Diffuse intrinsic brainstem tumors in neonates

Report of 2 cases

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The authors report on 2 newborn infants with the unusual presentation of intrinsic brainstem tumors. Both nondysmorphic, full-term neonates had cranial nerve palsies and hypotonia. Diagnoses of diffuse intrinsic brainstem gliomas were made on the basis of magnetic resonance imaging, which showed large expansive, nonenhancing intrinsic pontine masses. Intrinsic pontine tumors, characteristically seen in school-age children, are most often high-grade gliomas that are almost invariably fatal. However, the microanatomy and natural history of pontine tumors in neonates are unknown. With parental consent, both newborns were treated expectantly with supportive care but died of progressive disease by 2 weeks of age. In one child, postmortem examination revealed a primary brainstem primitive neuroectodermal tumor. The authors conclude that, as in older children, neonatal intrinsic brainstem tumors may be of a highly malignant nature. The rapid tumor progression in both cases indicates that where a diagnostic procedure may pose significant risks, supportive observation can aid in distinguishing malignant from benign tumor growth.

(DOI: 10.3171/PED/2008/1/5/382)

KEY WORDS • congenital disease • diffuse intrinsic brainstem glioma • primitive neuroectodermal tumor

Abbreviations used in this paper: DIPG = diffuse intrinsic pontine glioma; MR = magnetic resonance; PNET = primitive neuroectodermal tumor.
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Case Reports

Case 1

This full-term female infant was delivered by cesarean section at 42 weeks’ gestation due to delayed labor progression and fetal ultrasonographic findings of increased amniotic fluid and hydrocephalus. An 18-week prenatal ultrasound had shown normal findings. At birth, the infant had mild respiratory distress with Apgar scores of 5 and 9, at 1 and 5 minutes, respectively, and required continuous positive airway pressure treatment for 30 minutes. Newborn examination revealed no dysmorphism, an increased head circumference with a soft fontanelle, and hyperreflexia in the lower extremities. A brain MR imaging study on Day 2 of life revealed hydrocephalus and a large intrinsic pontine mass extending to the midbrain, upper cervical cord, and posterior fossa (Fig. 1A and C). The tumor had low T1 and high T2 signals and lacked contrast enhancement. Diffusion weighted imaging revealed no restriction, and MR spectroscopy showed markedly reduced N-acetyl aspartate and an elevated choline level. Spinal MR imaging showed normal features. The neuroimaging features were considered most compatible with those of a brainstem glioma. Dexamethasone administration was begun, but the infant quickly developed nystagmus, dysconjugate eye movements, left-sided facial palsy, and cycling arm movements. As the clinical and neuroimaging pictures were most consistent with a rapidly progressive malignant brainstem lesion, no further interventions were undertaken after discussion with the family. The infant was discharged home where she received palliative care with steroids and phenobarbitol and where she died at 12 days of age.

Postmortem examination revealed a multilobulated hemorhagic brain mass involving the pons, medulla oblongata, and adjacent left cerebellum with extension to the midbrain (Fig. 1B). The tumor was composed of small cells arranged in patternless sheets, with uniformly round nuclei containing clumped chromatin, unremarkable nucleoli, and small amounts of finely fibrillar eosinophilic cytoplasm (Fig. 1D). Immunohistochemical analyses revealed strong microtubule-associated protein–2 expression, absence of cytokeratin, vimentin, and myogenin expression in the majority of tumor cells and glial fibrillary acidic protein positivity in a small subset of cells. A diagnosis of PNET was based on these findings. Tumor cell cytogenetic analyses by G-banding revealed a normal female karyotype.

Case 2

This full-term female infant weighing 3.198 kg was delivered by spontaneous vaginal delivery at 37 weeks’ gestation to a G2P1 mother with gestational diabetes. At birth the infant required brief continuous positive airway pressure treatment. Newborn examination on Day 1 was significant for hypotonia, right facial palsy, stridor, abnormal eye movements, pooling of secretions, and abnormal gag reflex. Initial brain computed tomography scanning suggested a mass originating in the posterior fossa. Brain MR imaging on Day 2 revealed an intrinsic pontine mass measuring 3.5 cm in diameter with involvement of the medulla oblongata and the middle cerebellar peduncle (Fig. 2). The mass was homogeneously isointense on T1- and hyperintense on T2-weighted images and did not enhance after administration of a contrast agent. Magnetic resonance spectroscopy revealed increased choline uptake. Diffusion tensor imaging with tractography showed no restriction but revealed gross disruption of white matter tracts within the pons by the infiltrating tumor mass. Despite the unusually young age, the neuroimaging findings were considered most compatible with those of a malignant DIPG. Due to the substantial risk of a diagnostic biopsy, the parents were counseled and agreed for their child to undergo expectant management with dexamethasone for symptom control. However, similar to the child in Case 1, despite high-dose steroid treatment, the child rapidly developed progressive symptoms and died in hospital at 11 days of age. The family did not permit a postmortem examination.

Discussion

Diffuse intrinsic pontine tumors in childhood are most frequently high-grade gliomas with dismal outcome. A DIPG is
currently diagnosed on the basis of characteristic clinical and neuroimaging features, but rare cases of presumed DIPG with classic neuroimaging features but an indolent clinical course have been reported.\textsuperscript{7,11} In particular DIPG-like tumors in patients with neurofibromatosis Type 1 may be low-grade lesions. Notably, spontaneous regression of presumed diffuse brainstem gliomas in younger children, including a neonate, has been reported.\textsuperscript{14–16} Hence, any atypical clinical and neuroimaging features, such as the congenital presentation in our 2 cases, must be considered cautiously in the diagnosis and management of presumed DIPG.

Malignant brainstem lesions in neonates are rare, and to date only very few cases diagnosed at birth have been described.\textsuperscript{16,19} At our tertiary referral institute, only 3 cases, including the 2 presented here, of diffuse neonatal brainstem lesions have been recorded in the last \~20 years.\textsuperscript{12} The differential diagnosis of brainstem lesions in this age group includes both neoplastic and nonneoplastic origins that may be distinguished by clinical features and imaging studies. Nonneoplastic causes include hypoxic or metabolic encephalopathy, birth trauma, and infectious rhombencephalitis of viral or bacterial origin.\textsuperscript{3} In neither of our cases was there a documented risk for unusual infections or hypoxic events; thus, we considered nonneoplastic lesions to be most likely. Neuroimaging features in our 2 cases were considered most compatible with those of diffuse pontine gliomas; to our knowledge, histologically confirmed intrinsic high-grade gliomas of the brainstem in neonates have not been reported. In addition to malignant gliomas, diffuse low-grade brainstem gliomas, described in older children, were also considered. Neither family in our 2 cases had a history of neurofibromatosis Type 1 or cancer predisposition. Rare cases of histologically proven congenital embryonal brainstem tumors including medulloepithelioma,\textsuperscript{13} atypical rhabdoid teratoid tumors,\textsuperscript{4} and PNETs\textsuperscript{17,18} have been reported. Although these lesions may present with nonclassic DIPG-like imaging features, we also considered these tumors in the differential diagnosis in our patients.

Among the embryonal brainstem tumors, the largest therapeutic experience has been reported in the PNET group. Brainstem PNETs, which present at a younger age than pontine gliomas, are rare entities, with only 23 cases reported to date.\textsuperscript{3–5,13,18,19} The majority of central nervous system PNETs that arise in the cerebrum are substantially more aggressive than medulloblastomas. A modest overall survival rate of \~35% has only been achieved using high-dose myeloablative chemotherapy and craniospinal irradiation. Although radiation-free cures have been reported, these remain in the minority.\textsuperscript{4} For brainstem PNETs, the prognosis is even more dismal, with only 2 survivors reported among 17 treated patients,\textsuperscript{3,15} both of whom required craniospinal irradiation after disease progression despite having received high-dose myeloablative treatment. Our Case 1 represents only 1 of the 2 histologically confirmed congenital brainstem PNETs of which we are aware. The only other case—reported by Fangusaro et al.\textsuperscript{3}—was in a 2-month-old child who died despite treatment with myeloablative chemotherapy and stem cell transplantation.

Because no safe or efficacious treatment for malignant brainstem gliomas or PNETs in neonates has been clearly established, we recommended a period of observation during which medications were prescribed for symptom control in both our patients. Had our neonates been clinically stable, we would have explored options for continued observation or treatment of a presumed low-grade brainstem glioma. Although we had histopathological confirmation only in a single case, the rapid clinical progression in the second neonate indicated it was also an aggressive, malignant brainstem lesion for which successful intervention was very unlikely.

Conclusions

In summary, the treatment of newborns with malignant brain tumors is fraught with ethical and physiological challenges. We propose that in the congenital presentation of brain tumors, such as ours, in which the therapeutic benefits of a risky tumor biopsy are questionable, a period of expectant observation involving supportive care is a reasonable and practical approach to assess speed of tumor growth and aid in distinguishing between low- and high-grade lesions. The distinct postmortem histological diagnosis of brainstem PNET in 1 of our patients may not have been predicted on the basis of the limited current literature on congenital brainstem tumors. Our experience highlights the value of counseling families on the importance of postmortem investigations in such rare cases to allow a better understanding of the histological spectrum of congenital brain tumors. Such investigations would be a step toward establishing more specific diagnostic and therapeutic approaches for brain tumors in these very young children who are most susceptible to morbidities of surgical and nonsurgical interventions.

References

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