Correlation among magnetic resonance imaging findings, prognostic factors for survival, and histological diagnosis of intrinsic brainstem lesions in children

Clinical article

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Object. The aim of this study was to compare MR imaging characteristics with histopathological findings of intrinsic brainstem lesions and also to show the prognostic factors in patients with diffuse brainstem glioma.

Methods. Between February 1988 and August 2007, 44 brainstem biopsies were performed at the Roger Salengro Hospital in Lille, France, in children with intrinsic brainstem lesions not amenable to excision. Twenty-six were female and 18 male, and the mean age was 6 years.

Results. Histological evaluation revealed diffuse brainstem glioma in all patients with diffuse nonenhancing brainstem lesions. Diffuse brainstem glioma was found in 18 patients (90%) with diffuse enhancing brainstem lesions. Pathological entities different from diffuse glioma were verified in 2 patients (10%)—1 with ependymoma and 1 with ganglioglioma.

In 4 of 5 patients with a focal nonenhancing brainstem lesion, the histopathological diagnosis was diffuse low-grade glioma. In 6 of 10 patients with focal enhancing brainstem lesion, the diagnosis was diffuse brainstem glioma, and pathological entities different from diffuse brainstem glioma were verified in 2 (20%), both with pilocytic astrocytoma.

The mean 1-year actuarial survival rates for patients classified with low-grade and high-grade glioma were 80.4% ± 0.08% and 48.6% ± 0.14%, respectively.

Conclusions. The impact of stereotactic biopsy on intrinsic brainstem lesions was greater in patients with MR imaging–documented enhancing lesions in whom the diagnosis of diffuse glioma was less frequent. Patients with low-grade glioma seem to have longer survival than those with high-grade glioma. (DOI: 10.3171/2011.9.PEDS1167)

Key Words • brainstem tumor • biopsy • children

THE management of brainstem mass lesions remains controversial, particularly when the lesion cannot be removed and is infiltrating in nature, while the benefits of a stereotactic procedure are still debatable.11

In most studies, treatment decisions are based on MR imaging features alone and do not include histopathological diagnosis. Most authors regard a biopsy of intrinsic brainstem tumors as too dangerous4 and consider imaging methods to be sufficiently reliable.3 Thus, the impact of MR imaging findings on treatment decisions for brainstem tumors is very high, but the accuracy of MR imaging–based diagnosis of diffuse brainstem gliomas has not been fully verified by histopathological findings.14

The aim of this study was to compare MR imaging characteristics with histopathological findings of intrinsic brainstem lesions. Moreover, the study demonstrates the outlines of prognostic factors for survival in children with diffuse gliomas.

Methods

Between February 1988 and August 2007, 44 brainstem biopsies were performed at the Roger Salengro Hospital in Lille, France, in children with intrinsic brainstem lesions not amenable to excision. Twenty-six were female and were 18 male, and the mean age was 6 years. The follow-up period ranged from 4 days to 246 months after biopsy (mean 46 months).

Symptoms persisted for 4 months on average and consisted of waking disturbance in 21 patients, visual impairment in 27, dysphagia in 10, signs of intracranial
hypertension in 12, facial paresis in 13, and hemiparesis in 15.

Brainstem lesions are differentiated by MR imaging findings into 4 groups: 1) diffuse nonenhancing brainstem lesions (MR imaging showing a diffuse hypointense lesion on T1-weighted imaging; noncontrast enhancing lesion on T1-weighted imaging; and diffuse hyperintense lesion on T2-weighted imaging); 2) diffuse enhancing brainstem lesions (MR imaging showing a diffuse hypointense lesion on T1-weighted imaging; contrast-enhancing lesion on T1-weighted imaging; and diffuse hyperintense lesion on T2-weighted imaging); 3) focal nonenhancing brainstem lesions (MR imaging showing a focal hypointense lesion on T1-weighted imaging; noncontrast enhancing lesion on T1-weighted imaging; and focal hyperintense lesion on T2-weighted imaging; and 4) focal enhancing brainstem lesions (MR imaging showing focal hypointense lesion on T1-weighted imaging; noncontrast enhancing lesion on T1-weighted imaging; and focal hyperintense lesion on T2-weighted imaging).

Focal tumors have well-defined margins on MR imaging and occupy less than 50% of the axial diameter of the brainstem, whereas diffuse tumors have poorly defined margins and occupy more than 50% of the axial diameter of the brainstem.

Radiological findings consisted of diffuse nonenhancing brainstem lesions in 9 patients, diffuse enhancing brainstem lesions in 20 patients, focal nonenhancing brainstem lesions in 5 patients, and focal enhancing brainstem lesions in 10 patients.

**Surgical Technique**

Following the induction of general anesthesia, 37 patients underwent a stereotactic biopsy procedure in which a Talairach frame was used and 7 patients underwent a robotic brainstem biopsy procedure (neuromate, Renishaw). In all patients, MR imaging was used to target the biopsy site within the lesion. Serial sampling was performed every 10 mm of the trajectory, using a side-cutting Sedan needle. The center of the lesion was targeted, and, when enhancement was identified, this region was also targeted. A transfrontal approach was used in 42 patients and a transcerebellar approach in 2 patients. All biopsy specimens were formalin fixed and analyzed after staining with H & E, Masson trichrome, and immunostains.

**Data Analysis and Statistical Analysis**

Data analysis was performed using Epi info 6.02 and Medicale 9.3.0.9. Univariate analysis of the following variables was performed with regard to the radiological findings and histological diagnosis. The analyzed variables demonstrated on T1-weighted imaging were diffuse versus focal and enhanced versus nonenhanced contrast. All lesions on T2-weighted imaging were hyperintense.

Survival time was measured from the time of biopsy to the date of last follow-up or death of patients with diffuse glioma. Survival was estimated by the Kaplan-Meier method, with 95% confidence intervals. Comparison of Kaplan-Meier curves between low-grade and high-grade glioma was performed using the log-rank statistic. Parameters were deemed to be statistically significant at a value of p < 0.05.

**Results**

**Histological Results and Complications**

A precise histological diagnosis was established in 41 patients (93.1%), and the diagnosis was confirmed by the clinical course of the patient. A diagnosis of diffuse brainstem glioma was verified in 37 patients.

Other neoplastic diseases were diagnosed in 4 children: 2 pilocytic astrocytoma, 1 ependymoma, and 1 ganglioglioma.

The overall morbidity rate associated with biopsy was 9%, with 4 patients exhibiting slight deterioration compared with their preoperative condition: aggravation of hemiparesis in 2 and worsening of facial paresis in 2.

**Correlation of Histological and Radiological Findings**

Histological evaluation revealed diffuse brainstem glioma in all patients with diffuse nonenhancing brainstem lesions. Of these, 8 cases were low-grade glioma and 1 was high-grade glioma. Diffuse brainstem glioma was revealed in 18 patients (90%) with diffuse enhancing brainstem lesions. Of these, 4 cases were low-grade glioma and 14 cases were high-grade glioma. Pathologies different from diffuse glioma were verified in 2 patients (10%): 1 ependymoma (Fig. 1 left) and 1 ganglioglioma (Fig. 1 right).

In patients with a focal nonenhancing brainstem lesion, the histopathological diagnosis in 4 of 5 patients was diffuse low-grade glioma. The histological examination was inconclusive in 1 patient. In patients with a focal enhancing brainstem lesion, diffuse brainstem glioma was diagnosed in 6 patients; of these, 2 cases were low-grade glioma and 4 were high-grade glioma. Pathologies different from diffuse brainstem glioma were verified in 2 patients (20%), both with pilocytic astrocytoma. The examination was inconclusive in 2 patients.

Although the diagnosis of pathologies different from diffuse glioma was more common in patients with contrast-enhancing lesions, this difference was not statistically significant.

**Prognostic Factors for Survival in Patients With Diffuse Glioma**

At the time of the last follow-up visit in August 2007, 21 patients (56.8%) diagnosed with diffuse glioma had died. The mean overall survival of this population, measured from the date of biopsy, was 56 months for diffuse low-grade glioma and 12 months for diffuse high-grade glioma (p = 0.0755).

Figure 2 shows a comparison of Kaplan-Meier survival curves of the 2 subgroups of diffuse brainstem glioma. The 1-year actuarial survival rates for patients with low-grade and high-grade glioma were 80.4% ± 0.08% and 48.6% ± 0.14%, respectively. Despite the longer survival of patients with low-grade glioma, the difference was not statistically significant (p = 0.0755) (Fig. 3).
Intrinsic brainstem lesions

Discussion

Although the use of image-guided stereotactic brain biopsy is regarded as a safe and reliable procedure for the management of supratentorial lesions, its application in lesions involving the brainstem remains limited. Recent progress in modern neuroimaging techniques, especially high-resolution MR imaging, permits more precise determination of the location and extension of brainstem tumors and can provide certain specific characteristics of their nature.

Hence, the challenge is to know whether the use of MR imaging alone is precise enough to provide an accurate diagnosis or at least to permit the classification of cases into specific treatment groups and, consequently, whether a pathological diagnosis is still mandatory before initiating any therapy. Schumacher et al. in a series of 142 pediatric patients with brainstem lesions, reported correct classification by the radiologist of up to 90%. In contrast, Rachinger et al. showed that in adults, MR imaging specificity and sensitivity for diagnosing low-grade glioma was only 46.6% and 62.5%, respectively, and high grade glioma it was 61.7% and 58.3%, respectively.

Histological Results and Complications

Although several authors have reported a wide variety of histological results in brainstem masses after using brainstem biopsy, the indication for this procedure is still a matter of debate. One objection to performing a brainstem stereotactic biopsy procedure is that it may not be reliable because the tumor may be heterogeneous.

Additionally, heterogeneity often requires multiple sampling, which is potentially dangerous in the brainstem. Even in the most recent study by Kesari et al., published in 2008 and involving a large series, a histological diagnosis was obtained in only 53% of the patients. Many authors claim a very restrictive indication for radiologically unclear lesions due to the presumed high-risk profile.

In contrast, in the present study the rate of diagnosis was 93.1%, similar to other reports in the literature that range from 87% to 100%.

In some published studies, a high number of complications occurred in association with stereotactic brainstem biopsy, reaching up to 10%. As a consequence, the authors of those studies propagate a noninvasive approach; however, other studies have proven that stereotactic biopsy is a safe and reliable method with a high diagnostic yield. In the present study, no procedure-related deaths occurred, despite the highly eloquent target location, although 4 patients showed slight deterioration in preoperative symptoms.

Fig. 1. Axial Gd-enhanced T1-weighted MR images showing a diffuse enhancing brainstem lesion that was confirmed to be an ependymoma after biopsy sampling (left) and a diffuse enhancing brainstem lesion that was confirmed to be a ganglioglioma after biopsy sampling (right).

Fig. 2. Comparison of Kaplan-Meier curves of the 2 histological grade subgroups. The solid line represents diffuse low-grade glioma, and the dotted line represents diffuse high-grade glioma (p = 0.0755, log-rank test).

Fig. 3. Kaplan-Meier curves for 1-year actuarial survival rates. The solid line represents diffuse low-grade glioma, and the dotted line indicates diffuse high-grade glioma.
Correlation of Histological and Radiological Findings

In the present study, we analyzed correlations between histological and radiological findings in patients with brainstem tumors. Similarly, the risk profile for stereotactic brainstem biopsies was also analyzed, and MR imaging characteristics associated with diagnoses different from diffuse brainstem glioma were identified.

In the current series, 18 of the 20 patients with a diffuse enhancing brainstem lesion and 6 of the 8 patients with a focal enhancing brainstem lesion had a histological diagnosis of diffuse brainstem glioma. The remaining 4 histological findings were ependymoma, ganglioglioma, and 2 pilocytic astrocytomata. In patients with pathologies different from diffuse glioma, the biopsy results had an impact on the treatment because traditionally diffuse glioma patients underwent radiotherapy, which is not suitable in the cases aforementioned.

However, regarding the therapeutic consequences of radiotherapy and combined radio- and chemotherapy, patients with pathological entities different from diffuse glioma might have gained some benefit from the biopsy procedure since treatment based solely on a radiological diagnosis might have had severe consequences.14

Prognostic Factors for Survival in Patients With Diffuse Glioma

The biopsy was important in establishing the degree of malignancy in diffuse gliomas, which according to some authors is an important factor in the prognosis of these patients. The present study showed that patients with low-grade glioma have a longer survival than those with high-grade glioma, but this difference was not statistically significant, probably due to the small number of cases. Rachinger et al.14 recently reported that in patients with diffuse low-grade glioma there was a 1-year survival rate of 93%, whereas in patients with diffuse high-grade glioma the rate was 42%.

Nevertheless, current data concerning prognosis and prognostic factors in brainstem gliomas are scarce.4 This may be due to the low incidence of the tumors and the fact that histopathological diagnosis is rarely confirmed. However, it is highly probable that conventional fractionated radiotherapy will not remain the only efficient treatment in diffuse brainstem glioma in the next few decades. In addition, for patients with low-grade gliomas, an initial observational policy is being adopted, followed by treatment when the patient’s disease progresses clinically.17

Indeed, radiosurgery and new chemotherapies, gene therapies, or immunotherapies, separately or in combination, will certainly succeed in improving outcomes in this patient population. These therapies will undoubtedly require tissue sampling for diagnostic confirmation and tumor grading, for molecular marker studies, or for immunological purposes prior to adopting target therapies.5

Conclusions

The impact of stereotactic biopsy procedures on intrinsic brainstem lesions was greater in patients with enhancing lesions on MR imaging, in whom the diagnosis of diffuse glioma was less frequent. Patients with low-grade gliomas seem to have longer survival than patients with high-grade gliomas. Stereotactic biopsy of brainstem tumors is a low-risk procedure with a high diagnostic value in experienced hands and thus should be regarded as standard of care in children with enhancing brainstem lesions.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Dellaretti, Touzet, Blond. Acquisition of data: Dellaretti, Touzet. Analysis and interpretation of data: Dellaretti, Touzet, Blond. Drafting the article: Dellaretti, Blond. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Dellaretti. Statistical analysis: Dellaretti, Gusmão.

References

12. Pincus DW, Richter EO, Yachnis AT, Bennett J, Bhatti MT, M. Dellaretti et al.
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