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Spontaneous regression of a diffuse brainstem lesion in the neonate

Report of two cases and review of the literature

WILLARD DARRELL THOMPSON JR., M.D., AND EDWARD J. KOSNIK, M.D.

Section of Pediatric Neurosurgery, Department of Surgery, Children's Hospital of Columbus, Ohio

✓ The authors present two cases of diffuse brainstem lesions that regressed without treatment. Two newborns presented with cranial nerve palsies and limb weakness at birth. Magnetic resonance (MR) images obtained in the 1st week of life revealed a large, expansive pontomedullary lesion in each patient. Findings of clinical and imaging examinations were highly consistent with the characteristics of diffuse brainstem glioma. After consultation with the parents of both infants, all parties agreed to forgo the treatment modalities available at the time. Neither patient underwent surgery, radiation treatment, or chemotherapy; both underwent routine neurological and MR imaging examinations. Within weeks the patient in Case 1 started to improve clinically and at 4 years of age has reached nearly all developmental milestones. Serial MR images demonstrated a steady decrease in the size of the lesion. The patient in Case 2 improved in a similar manner and is now 10 years old. The findings from these two cases should encourage families and clinicians to consider that a subcategory of diffuse lesions may exist, particularly in the neonatal period. It must be stressed, however, that nearly all patients with diffuse brainstem lesions experience a poor outcome, regardless of tumor grade or treatment. Brainstem gliomas, spontaneous regression of central nervous system tumors, and the differential diagnoses of brainstem lesions are discussed.

KEY WORDS • brainstem glioma • diffuse pontine lesion • spontaneous regression • benign brainstem lesion • pediatric neurosurgery

THE spontaneous regression of diffuse brainstem tumors is exceedingly rare; only one such case has been reported previously.[29] There are several reports on the regression of more focal brainstem tumors and lesions, particularly in patients with NF.[23,40,44] In this paper, we report the cases of two neonates who experienced what might be termed a "miraculous" clinical recovery and MR imaging–documented regression of a diffuse, pontine-based lesion. The characteristics of these lesions as observed on clinical presentation and MR imaging were consistent with those of a high-grade glioma; the diagnosis, however, was not histologically confirmed. Although predictors of poor outcome were evident in both cases, the patients, now 4 and 10 years of age, have fared extremely well. We review the literature on brainstem gliomas, present the few reports of spontaneous regression of these lesions, and discuss the differential diagnosis of these pediatric brainstem lesions. The possible implications of these cases for our understanding of diffuse brainstem lesions as well as potential changes in patient care are assessed.

Abbreviations used in this paper: CT = computerized tomography; MR = magnetic resonance; NF = neurofibromatosis; NF1 = NF Type 1.

Case Reports

Case 1

This full-term baby boy was vaginally delivered after an uneventful pregnancy. At birth inspiratory stridor and decreased muscle tone were apparent in the patient. Other physical findings included facial palsy, vertical nystagmus, and disconjugate gaze. At 2 days of age, the child underwent MR imaging of the brain that revealed a large expansive mass involving the brainstem, predominantly the pons and extending into the medulla. The lesion was hypointense on T_1-weighted and hyperintense on T_2-weighted MR images (Fig. 1). These characteristics were considered consistent with those of a diffuse infiltrating brainstem glioma. Following consultation with the patient's family regarding the apparent grave prognosis, the parents, oncologist, and neurosurgeon agreed to send the patient home with supportive care and not to resuscitate if his condition were to deteriorate. On the 5th day of life the patient left the hospital

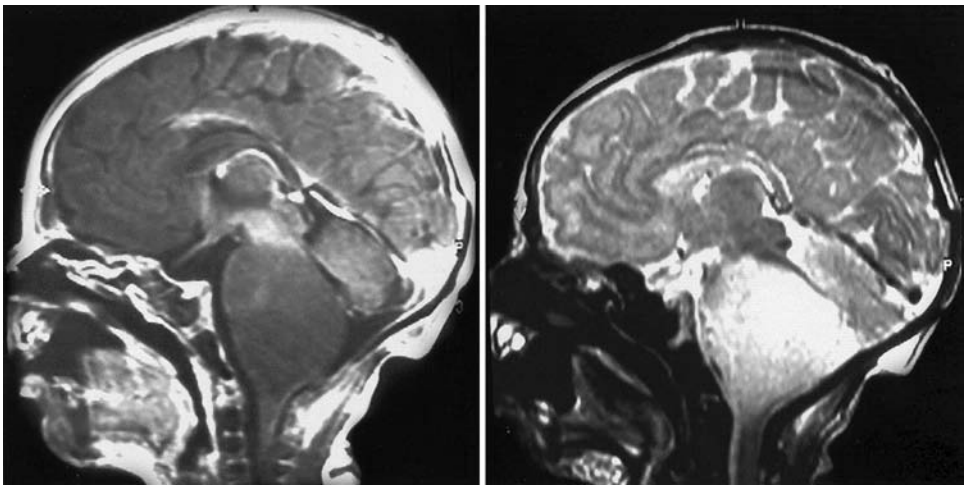

FIG. 1. Case 1. Sagittal MR images of the brain obtained in a 2-day-old infant. *Left*: A Gd-enhanced T_1-weighted image demonstrating a large expansive pontomedullary mass and minimal-to-no enhancement. *Right*: A T_2-weighted image revealing a hyperintense signal extending throughout most of the brainstem.

with a nasogastric feeding tube. No surgery, radiation treatment, steroid medication, or chemotherapy was administered.

Remarkably, the patient showed signs of improvement. Within 1 week, the patient was tolerating bottle feeding, which allowed tube feeding to be discontinued by Week 2. At 1 month of age, the patient displayed no signs of nystagmus or seventh cranial nerve palsy, and by 6 weeks of age the disconjugate gaze was nearly nonexistent. Measurements of the child's head circumference were ranked near the 50th percentile and nearly all developmental milestones were met. By 5 months, the patient smiled and by 14 months of age he was able to walk. The patient has been continuously followed and at 5 years of age has, with the exception of a slight speech delay, developed normally.

Follow-up MR imaging studies demonstrated regression of the lesion at 6 weeks and 4 months of age (Fig. 2). Repeated MR imaging performed when the patient was approximately 4 years of age (Fig. 3) revealed a brainstem contour that, although improved, remains abnormal. Note that no NF1 stigmata and no family history of NF1 were evident.

Case 2

We first examined this full-term baby girl at birth. She was delivered after an uneventful pregnancy, although the birth was complicated by meconium aspiration. In the nursery, she demonstrated signs of facial palsy and hemiparesis. On further examination, a weak cough/gag, disconjugate gaze, and hypertonicity were also detected. Brain MR imaging performed at 1 week of age revealed a large mass

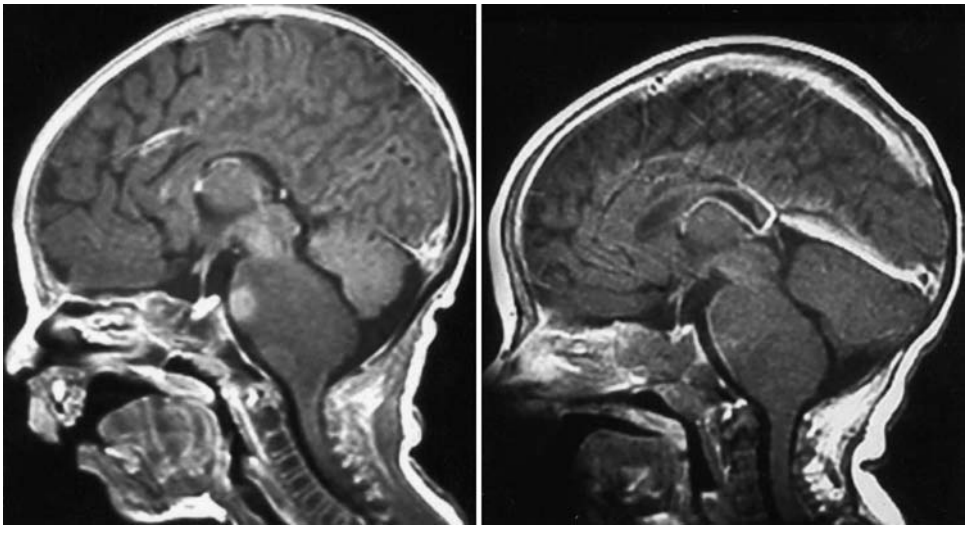

FIG. 2. *C*ase 1. Serial Gd-enhanced T_1-weighted sagittal MR images of the brain obtained when the child was 6 weeks of age *(left)* and 4 months of age *(right)*. A slight decrease in the overall dimensions of abnormality in the pontomedullary mass is demonstrated. An enhancing nodule appears at the anterior left aspect of the mass at 6 weeks of age, and by 4 months of age only scant enhancement exists.

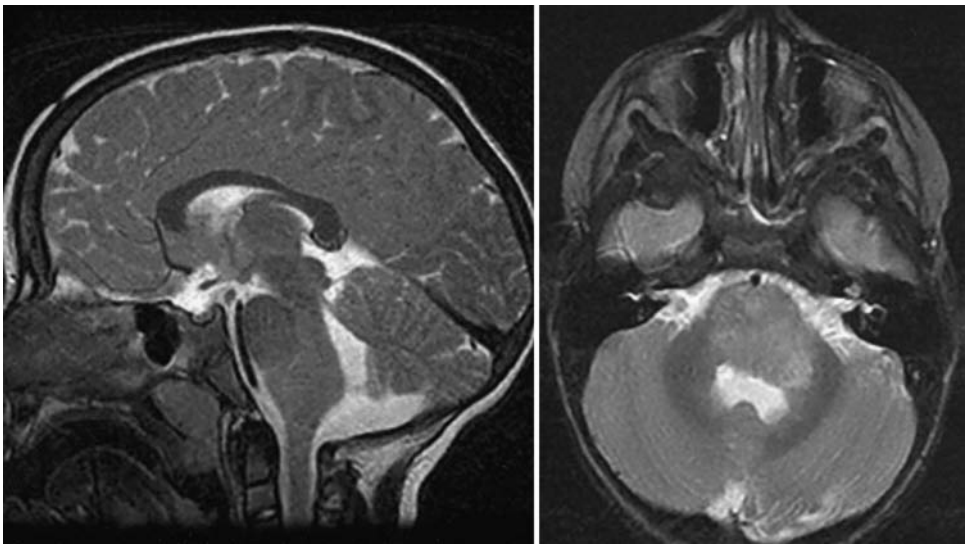

FIG. 3. Case 1. Magnetic resonance T_2-weighted images of the brain, obtained in the child when he was 4 years of age. *Left*: Sagittal image demonstrating a much less deformed abnormal brainstem contour. *Right:* Axial image revealing a signal abnormality in the brainstem extending into the left middle cerebellar peduncle. Note the mild fourth ventricular effacement.

centered within the pons extending from the inferior medulla oblongata up to the midbrain. The mass appeared infiltrative in nature and heterogeneous in signal intensity (Fig. 4a). As in Case 1, the characteristics of this mass were consistent with those of a diffuse infiltrating glioma, and the associated prognosis was grave. The family was informed that the available treatment options might not result in an improved outcome for the patient. All parties agreed to forgo any treatment, and the patient was discharged home with supportive care. No radiation treatment, chemotherapy, or steroid therapy was undertaken.

Like the child in Case 1, this patient demonstrated remarkable clinical and MR imaging–documented improvements. She has been followed for 10 years and her intellectual development has been completely normal. She continues to suffer slight facial asymmetry, and a subtle dysmetria is apparent on the right side during finger-to-nose testing. The child's mother describes her as very clumsy. Serial MR images revealed the remarkable regression of the lesion (Fig. 4b and c). Note the many areas of cystic degeneration and the absence of abnormal enhancement. As in Case 1, no NF1 stigmata nor family history of NF1 was evident.

Discussion

Brainstem Gliomas

Brainstem gliomas account for 10 to 20% of pediatric central nervous system neoplasms;[2,22] the mean age at presentation is between 6 and 10 years.[4,10,36] The 5-year survival rate for patients with these lesions when the tumors are grouped as one entity is approximately 30%.[10] Several authors have reported that patients with focal tumors experience better outcomes than patients with diffuse tumors.[4,16,25] Cases of long-term survival in patients with focal tumors such as dorsal exophytic tumors,[25,37] cervicomedullary tumors,[3,15,41,42] tectal plate gliomas,[42,48] and brainstem lesions in patients with NF[11,12,32,35,38] are now well documented in the literature. Many authors categorize this heterogeneous group of tumors according to anatomy and imaging characteristics—diffuse, focal, dorsal exophytic, or cervicomedullary.[1,2,16,22] This classification correlates well with the prognosis and treatment plan for each entity.

Despite these subgroups in which good patient outcome occurs, 50 to 80% of patients with brainstem gliomas harbor diffuse infiltrating tumors with grim prognoses.[7,16,18,34] Considered as a separate entity, diffuse lesions are associated with poor outcome; 80% of patients, including those who undergo radiation therapy, will die within 2 years.[9] The mean survival time with or without radiation treatment was estimated by one group of authors at 8.8 and 3.9 months, respectively.[28] In two large series of 136 and 84 patients treated with conventional radiation therapy, the 5-year survival rate was approximately 15% for patients with diffuse lesions.[5,24] Little improvement in outcome has occurred for patients with diffuse lesions.

The following predictors of poor outcome for brainstem gliomas are well reported in the literature: younger age,[24,36,46] pontine location,[17,19,24,43] diffuse appearance of the lesion on CT scans or MR images,[6,17,47] degree of brainstem enlargement,[9] duration of symptoms less than 2 months,[19,24,36,43] cranial nerve palsies,[6,19,43] and engulfment of the basilar artery.[19,30,35] Sanford, et al.,[43] reported that 35 of 36 patients died of these lesions in less than 18 months if the patients presented with two of the three following conditions: cranial nerve palsy, long tract findings, or cerebellar signs. In the cases presented here the two neonates demonstrated most of these predictors on presentation.

The historical treatment for the diffuse infiltrating glioma is conventional external-beam radiation therapy. A consensus is emerging that surgery for diffuse brainstem gliomas is generally not indicated; surgery for tumors in this location is associated with high morbidity and has not

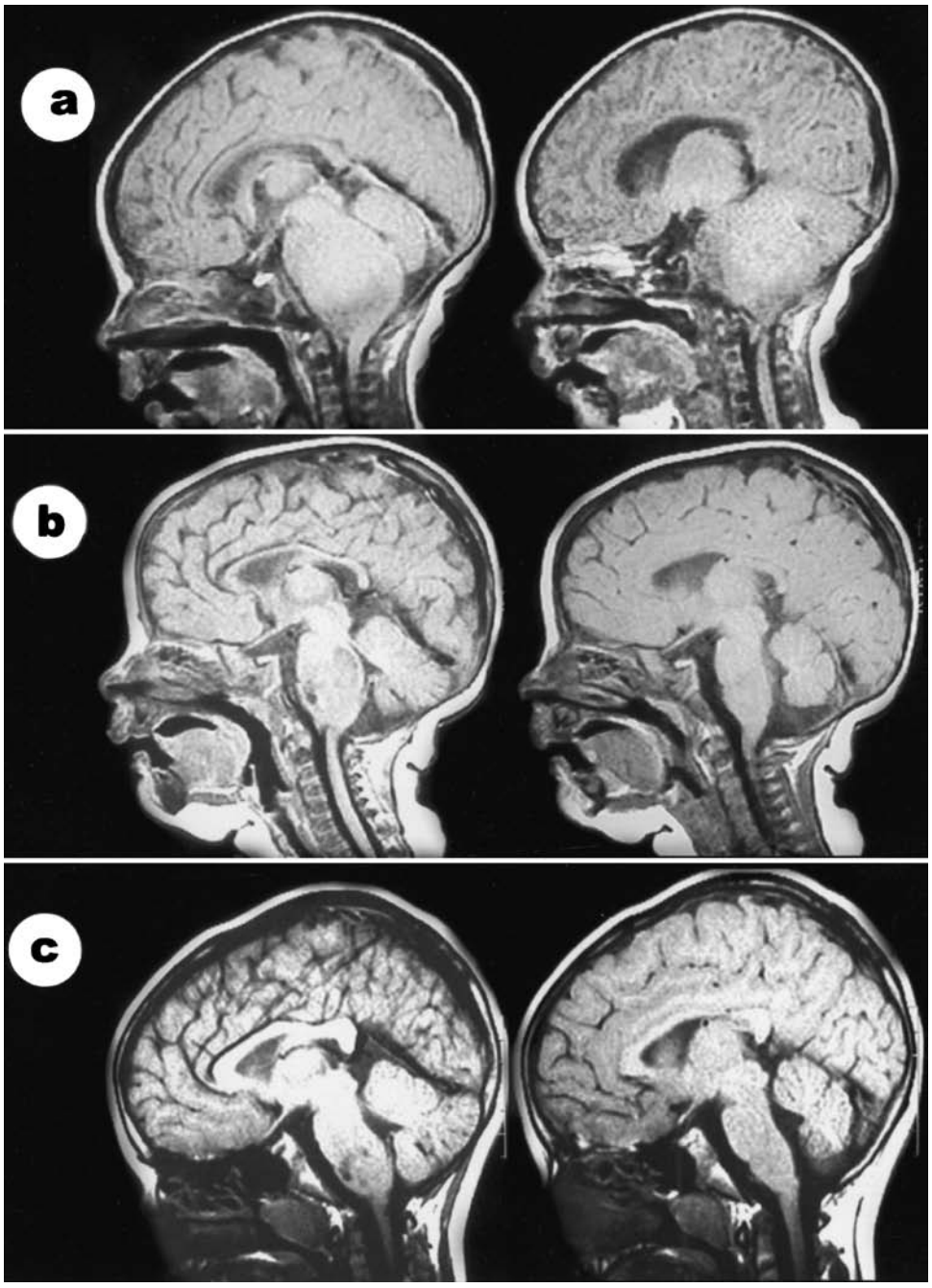

FIG. 4. Case 2. Midsagittal *(left)* and right parasagittal *(right)* serial T_1-weighted MR images. a: Images obtained when the patient was 7 days old, demonstrating a large expansive mass centered within the pons and extending down to the medulla oblongata which appears infiltrative in character and heterogeneous in signal intensity. Note the effacement of the fourth ventricle. b: Image obtained at 3 months of age, revealing regression of the expansive brainstem mass. c: Image obtained at 9 years of age demonstrating a more normal contour of the brainstem with a small area of signal abnormality in the right side of the upper medulla and lower pons with extension into the right middle cerebral peduncle.

been shown to prolong survival.[5] Mixed results have been reported in an attempt to correlate the pathological diagnosis with outcome.[46] Most clinicians have observed diffuse brainstem gliomas with demonstrated low-grade pathological characteristics that behave like high-grade tumors; this phenomenon is attributed to histological sampling errors or to rapid differentiation of the lesion into a more malignant tumor.[4,36] Although conventional radiotherapy has been the only modality that has consistently demonstrated temporary reduction of symptoms and prolonged survival, it has been minimally effective in stopping the progression of a diffuse infiltrating tumor or preventing the eventual death of the patient.[27] Trends toward better outcome are associated with hyperfractionated radiotherapy, but there is no

proof that this modality is more beneficial than conventional radiotherapy.[30,31] The results of chemotherapy have been discouraging as well; no study has established a role for adjuvant chemotherapy.[8] Given the contraindication of using radiation treatment in newborns, few options were available for the two patients presented in this paper.

Spontaneous Regression of Brainstem Lesions

There are several reports of spontaneous regression of brain tumors in the literature, particularly in patients with NF and low-grade tumors of the hypothalamic–chiasmatic region. Regression of diffuse brainstem lesions has rarely been reported, however, and the possibility of such regression is met with suspicion by most oncologists and neurosurgeons.

Rao, et al.,[40] reported on a 4-year-old child who presented with a 9-month history of diplopia, facial asymmetry, and unsteadiness. On examination the patient was found to suffer from sixth and seventh cranial nerve palsies, nystagmus, and pyramidal and dysmetric signs. An enhancing pontine lesion with small exophytic component was revealed on MR imaging. The patient did not undergo surgery, radiation treatment, or chemotherapy. He was followed for 4 years and demonstrated dramatic improvements during clinical examinations and on neuroimaging studies. No confirmatory pathology report was ever obtained.

Lenard, et al.,[29] reported on a 2-year-old patient in whom complete remission of a diffuse pontine lesion occurred. Tissue biopsy confirmed a low-grade fibrillary astrocytoma. With a several-month history of unmet developmental milestones, this patient presented with acute elevated intracranial pressure. Clinical examination by the neurosurgeon revealed ataxia, hypotonia, intention tremor, bilateral sixth cranial nerve palsy, vertical gaze palsy, and upbeat nystagmus. An expansive pontine-based, nonenhancing lesion with associated obstructive hydrocephalus was demonstrated on MR images. A ventriculoperitoneal shunt was placed and a biopsy was performed at that time. The patient underwent no surgical debulking, radiation treatment, or chemotherapy. Near-complete resolution, which was confirmed clinically and by neuroimaging, occurred during the next 4 years.

Schmandt, et al.,[44] reviewed 22 patients in whom regression of astrocytomas was demonstrated. In this review, 20 of the lesions were in the hypothalamic–chiasmatic region and two were in the brainstem with a pontine epicenter (the cases reported by Rao[40] and Lenard[29] and their colleagues). Patients ranged in age from 5 months to 8 years at the time of presentation. In 12 of the patients evidence of NF1 was apparent. These authors discuss the subset of patients known to harbor low-grade astrocytomas of the hypothalamic–chiasmatic region that are associated with regression and good outcome, particularly among patients with NF1. The behavior of these tumors, which have been reported to remain dormant for years and even demonstrate regression on neuroimaging,[32] is not well understood.

Differential Diagnosis

Because the presumptive diagnosis of glioma is uncertain in our two patients, a discussion of the differential diagnosis must be undertaken. All categories of disease can affect the brainstem. Any pathological entity that produces significant edema can produce the type of initial MR imaging findings observed in the cases of our two patients. Clinical information and MR imaging studies can, however, differentiate most categories. Lesions such as tuberculomas, cysticercosis, pyogenic abscesses, cavernous angiomas,[33] demyelination, and even infarctions have all been reported to mimic brainstem gliomas.[50] Most of these entities are well demarcated, less common in children, and associated with patient histories that differentiate them from brainstem gliomas.[5] Maple syrup urine disease can produce reversible brainstem swelling during periods of decompensation, although there is usually an associated severe metabolic acidosis and the characteristic maple syrup urine odor.[26,50] Rhombencephalitis can also mimic brainstem glioma but is usually associated with fevers.[7,45] The primary differential diagnosis for rhombencephalitis includes viral and bacterial infections, particularly herpes simplex, varicella, cytomegalovirus, adenovirus, *Mycoplasma pneumoniae*, and *Listeria* monocytogenes.[49] Usually some meningeal or supratentorial component is also present.[7] The two patients in the present case did not suffer from fevers or any systemic signs of infection.

The CT-guided biopsy has also been used to help differentiate brainstem lesions. Complication rates can be significant and the likelihood of obtaining nondiagnostic tissue can also be a problem. One group of authors estimates the complication rate at 6%.[13] Other authors report that diagnostic tissue can be obtained in approximately 96% of cases.[5] Franzini, et al.,[20] have reported that 20 of 21 diffuse lesions obtained at biopsy turned out to be gliomas and the remaining one was a primitive neuroectodermal tumor. Rajsheklar and Chandy,[39] found that six of 52 children with diffuse brainstem lesions suffered from benign entities and the remaining 46 from gliomas. The pathology reports of the benign lesions detected three tuberculomas, one epidermoid lesion, one abscess, and one case of encephalitis. An MR imaging study was performed in only 16 of the 52 cases. Chico-Ponce de Leon, et al.,[13] recently reported on 50 pediatric patients who underwent CT-guided biopsy when MR imaging was not available. The diagnoses included 30 low-grade astrocytomas, 13 high-grade astrocytomas, two primitive neuroectodermal tumors, two rhabdoid lesions, one ependymoma, and two nonspecific entities. It can be inferred that an MR imaging study may have been used to predict the benign diseases in the two previous reports. In fact, several senior authors indicated that they had yet to witness the diagnosis of a benign lesion in a child in whom MR imaging demonstrated typical diffuse brainstem enlargement.[5]

A common link between the two patients in the present report is that in addition to the natural history of their diseases, both suffered from congenital lesions. Our review of the literature did not locate any congenital diffuse brainstem gliomas with a good outcome. A large review of 200 patients younger than 3 years of age with brain tumors found only four patients with brainstem gliomas—all of whom died of their disease quickly.[14] Zimmerman[50] has reported four cases of brainstem hamartomas in which the patients presented at the time of birth. Two patients suffered from cranial nerve conditions, one from hydrocephalus, and the other from microophthalmus. Long-

term follow-up examinations conducted until the patients were 12 years old demonstrated no neurological sequela or progression. The description of the initial MR imaging findings is clearly different from those of the two patients in the cases presented here, although the most recent MR images look very similar.

The differential diagnosis in these two children remains substantial. The patients' histories and MR imaging findings appear to be contradictory when compared with the known biological behavior of diffuse brainstem tumors. Certain alternative diagnoses, such as a glioma with spontaneous regression, rhombencephalitis without fevers, or a hamartoma with atypical presentation, must be considered. The broad differential diagnosis must include an infectious, metabolic, or immunological entity; nevertheless the neurological findings at birth and clinical improvements of these patients are atypical. Perhaps a new subcategory of diffuse brainstem lesions in the neonatal period should be created.

Conclusions

Because no histological diagnosis was made in these two cases no definitive conclusions can be drawn. One might infer from an analysis of the findings in these cases that another subcategory of brainstem lesions with a good prognosis, particularly in the neonate, should be considered. The subgroups with good prognoses have thus far included focal lesions; the proposed new subgroup would consist of diffuse pontine-based lesions with good prognoses and may be observed only in the neonate. The findings in the two cases presented here indicate that an observation period prior to treatment should be recommended. Long-term survivors of such lesions suffer sequelae from conventional and hyperfractionated radiotherapy;[21] therefore, it might be advisable that patients receive radiation treatment only after the progression of disease has been confirmed on MR imaging studies. Last, we believe these cases should influence parental counseling as it has at our institution. Full resuscitation and aggressive supportive care should be undertaken until disease progression is confirmed by MR imaging, particularly in cases involving neonates. Some hope can be offered to families, but it must be stressed that the prognosis for the vast majority of these patients is dismal.

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Address reprint requests to: Willard Darrell Thompson Jr., M.D., 2808 McKinney Avenue, Apt. 443, Dallas, Texas 75204. email: willarddthompson@earthlink.net.