Treatment options and prognosis for multicentric juvenile pilocytic astrocytoma

ADAM N. MAMELAK, M.D., MICHAEL D. PRADOS, M.D., WILLIAM G. OBANA, M.D., PHILIP H. COGEN, M.D., PH.D., AND MICHAEL S. B. EDWARDS, M.D.

Department of Neurological Surgery, Division of Pediatric Neurosurgery, and the Neuro-Oncology Service of the Brain Tumor Research Center, and Department of Pediatrics, School of Medicine, University of California, San Francisco, California

Little is known about the risk of developing multicentric disease in patients with juvenile pilocytic astrocytoma (JPA), and even less about its prognosis. Only five cases have been reported. Between 1986 and 1992, the authors treated 90 patients with either primary or recurrent JPA, 11 of whom developed multicentric spread. Ten patients had primary tumors in the hypothalamic region, eight were under 4 years of age at initial diagnosis, all had initially undergone a subtotal resection or biopsy, and 10 received postoperative multimodal chemotherapy or irradiation for residual disease. Multicentric spread was discovered immediately to 108 months after initial diagnosis; nine patients were asymptomatic at the time. Most patients received chemotherapy for the multicentric disease, which was found throughout the craniocerebral axis. During 21 to 148 months of follow-up monitoring, seven patients had stabilization or regression of multicentric disease and four died. Patients with hypothalamic region tumors were 23 times more likely to develop multicentric spread than were those with primary tumors located elsewhere ($p < 0.001$). Based on this review, it is concluded that multicentric spread of JPA occurs more frequently than was previously recognized. In patients with subtotally resected JPA and several years of follow-up review via magnetic resonance imaging, the incidence of recurrence in a site different from the original was 12%. Patients with subtotally resected JPA in the hypothalamic region should be considered to be at high risk for developing multicentric spread. Chemotherapy appears useful in stabilizing multicentric disease. Earlier detection and intervention may result in longer disease-free survival in patients with multicentric spread of JPA.

**Key Words** • juvenile pilocytic astrocytoma • multicentric metastasis • chemotherapy

J U V E N I L E pilocytic astrocytoma (JPA) is an unusually benign variant of astrocytoma that rarely spreads along the craniospinal axis and has the best prognosis for cure and long-term survival.\textsuperscript{9,10,13,21,25} Ten- and 20-year survival rates between 90% and 100% have been reported in patients who underwent gross total resection.\textsuperscript{10,11,25} Even subtotal resection followed by adjuvant radiation therapy has resulted in 20-year survival rates ranging from 70% to 80%.\textsuperscript{17,25}

Despite these encouraging results, JPA often recurs and occasionally exhibits atypically aggressive behavior. Three distinct patterns of recurrence have been reported. 1) Local recurrence at the primary site is by far the most common and is often asymptomatic when discovered.\textsuperscript{7} 2) Malignant transformation of JPA to a higher grade of astrocytoma has been described, typically after disease-free intervals of 10 to 30 years.\textsuperscript{13,15,24,26} 3) Multicentric or metastatic spread of JPA has been reported only five times,\textsuperscript{2,15,17,19} suggesting that dissemination of JPA along the craniospinal axis is exceedingly rare. No authors discuss risk factors for developing multicentric disease, or the treatment and prognosis for patients with this type of recurrence.

Since the use of magnetic resonance (MR) imaging has become routine in surveying the craniospinal axis of patients with brain tumors, we have noted a sharp increase in the number of cases of multicentric JPA treated at our institution. This prompted us to characterize patients who developed multicentric tumor spread and to evaluate treatment options and their efficacy.

**Clinical Material and Methods**

The database of all patients treated by the Neurosurgery Department or the Neuro-Oncology Service at the University of California, San Francisco (UCSF), between January, 1986, and December, 1992, was searched to identify all patients with a primary diag-
Multicentric juvenile pilocytic astrocytomas

TABLE 1

Demographic characteristics and clinical course of 11 patients with multicentric spread of juvenile pilocytic astrocytoma

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex, Age at Initial Diagnosis</th>
<th>Location of Primary Tumor</th>
<th>Extent of Surgical Removal</th>
<th>Postoperative Therapy*</th>
<th>Location of Multicentric Spread</th>
<th>Therapy for Multicentric Spread*</th>
<th>Follow-Up Period (mos)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F, 4 yrs</td>
<td>hypothalamic</td>
<td>subtotal</td>
<td>none</td>
<td>spinal cord (T-S)</td>
<td>48 Gy RT, VCN</td>
<td>37</td>
<td>stable</td>
</tr>
<tr>
<td>2</td>
<td>M, 34 yrs</td>
<td>hypothalamic</td>
<td>biopsies</td>
<td>multiagent chemotherapy</td>
<td>subependymal</td>
<td>PCB, CCNU, VCN</td>
<td>26</td>
<td>stable</td>
</tr>
<tr>
<td>3</td>
<td>M, 43 yrs</td>
<td>hypothalamic</td>
<td>biopsy</td>
<td>54 Gy RT, hyperfractionation</td>
<td>temporal lobe, subependymal</td>
<td>6TG, BCNU</td>
<td>21</td>
<td>regression</td>
</tr>
<tr>
<td>4</td>
<td>F, 3 yrs</td>
<td>hypothalamic</td>
<td>subtotal</td>
<td>multiagent chemotherapy</td>
<td>leptomeningeal</td>
<td>60 Gy craniospinal RT</td>
<td>34</td>
<td>stable</td>
</tr>
<tr>
<td>5</td>
<td>M, 9 mos</td>
<td>hypothalamic</td>
<td>subtotal</td>
<td>carmustin</td>
<td>rt occipital lobe, subependymal</td>
<td>ifosfamide</td>
<td>20</td>
<td>stable</td>
</tr>
<tr>
<td>6</td>
<td>M, 6 mos</td>
<td>hypothalamic</td>
<td>biopsy</td>
<td>multiagent chemotherapy</td>
<td>brain stem, cerebellum, spinal cord</td>
<td>VP-16</td>
<td>65</td>
<td>death</td>
</tr>
<tr>
<td>7</td>
<td>M, 16 mos</td>
<td>hypothalamic</td>
<td>subtotal</td>
<td>57 Gy RT</td>
<td>cauda equina, leptomeningeal cerebellum, brain stem</td>
<td>6TG, BCNU</td>
<td>148</td>
<td>death†</td>
</tr>
<tr>
<td>8</td>
<td>M, 5 mos</td>
<td>hypothalamic</td>
<td>biopsy</td>
<td>multiagent chemotherapy</td>
<td>multiagent chemotherapy</td>
<td>23</td>
<td>32</td>
<td>regression</td>
</tr>
<tr>
<td>9</td>
<td>M, 5 mos</td>
<td>hypothalamic</td>
<td>subtotal</td>
<td>multiagent chemotherapy</td>
<td>multiagent chemotherapy</td>
<td>subependymal</td>
<td>32</td>
<td>death</td>
</tr>
<tr>
<td>10</td>
<td>M, 11 yrs</td>
<td>cerebellum</td>
<td>near-gross total biopsy</td>
<td>54 Gy RT</td>
<td>spinal cord (T10–11)</td>
<td>leptomeningeal</td>
<td>46</td>
<td>stable</td>
</tr>
<tr>
<td>11</td>
<td>M, 11 mos</td>
<td>hypothalamic</td>
<td>biopsy</td>
<td>VCN, cyclophosphamide, actinomycin</td>
<td></td>
<td>cyclophosphamide</td>
<td>41</td>
<td>death</td>
</tr>
</tbody>
</table>

* RT = radiation therapy; VCN = vincristine; PCB = procarbazine; CCNU = carmustine; 6TG = 6-thioguanine; BCNU = carmustine; VP-16 = etoposide. Multiagent chemotherapy consisted of therapy with 6TG, CCNU, dibromodulcitol, PCB, and VCN.

† Death caused by pulmonary interstitial fibrosis presumably from BCNU toxicity. Multicentric disease was clinically and radiologically stable at the time of death.

Results

Demographic and Clinical Characteristics

Between January, 1986, and December, 1992, 90 patients with a primary diagnosis of JPA were identified; 33 had a primary tumor located in or around the hypothalamic region (including the third ventricle and optic chiasm) and 57 had tumors in other locations, predominantly the cerebellum.

Eleven patients (12%) developed multicentric disease. Seven of these patients, all of whom were children, were initially treated by the Neurosurgery Service and four by outside neurosurgeons. Once a recurrence or multicentric spread developed, all patients were evaluated and treated by the Neuro-Oncology Service. The demographic characteristics of these patients at initial diagnosis and a summary of their clinical course are presented in Table 1. The median age at initial diagnosis of the primary tumor was 16 months (range 5 months to 43 years); eight were under 5 years of age. There were nine males and two females. All patients with multicentric tumors underwent follow-up review with MR imaging throughout the study period.

Multicentric spread developed in 10 patients whose primary tumor was located in the hypothalamic region (Fig. 1); two had multicentric disease, discovered at initial diagnosis. Only one patient with a nonhypothalamic tumor developed multicentric spread; that tumor was located in the cerebellar vermis. All primary tumors were large, measuring 4 to 9 cm in the widest...
dimension on MR images, and were predominantly solid. One patient (Case 3) with a hypothalamic region tumor (Fig. 1) had suffered panhypopituitarism since the age of 16 years, which was controlled with hormone replacement therapy. A large suprasellar mass was found in this patient at age 43 years, when he presented with bitemporal hemianopsia and headaches. The MR image revealed an expanded sella turcica, suggesting that his primary JPA had been slowly growing for as long as 27 years.

Surgery for the Primary Tumor

Five of the 11 patients who developed multicentric spread had undergone a subtotal resection of the primary tumor, three a stereotactic biopsy, one a transsphenoidal biopsy, and one a stereotactic biopsy followed by a cranietomy for subtotal resection. The patient with a cerebellar tumor had a near-gross total resection, but there was still concern about microscopic residual disease. The histological diagnosis of all 11 tumors was JPA. No unique histological features, such as rare or absent mitosis, fibrillary and microcystic regions, Rosenthal fibers, or leptomeningeal involvement, helped differentiate these tumors from those in patients who did not develop multicentric spread.

Primary Postoperative Treatment

Chemotherapy was given to six of the eight children aged 5 years or less and to one adult with diffuse subependymal spread (Case 2). The most commonly used protocol consisted of vincristine, CCNU (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea), dibromodulcitol, 6-thioguanine, and procarbazine. Three patients (Cases 3, 7, and 10) received focal radiation therapy at a total dose of 54 to 57 Gy; one of these patients (Case 7) was a 16-month-old boy who was initially treated at another institution. One child (Case 1) who was initially treated elsewhere had not received initial adjuvant therapy.

Tumor Progression and Recurrence

Tumor progression took place within 2 years of initial diagnosis in eight of the 11 patients who developed multicentric spread. The time to first recurrence or tumor progression ranged from 4 to 108 months (median 12 months). One patient suffered diffuse subarachnoid enhancement of the basal cisterns 3 weeks after focal radiation therapy began; the irradiation field was widened to encompass the basal cisterns, and the enhanced areas subsequently resolved. One patient who presented with multicentric disease and was initially treated with chemotherapy had no tumor progression.

Multicentric Spread

The characteristics and treatment of multicentric spread in the 11 patients are summarized in Table 2. Multicentric spread developed immediately to 108 months (median 22 months) after initial diagnosis. It was discovered at initial diagnosis in two patients and developed less than 3 years after initial diagnosis in eight. Multicentric spread coincided with first tumor recurrence in four patients and developed after the first recurrence in five.

Multicentric spread was found throughout the craniospinal axis (Fig. 2); in five patients, tumor was discovered in more than one location. Nine patients had asymptomatic multicentric disease. One patient with extensive spinal metastases suffered abdominal and
Multicentric juvenile pilocytic astrocytomas

![Images of MRI scans showing multicentric spread.]

**Fig. 2.** Characteristic magnetic resonance imaging patterns of multicentric spread. Upper Pair: Metastatic nodular spread along the brain stem and cerebellum. Lower Left: Metastatic nodular spread along the spinal cord and cauda equina. Lower Right: Diffuse subependymal spread in the third ventricle and associated leptomeningeal spread in the basal cisterns.

...back pain. One patient with extensive subependymal spread had complained of a worsening memory; his tumor encased the third ventricle, causing damage to fornices.

Histopathological diagnosis confirmed the presence of multicentric disease in six patients: three by biopsy, one by cytological examination of cerebrospinal fluid (CSF), one by both biopsy and cytological examination of CSF, and one by total removal of a metastatic nodule. Histologically, multicentric disease could not be distinguished from the primary tumor. The remaining five patients did not have histological confirmation of their multicentric disease.

**Treatment for Multicentric Disease**

Chemotherapy was given to eight patients with multicentric disease. One patient underwent radiation therapy to the craniospinal axis, and one received a combination of craniospinal radiation therapy and che-

![Images of MRI scans showing treatment response.]

**Fig. 3.** Magnetic resonance images before (left) and after (right) chemotherapy in a child treated for multicentric disease throughout the brain stem and cerebellum, as well as a primary hypothalamic region mass. After six cycles of multiantigen chemotherapy, the size of the primary tumor and all areas with metastatic disease were dramatically reduced. This patient’s disease remained in regression 11 months after chemotherapy was completed.

**TABLE 3**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Multicentric Spread</th>
<th>No Multicentric Spread</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
<td>11</td>
<td>79</td>
<td>90</td>
</tr>
<tr>
<td>primary tumor location*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypothalamic</td>
<td>10</td>
<td>23</td>
<td>33</td>
</tr>
<tr>
<td>nonhypothalamic</td>
<td>1</td>
<td>56</td>
<td>57</td>
</tr>
<tr>
<td>age (yrs) at initial diagnosis†</td>
<td>9.0 ± 15.0</td>
<td>8.3 ± 7.7</td>
<td>8.3 ± 8.7</td>
</tr>
<tr>
<td>sex (M:F)</td>
<td>9:2</td>
<td>41:38</td>
<td>50:40</td>
</tr>
</tbody>
</table>

* Significantly associated with multicentric disease, p < 0.001 (chi-square test).
† Values are expressed as the mean ± standard deviation.

...mothery. Chemotherapy was administered to every patient in whom tumor progression occurred despite radiation therapy, and to children under 4 years of age. One patient underwent a repeat craniotomy to debulk an enlarged hypothalamic mass. Another patient received no further therapy once multicentric spread was documented; follow-up visits consisted of serial MR imaging only.

After a median follow-up review of 31 months (range 21 to 148 months), multicentric disease had either stabilized or regressed in seven of the 11 patients. An example of a dramatic reduction in both primary and metastatic disease is shown in Fig. 3. Four patients died; all had extensive metastasis along the craniospinal axis and were 5 years old or younger at the time of death.

**Characterizing Patients at Risk for Multicentric Spread**

Of the 90 patients treated for JPA, 11 (12%) developed multicentric spread (Table 3). Ten (30%) of the 33 patients with primary tumors in the hypothalamic...
region developed multicentric spread, whereas only one (2\%) of the 57 patients with nonhypothalamic primary tumors did (odds ratio = 23.4; p < 0.001). These results indicate that, while 12\% of all patients with JPA developed multicentric spread, those with hypothalamic tumors were much more likely to develop multicentric spread than those with tumors outside the hypothalamic region. Age at initial diagnosis and sex were not associated with the development of multicentric spread.

Discussion

Our results allow us to draw three important conclusions about the development of multicentric spread in patients with JPA. 1) Multicentric spread occurs much more often than previous estimates suggest; 12\% of our patients with JPA either had multicentric spread at initial diagnosis or developed it within 5 years. 2) For patients with JPA in the hypothalamic region, the odds of developing multicentric spread were 23 times higher than in those with nonhypothalamic tumors; 30\% of patients with hypothalamic tumors developed multicentric spread within 5 years of initial diagnosis, compared to 2\% of patients with nonhypothalamic tumors. 3) Patients with multicentric spread of JPA survive longer than those patients with multicentric spread of other types of astrocytomas.

Only five other cases of multicentric spread of JPA have been reported,\textsuperscript{2,15,17,19} one\textsuperscript{19} of which is included in our series. Two cases were discovered incidentally at autopsy\textsuperscript{17} and only two\textsuperscript{15} have been reported in the MR imaging era. In contrast, 12\% of our patients developed multicentric disease. Most of them were asymptomatic when multicentric disease was discovered, which emphasizes the value of MR imaging of the craniospinal axis in “high-risk” patients and best explains the discrepancy between the few cases of multicentric spread reported in the past and the high number in our study. Magnetic resonance imaging has been used routinely at UCSF since 1986 for surveillance of brain tumor progression, and all patients in this series had follow-up review with serial MR imaging. Gadolinium-enhanced MR images have made detection of multicentric disease much more sensitive and accurate. In addition, MR images are more likely than computerized tomography (CT) scans to detect nodular disease and leptomeningeal or ependymal spread, especially in the posterior fossa and spine. Furthermore, because MR imaging of the craniospinal axis is less risky and invasive than CT myelography, images can be obtained more frequently, thereby increasing the chance of detecting multicentric disease.

In a study by Davis and Joglekar,\textsuperscript{7} CT revealed that 12 of 31 patients with previously resected cerebellar JPA had asymptomatic local tumor recurrence. This finding suggests that the incidence of asymptomatic recurrence of JPA is higher than has been previously assumed. Both the study by Davis and Joglekar and our current study underscore the need for regular MR imaging in patients who are at high risk for recurrent, residual, or multicentric tumor progression.

A potential confounding variable in our series is patient referral patterns. The majority of patients with a totally resected JPA are not typically referred to the Neuro-Oncology Service for further therapy because the surgical cure rate of such patients is as high as 95\% to 100\%.\textsuperscript{14,12,21,23,25} Even in patients with subtotally resected cerebellar or cerebral astrocytoma, a single course of radiation therapy at a total dose of 50 to 60 Gy results in survival periods greater than 20 years in 70\% to 80\% of patients;\textsuperscript{16,23} thus, regular follow-up review was often not required. In 34 of the 47 patients who were treated by the Neuro-Oncology Service, tumor size or location almost always precluded total resection, and concern about residual disease was much greater. It is therefore reasonable to assume that the risk of multicentric spread in our patients was higher than in the total population of patients with JPA. However, seven of the 11 patients who developed multicentric spread were referred from the Neurosurgery Service and only four of the 47 patients received primary treatment from the Neuro-Oncology Service. This suggests that secondary referral bias to a specialized neuro-oncology service was not an important factor in determining the risk of spread in our series. Even with this selection bias taken into account, our study suggests that the risk of multicentric spread in patients with hypothalamic JPA is still much higher than the previous literature would indicate.

As MR imaging of the craniospinal axis becomes routine in patients with JPA, we anticipate that other institutions will report increased detection rates of multicentric disease. Communications with neurosurgeons in other major referral centers already support this conclusion (RM Scott and L Albright, personal communication, 1992).

Predictors of Multicentric Spread

Tumor location and male sex were both associated with developing multicentric spread of JPA. Patients with JPA of the hypothalamic region were 23 times more likely to develop multicentric spread than those with nonhypothalamic tumors. These findings help define “high-risk” patients, and indicate the need for MR imaging of the craniospinal axis to look for multicentric spread in all patients with newly diagnosed hypothalamic region JPA.

Although we examined the associations of multicentric disease with tumor location, age at diagnosis, and sex, the effect of other variables (such as extent of resection of the primary tumor and type of postoperative therapy) must also be considered. Age at initial diagnosis was not significantly associated with the development of multicentric spread; however, patients with hypothalamic region tumors were generally younger than those with nonhypothalamic tumors. The proportion of each group that was less than 3 years old at initial diagnosis was 64\% and 21\%, respectively, which explains why most of our patients with multicentric disease were treated primarily with chemotherapy rather than with radiation therapy. It is a widely ac-
Multicentric juvenile pilocytic astrocytomas

tected policy not to administer radiation therapy to children until they are aged at least 3 years, and preferably 5 years, because of the tremendous risk to neural development. Tumor location was the main reason why patients with hypothalamic region JPA underwent subtotal resection or biopsy; the hypothalamic location generally precludes total resection because of the risk to neural and vascular structures. It therefore seems difficult, if not impossible, to separate the roles of tumor location and extent of surgical resection, and the roles of tumor location, patient age at initial diagnosis, and type of therapy. Nonetheless, we can draw a characteristic profile of the patient at highest risk for developing multicentric spread of JPA: this patient is most likely to be a child under 4 years old with a primary JPA in the hypothalamic region treated by subtotal resection or biopsy followed by adjuvant multiagent chemotherapy. To be conservative, we still consider any patient with a hypothalamic region JPA to be at high risk.

Prognosis

Seven of the 11 patients in our series had either disease remission or stabilization after treatment for multicentric JPA and are still alive after a median of 31 months of follow-up review. This survival rate is far better than that reported for patients with higher-grade astrocytomas or other central nervous system tumors; in those patients, the discovery of multicentric spread is almost uniformly fatal within a few months to 1 year.6,8,12,18,20 Even in patients with low-grade infiltrative astrocytomas, the development of multicentric spread is usually fatal within a few months of discovery.20 This difference in survival statistics suggests that the slow-growing potential of JPA persists even after multicentric spread has occurred, and that the prognosis for prolonged survival may still be favorable. However, we think it is unlikely that outcome and survival time in patients with multicentric spread of JPA is as good as in patients with localized recurrence or totally resected primary disease. Multicentric spread indicated a more aggressive variant of this typically benign tumor and, as our results indicate, this more aggressive behavior is associated with a higher mortality rate than is normally seen in patients with JPA.

Malignant Transformation of JPA and Atypical Multicentric Spread

Malignant transformation of JPA is very rare,1,4,5,14,24 and typically occurs after a long quiescent period following initial therapy, as long as 48 years in one case.14 Malignant transformation has been reported only at the site of initial tumor resection and is uniformly associated with rapid death. Histopathological verification of multicentric disease was obtained in only six of the 11 patients in our series; however, the pattern of recurrence and outcome in all 11 patients is not consistent with previously reported patterns of malignant transformation. In addition, we do not know of a reported case of multicentric spread of JPA and simultaneous malignant transformation. Therefore, we do not think histopathological verification of multicentric spread of JPA is mandatory; radiographic confirmation seems adequate for deciding to initiate therapy.

Treatment Recommendations

Patients with hypothalamic region JPA should undergo gadolinium-enhanced MR imaging of the craniospinal axis and cytological examination of the CSF to look for multicentric disease at the time of initial diagnosis. If multicentric disease is discovered, MR imaging of the craniospinal axis should probably be performed at each follow-up assessment, the regularity of which would depend on the treatment protocol. Biopsy or, if possible, total resection of the tumor is recommended. If the tumor is totally resected, patients can then be followed with serial MR imaging of the craniospinal axis at regular intervals without additional therapy. If the tumor is subtotally resected, adults and children over the age of 5 years should generally undergo focal irradiation at a total dose of 54 to 56 Gy because these doses are clearly successful in treating residual or recurrent JPA.10,11,16,25 Patients under 3 years of age should be treated with multiagent chemotherapy until they are at least 3 to 5 years old, at which time radiation therapy can be considered.

Although no data currently exist to demonstrate that earlier detection of multicentric disease will result in longer survival, we suggest that all patients with hypothalamic region JPA undergo annual MR imaging of the craniospinal axis, particularly for the first 5 years of treatment and follow-up monitoring. If multicentric disease is discovered, pathological confirmation by either cytological examination of the CSF or a biopsy is useful, although not mandatory to make a diagnosis of multicentric JPA. If a solitary, surgically accessible metastatic nodule is discovered, gross total removal can be considered. Chemotherapy or radiation therapy for multicentric disease should then be given. We anticipate that this approach will lead to earlier discovery of multicentric disease, resulting in earlier treatment of less bulky disease, better treatment responses, and longer survival times.

Acknowledgments

The authors gratefully acknowledge Pamela Derish for her excellent editorial assistance and review of our statistics, and Cheryl Christensen for manuscript preparation.

References

18. Moore MT, Eisinger G: Extra primary seeding of glioblas-

Manuscript received May 27, 1993.
Accepted in final form October 6, 1993.
This paper was supported by National Institutes of Health Grant NS-31076.
This work was presented in part at the Annual Meeting of the Pediatric Section of the American Association of Neurological Surgeons, December 4–9, 1992, Vancouver, British Columbia, Canada.
Address reprint requests to: Michael D. Prados, M.D., Department of Neurological Surgery, c/o The Editorial Office, 1360 Ninth Avenue, Suite 210, San Francisco, California 94122.