schemes include MRI sequences. All these systems categorize the tumor by epicenter (diffuse or focal) or imaging characteristics. The simplest classification divides these tumors into two groups, either focal or diffuse, regardless of tumor epicenter. The more complex schemes subdivide these tumors by location, focality, presence of hydrocephalus or hemorrhage, and growth pattern.

The diffuse gliomas are the most commonly encountered tumor of the brainstem, accounting for 58–75% of all tumors [1, 7]. On T1-weighted MRI scan, they appear hypointense, with indistinct margins, reflecting the infiltrative nature of these high-grade lesions. Diffuse gliomas of the brainstem are generally greater than 2 cm in size at the time of presentation. They are characterized by diffuse infiltration and swelling (or hypertrophy) of the brainstem. The epicenter of the lesion is usually the pons; however, rostral or caudal tumor extension is not unusual. These diffuse gliomas are distinguished from focal tumors by their indiscrete hyperintensity on T2-weighted imaging. Gadolinium enhancement can be variable and has no prognostic implication [8]. These diffuse gliomas are typically malignant fibrillary astrocytomas (grade III or IV).

These lesions invariably have a rapidly progressive course. Children with diffuse brainstem gliomas will often present acutely with multiple cranial nerve signs, ataxia, long tract signs, and cerebellar signs. Most children die within 18 months from diagnosis, similar to the clinical course for glioblastoma multiforme [2, 11].

Since these diffuse, inoperable BSTs have a poor prognosis and cannot be treated with surgical resection. Current treatment options for these tumors are limited to radiotherapy with or

without adjuvant chemotherapy. Despite aggressive multimodal adjuvant therapy, patients
succumb to their disease within a relatively short period of time.

While chemotherapy has been incorporated into the treatment of various intracranial neoplasms, the role of chemotherapy agents for BSTs remains undefined. Systemic chemotherapy has been used in the treatment of these inoperable tumors, but the efficacy of this approach needs to be confirmed with larger studies. The discovery of more potent and specific antineoplastic agents, and the development of novel drug delivery systems for CNS malignancies, including controlled-release polymers, local therapy, and convection-enhanced delivery, among others, could benefit the treatment of BSTs; however, testing of these novel treatments requires a reproducible and accessible animal model of BSTs for preclinical testing.

Current literature lacks a comprehensive animal model for BSTs, and the development of such a model is a requisite for future investigations. An ideal animal model for this disease should be accessible and have a reproducible course of onset of paraparesis, with a predictable pattern of tumor infiltration and a therapeutic window adequate for experimental intervention; it must be amenable to radiological monitoring and also resemble the infiltrative nature of human BSTs.

Experimental neonatal tumors have been expressed by treating pregnant animals with carcinogenic agents or by inoculating newborn animals with tumor cells. The former technique is less suited to studies of drug efficacy for several reasons. The carcinogens may have variable in utero distribution and produce different types of tumors. Some littermates may be unaffected, while others may have small or large tumors. Although direct inoculations can achieve highly uniform tumor doses, the capacity of the developing brainstem to tolerate inoculations and tumor cell challenges is unknown. There is a significant risk or surgical morbidity because the brainstem, unlike the cerebral cortex, has little functional redundancy. A second question to be answered was whether the tumor-cell-challenged animals could be returned to the mother for nursing. We have a clinical impression that female Fischer rats, which are commonly used in studies of brain tumor therapy, reject pups that have been marked by experimental manipulations.

Several studies involving neonatal inoculations in the cerebral cortex of mice and rats have used hypothermia for anesthesia. These results suggest that the method may be adapted to the preparation of brainstem models.

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