

Juvenile pilocytic astrocytoma of the brainstem in children

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Object. In reports involving the operative treatment of brainstem tumors, multiple histological types are often grouped together. To determine prognosis after resection, histology-specific data may be helpful.

Methods. Twenty-eight patients with juvenile pilocytic astrocytoma (JPA) of the brainstem (six in the midbrain, four in the pons, and 18 in the medulla) were identified from the medical records. Initial treatment was resection in 25 and biopsy sampling in three. Postoperative imaging revealed gross-total resection (GTR) or resection with linear enhancement (RLE) in 12 of 25 patients and solid residual tumor in the other 13.

In 10 of the 13 patients harboring solid residual tumor, observation was undertaken; the residual lesion disappeared in one, was stable in four, and progressed in five. Of the 12 patients with complete excision or RLE only, seven underwent no further treatment, with tumor progression occurring in one. All patients were alive at last follow-up examination (range 0.3–20.4 years, mean 6 years). New neurological deficits commonly appeared immediately after resection but often resolved. In six of the 28 patients, the new postoperative deficit was still present at last follow-up visit. The 5- and 10-year progression-free survival was 74 and 62%, respectively, after GTR or RLE and 19 and 19%, respectively, when solid residual tumor was present.

Conclusions. Long-term survival after resection of JPAs of the brainstem has been observed and appears to be related to the extent of initial excision.

KEY WORDS • astrocytoma • brainstem • pediatric

Clinical Material and Methods

Patients were identified by a search of our operative database, tumor registry, and hospital discharge ICD-9 codes. The medical records of all patients with brainstem tumors treated after 1980 were reviewed. Patients were included if their tumor was centered in the brainstem and was consistent with features of JPA on pathological examination. Patients were excluded if their tumor was reported to be low-grade astrocytoma, fibrillary astrocytoma, anaplastic astrocytoma, glioblastoma, or nonastrocytoma. In addition, cases involving tectal plate gliomas, diffuse pontine gliomas, and cerebellar tumors were excluded. All cases involving pilocytic astrocytomas were reviewed and reported by one neuropathologist who used current World Health Organization classification.⁸ The medical records and imaging studies were reviewed. The extent of resection was assessed by examining postoperative images (Fig. 1). Resection was categorized as GTR if there was no visible enhancement, linear enhancement in the resection cavity, or residual solid tumor. Disease progression was defined as the appearance of recurrent tumor after GTR or growth of residual tumor after partial resection on

P RIMARY tumors of the brainstem were once considered incurable lesions. With the description of dorsally exophytic tumors⁶ and the classification of subtypes of brainstem gliomas,^{4,13} surgical approaches to these difficult lesions were introduced. Investigators at various centers have described their experience and complications with these procedures.^{3–7,10,13}

As experience in the surgical treatment of brainstem tumors has increased, a number of pathological diagnoses have been discovered, including pilocytic astrocytoma, fibrillary astrocytoma, ganglioglioma, primitive neuroectodermal tumor, ependymoma, and gangliocytoma.² When the results of treatment are described, the different histological cell types are often grouped together, making diagnosis-specific counseling and treatment difficult. For this reason, it was our intention to describe the treatment and results at Primary Children's Medical Center for the most commonly encountered histological tumor type: JPA.

Abbreviations used in this paper: GTR = gross-total resection; JPA = juvenile pilocytic astrocytoma; PFS = progression-free survival; RLE = resection with linear enhancement.

follow-up imaging. Status was considered to be stable if the tumor was demonstrated to be unchanged or smaller on follow-up images.

In patients who underwent open resection, the approach was individualized, but certain principles were followed. The shortest route through tissue was chosen. If there was an accessible tumor cyst, this was used as a corridor to approach the tumor (Fig. 2 *left*). The brainstem was entered through regions of distorted anatomy where the tumor was bulging toward the surface and often causing discoloration. When approaching intrinsic tumors in the medulla and/or cervical cord, the route was through the midline, but the superior limit of the midline incision in the medulla was kept below the obex to reduce the risk to the lower-region cranial nerves.³ Exophytic tumors (Fig. 2 *right*) were approached so that the exophytic portion was encountered first. Tumor resection was performed by entering the center of the lesion and gradually working toward the margins by using an ultrasonic aspirator. Resection was terminated when the tissue color and texture began to look normal. We did not attempt dissection outside the tumor at the tumor–brainstem interface.

Neurophysiological monitoring was used selectively, including brainstem auditory evoked responses, somatosensory evoked potentials, electromyography of the seventh and 11th cranial nerves, and, on one occasion, motor evoked potentials. Adjuvant radio- and/or chemotherapy were performed commonly in patients treated earlier in this series. As our experience evolved, these modalities were usually reserved for patients with progressive disease.

Results

Patient Population

Between 1981 and 2002, a diagnosis of brainstem tumor was established in 80 patients. In 52 cases the entry criteria for the study were not met (29 diffuse pontine gliomas, six tectal plate gliomas, six cerebellar astrocytomas, three Grade II astrocytomas, one Grade III astrocytoma, two acoustic neuromas, two gangliogliomas, and one oligodendroglioma). In two cases follow-up information was inadequate. The remaining 28 patients with JPA of the brainstem formed the basis of this study. There were 12 boys and 16 girls with a median age at presentation of 7.8 years (range 1.7–17.5 years).

Six tumors were located in the midbrain. The most common midbrain location, seen in four patients, was the cerebral peduncle (Fig. 3 *left*). The other two midbrain lesions were located near the aqueduct. There were four lesions in the pons, two in the cerebellar peduncle, and two beneath the floor of the fourth ventricle (Fig. 3 *right*). Eighteen of the tumors were in the medulla, 12 of which were intrinsic or focal tumors within the medulla. Three were dorsally exophytic with growth into the fourth ventricle, and three were cervicomedullary lesions.

The most common clinical presentation was a focal neurological deficit of cranial nerves and/or motor/sensory long tracts, which occurred in 24 patients. The nature of the deficit corresponded to the anatomical location of the tumor. Six of the 24 patients with a focal deficit also had hydrocephalus and one of them suffered seizures. Two

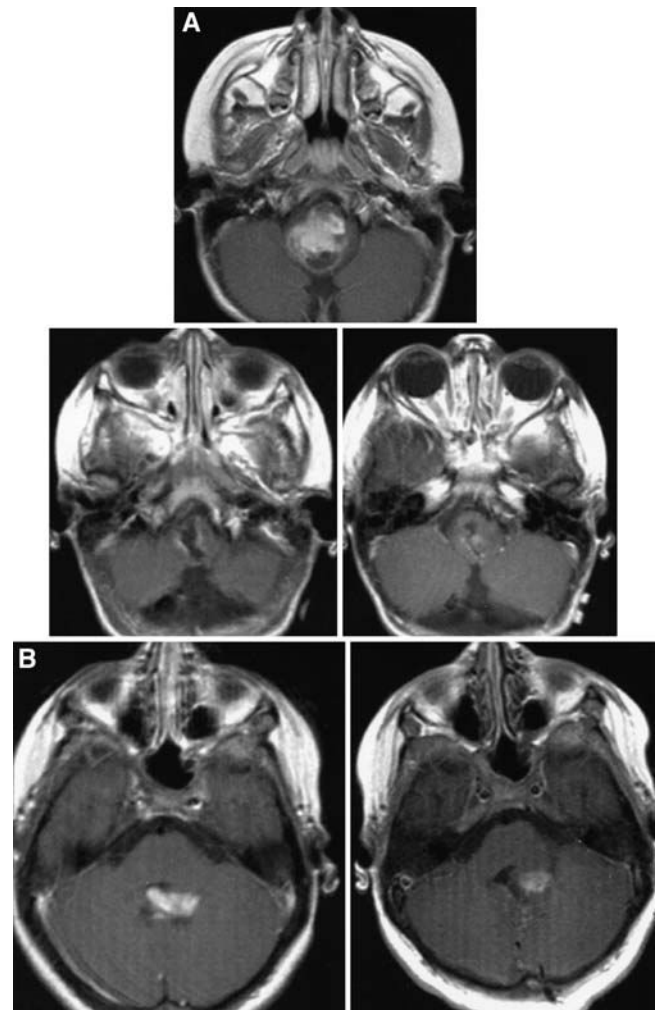


FIG. 1. A: Examples of resection classified as LE in the resection cavity. B: Examples of residual solid tumor.

patients presented with hydrocephalus alone and two others with headache alone.

The treatment modalities are outlined in Fig. 4. The initial treatment in three patients involved acquiring a biopsy sample. One patient harboring a midbrain lesion ventral to the aqueduct underwent an open procedure through the fourth ventricle. Adjuvant radiotherapy was performed and the patient remained stable 6 months after diagnosis. In one case a small lesion in the medulla near the eighth cranial nerve nucleus was sampled. No adjuvant radio- or chemotherapy was undertaken, and the lesion has remained stable for 3.3 years. In the third patient, a cerebral peduncle lesion was sampled stereotactically. A shunt was placed to treat hydrocephalus, and adjuvant radiotherapy was conducted. The tumor progressed 26 months later, at which time the patient underwent resection. Postoperative imaging revealed linear enhancement in the tumor bed, and there was no evidence of progression 9.5 years later.

Twenty-five of the 28 patients underwent resection as initial treatment. In 12 postoperative imaging demonstrated GTR or RLE in the tumor bed only. Seven of 12 patients with GTR or RLE received no further treatment, and in one

Juvenile pilocytic astrocytoma of the brainstem

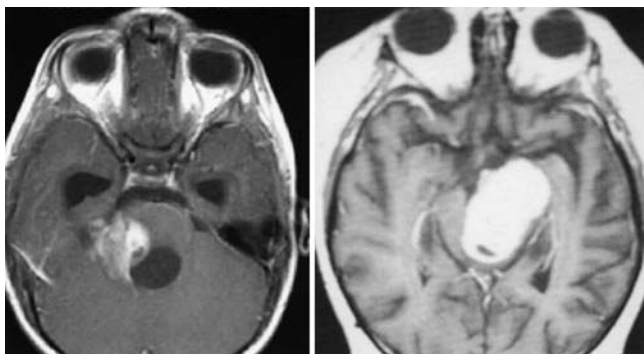


FIG. 2. *Left:* A JPA of right middle cerebral peduncle. Cystic component fills the fourth ventricle. The solid tumor was approached through the cyst. *Right:* Exophytic JPA of the left cerebral peduncle is approached via a transsylvian or subtemporal route to enter through exophytic part of tumor.

local tumor progression occurred 1.1 years later. In none of the other six was there evidence of JPA progression at follow-up examination 0.8, 3.3, 6, 6.6, 10, and 15.7 years later, respectively. In one of the patients in whom the JPA did not progress, a primitive neuroectodermal tumor developed in the pineal region after 6.6 years. Neither radiotherapy nor any other intervention had been performed. Four of 12 patients with GTR or RLE received radiotherapy (median dose 4750 cGy); progressive tumor growth was observed in one patient at 0.63 years and in the other three the tumor was stable at 9, 16, and 20.4 years, respectively. One patient with GTR or RLE was treated with adjuvant chemotherapy (and no radiotherapy) but local tumor progression was documented at 0.42 years.

In 13 of 25 patients who underwent open resection, residual solid tumor was revealed on postoperative imaging; in 10 of the 13 no adjuvant therapy was performed and in five of the 10 the tumor progressed, in four it remained stable, and in one progressive shrinkage of the residual tumor occurred without adjuvant therapy (Fig. 5). Two of 13 with residual solid tumor underwent radiotherapy (median dose 5600 cGy), and in both further tumor growth was documented 0.32 and 1.24 years postoperatively. One patient had undergone a biopsy procedure, radiation treatment, and chemotherapy 10 years prior but received no further adjuvant therapy after our resection; the tumor size remained stable during the short follow-up period (0.32 years).

All patients were alive at the last follow-up examination (mean 5.8 years, range 0.3–20.4 years). In the entire study population, PFS was 51% at 5 years and 44% at 10 years. The rate was higher (74% at 5 years, 62% at 10 years) when neuroimaging after the initial surgery revealed GTR or RLE rather than residual solid tumor (19% at 5 and 10 years) (Fig. 6).

In 11 of the 28 patients recurrence or progression of their JPA was demonstrated. At the time of recurrence, the management was radiotherapy alone in one patient and repeated resection in 10 patients. Neuroimaging after the repeated surgery revealed GTR or RLE in seven of 10 patients, with stable tumor in six (at 1, 5, and 11 months, and 4.7, 9.5, and 9.7 years of follow up) and progressive tumor growth in one (subsequently treated with chemotherapy). The other three

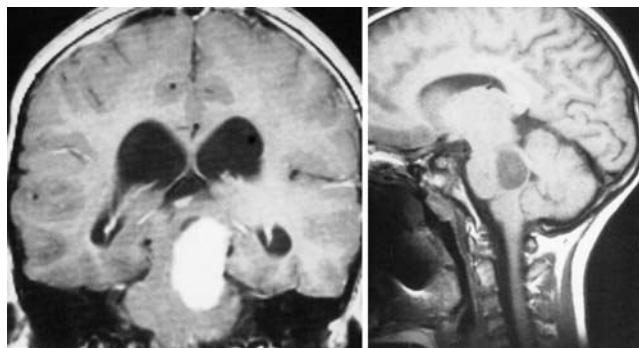


FIG. 3. *Left:* Axial view of a JPA of the left cerebral peduncle. *Right:* Sagittal view of a cystic JPA of the pons beneath the floor of the fourth ventricle.

patients harbored residual solid tumor after repeated surgery with two undergoing adjuvant radiotherapy.

Surgery-related neurological complications were present in the immediate postoperative period in 20 of 28 patients. These complications resolved often; at last follow-up evaluation persistent deficits remained in six patients (Table 1). These were observed in two of the 12 patients with GTR or RLE, three of 13 patients with residual solid tumor, and one of three patients in whom a biopsy sample was obtained. Deficits were persistent in two of six patients in whom surgery was performed in the midbrain, in one of four patients in whom it was performed in the pons, and in three of 18 patients in whom it was conducted in the medulla (one of whom required a permanent tracheostomy). In the three cases involving dorsally exophytic tumors, the patients were free of complications at last follow up.

Discussion

Excluding diffuse pontine glioma, surgery has been advocated for brainstem tumors. The multiple histological types reported in many series prompted our review, specifically of JPAs. In our experience with 28 JPAs of the brainstem, excision (GTR or RLE) was associated with the best chance of PFS at initial surgery and at the time of recurrence. The role of adjuvant radio- and/or chemotherapy was difficult to assess in this retrospective review, but neither appeared to have a significant impact on disease control.

Our results are similar to those reported by Pierre-Kahn, et al.,¹⁰ who included benign and malignant lesions; however, within the classification “benign lesions” they found a similar association between extent of resection and survival. Farmer and associates⁵ described 22 focal tumors of the brainstem, including seven tectal lesions. The pathological spectrum was mixed and included ganglioglioma, JPA, fibrillary astrocytoma, and the tectal lesions, of which tissue samples were not obtained for biopsy examination. They compared two approaches of therapy. In the first radical surgery was performed in nine patients, in four of whom the lesion progressed and was treated with radiotherapy. In this group no new neurological symptoms resulted from the treatment protocol. Seven other patients initially underwent radiotherapy, with four eventually undergoing radical surgery at the time of tumor progression. The neurological morbidity rate was considerably higher in

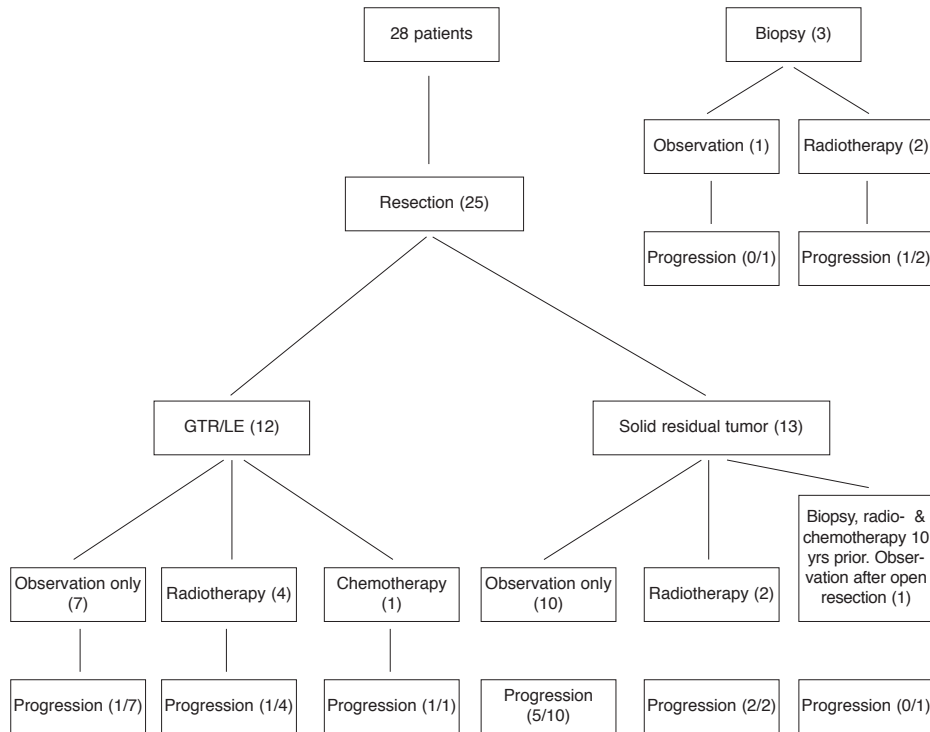


FIG. 4. Treatment pathway for this study population.

this group, with deficits occurring in five of seven patients. The initial radiotherapy may have made the surgery more difficult and contributed to the difference in morbidity rates between these two approaches.

The association between brainstem tumor location and pathological entity has been described previously. Khatib, et al.,⁷ reported that of 12 dorsally exophytic brainstem gliomas, 11 were JPAs. In this subgroup of patients the prognosis was very good; the authors attributed this to the histological type and the location, which allowed good resection. Our experience was similar—the dorsally exophytic JPAs were associated with the lowest resection-related morbidity rate.

The neuroimaging-based distinction between GTR and RLE did not appear to be of prognostic significance.

There were five patients with residual linear enhancement, none of whom received adjuvant therapy. Tumor progression occurred in one of these patients, who also had neurofibromatosis, at 1.1 years after surgery. In the other four there were no signs of progression during follow-up periods of 3.7, 4.2, 5.9, and 17.5 years, respectively.

We observed tumor shrinkage after partial resection in a patient in whom no other therapy was performed. This is compatible with other reports. Schmandt and colleagues¹¹ described a patient whose residual tumor regressed, grew, and then regressed a second time, all without intervention. They found 22 pediatric cases in the literature in which low-grade tumors spontaneously regressed. Some of the lesions were not confirmed histologically, but their review included a JPA of the temporal/hypothalamic region and

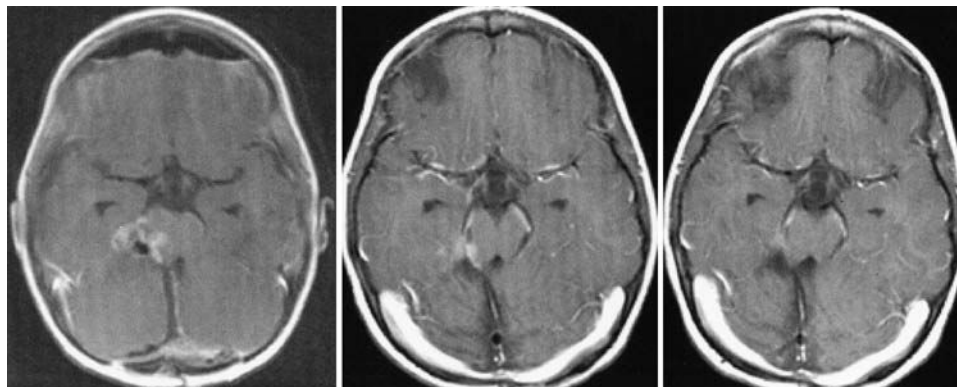


FIG. 5. Images demonstrating gradual regression of residual solid tumor without adjuvant radio- or chemotherapy.

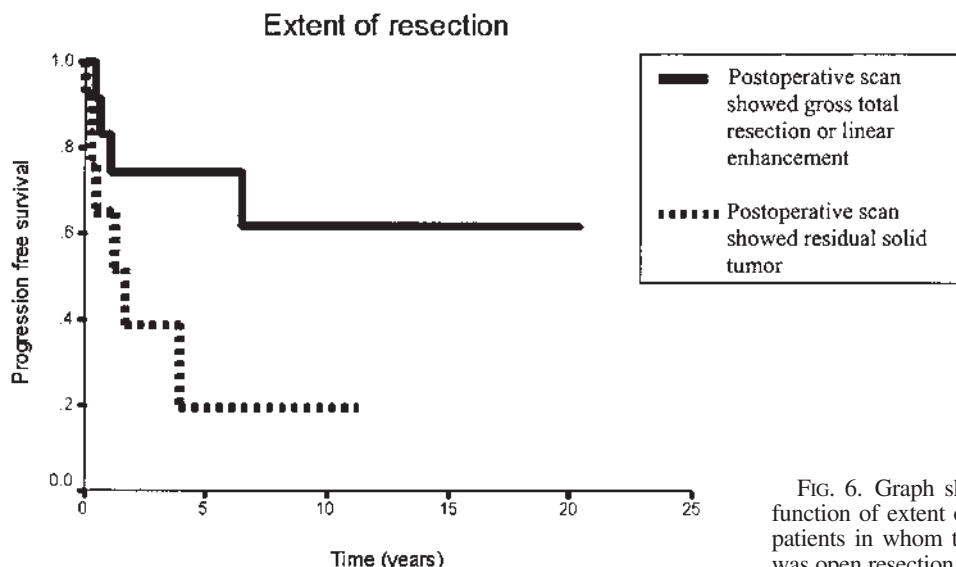


FIG. 6. Graph showing PFS as a function of extent of resection in 25 patients in whom the initial therapy was open resection.

four JPAs of the hypothalamic/chiasmatic area. There were two cases in which pontine lesions regressed, one in which a biopsy sample was not obtained and the other was described as a Grade II fibrillary astrocytoma. Parsa, et al.,⁹ identified 12 patients with optic pathway gliomas that regressed spontaneously without therapy or many years after therapy.

The role of surgery at the time of JPA recurrence has been reviewed by Bowers and coworkers.¹ Their report included four brainstem lesions; in one case a GTR was accomplished, but the tumor progressed 1.1 years later. In the other three cases involving the brainstem, there was significant residual tumor and disease progression at 0.3, 0.3 and 2.5 years after surgery, respectively. Our experience with repeated operation was favorable and was the initial approach in 10 of 11 recurrences. In our population, GTR or RLE was achieved in seven patients, in six of whom the tumor has remained stable, without other therapy. The follow-up period was less than 1 year in three of these patients, but in the other three cases tumor size was stable at 4.7, 9.5, and 9.7 years, respectively.

Patients were not treated with stereotactic radiosurgery, which has been reported in five pilocytic astrocytomas of

the brainstem that had progressed after surgery (three cases), radiotherapy (one case), or biopsy sampling (one case).¹² A significant decrease in tumor size was revealed on follow-up imaging in four patients; in one case the tumor remains stable. None of the patients suffered neurological dysfunction related to radiosurgery. The follow-up period for these patients was short and the role of focused-beam irradiation is not yet clear.

At present, our initial approach to residual disease is observation. Postoperative imaging is performed at 3 and 6 months after surgery and then annually (in cases with or without residual disease). Should the residual tumor progress, we have favored repeated operation. Stereotactic radiosurgery may be an attractive option in the future if there is evidence of its safety and efficacy.

Conclusions

At our center, JPA was the most common brainstem tumor histology among the surgically treated cases, with a preferential location in the medulla. Resection resulted in long-term PFS but was associated with neurological morbidity. The dysfunction apparent in the immediate postoperative phase improved but persisted in a significant portion (six [21%] of 28) of patients. The PFS rate was high for patients in whom a GTR or RLE was achieved. The use of adjuvant radiotherapy was not associated with an obviously longer PFS, regardless of the extent of the initial resection. At the time of recurrence, repeated resection alone resulted in further PFS.

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TABLE 1

Summary of neurological status after surgery for JPA of the brainstem

Postop Deficit	No. of Cases		
	GTR or RLE	Solid Residual Lesion	Biopsy Sampling
immediate	8 of 12	10 of 13	2 of 3
last follow up	2 of 12*	3 of 13†	1 of 3‡

* Dysfunction involved 1) a seventh cranial nerve palsy requiring reanimation (medullary tumor); and 2) ambulatory paraparesis treated with baclofen pump.

† Dysfunction involved 1) a seventh cranial nerve palsy (pontine tumor); 2) mild hemiparesis (midbrain peduncle tumor) (can write and walk); and 3) nonambulatory quadriplegia (medullary tumor) in a patient presenting with spastic triplegia.

‡ Dysfunction involved a third cranial nerve palsy (midbrain tumor).

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