Magnetic resonance spectroscopy of atypical diffuse pontine masses

MARK D. KRIEGER, M.D., STEFAN BLÜML, PH.D., AND J. GORDON MCCOMB, M.D.

Division of Neurosurgery, and Department of Radiology, Childrens Hospital Los Angeles; and Department of Neurological Surgery, Keck School of Medicine, University of Southern California, Los Angeles, California

Object. Diffuse pontine gliomas in children carry a dismal prognosis, with a mean survival of less than 1 year despite therapy. The diagnosis is based on the characteristic changes demonstrated on traditional magnetic resonance (MR) imaging. A few typically MR imaging–appearing pontine masses, however, do not behave in the expected fashion, which calls the original diagnosis into question.

Methods. The authors conducted a retrospective review of data obtained in 42 children (age 6 months–13 years) in whom diffuse pontine glioma had been diagnosed at their institution. Five of these patients (12%) survived longer than expected (> 18 months). There were no differences in these patients in terms of demographics, presentation, traditional imaging findings, or treatment compared with the group as a whole. Magnetic resonance spectroscopy, however, demonstrated two distinct patterns not seen in typical diffuse pontine gliomas. In two patients elevated lipid and lactate levels were shown, with decreased levels of choline, myoinositol, and \( \text{N}-\text{acetyl-aspartate} \) (NAA). In the other patients strikingly elevated choline/creatinine ratios and myoinositol levels were observed in comparison with typical pontine tumors.

Conclusions. These MR spectroscopy patterns demonstrated in this retrospective study seem to convey prognostic information and may lead to an expansion of this diagnostic tool.

KEY WORDS • magnetic resonance spectroscopy • diffuse pontine glioma • pediatric neurosurgery

Brainstem gliomas comprise approximately 10 to 15% of childhood brain tumors. They typically present during early childhood, with a peak incidence between the ages of 5 and 8 years. The presentation is usually subacute, with progressive neurological impairment developing over days to weeks. Signs and symptoms are most commonly due to disruption of function of the brainstem and/or cranial nerves.

In most cases, these are intrinsic tumors, arising within the neural substrate of the pons. The majority of tumors in the brainstem are high-grade gliomas that invade the brainstem, although low-grade gliomas also occur. Patients with diffuse tumors intrinsic to the pons have an extremely poor prognosis. With standard radiotherapy alone, the median time to progression is 5 to 6 months, and the median survival time is less than 1 year. The acuity of symptom onset is predictive of survival.

Histological diagnosis is not undertaken in the majority of cases. Three major reasons exist for proceeding with treatment without first examining a biopsy sample. First, these are intrinsic lesions located in extremely eloquent neural tissue. Biopsy sampling would thus carry risks of inducing brainstem dysfunction. Second, the typical appearance of these lesions on MR images is considered diagnostic, and further workup has been proven inefficacious. Third, in intrinsic pontine gliomas of childhood, histological type has not been shown to affect outcome. Although the MR images are highly predictive of these tumors, other lesions with similar radiographic appearances may occur. In rare cases, inflammatory and infectious lesions, or other tumor types may develop, with important treatment and prognostic implications.

Although the true course of the disease is invariably fatal, 6 to 10% of children live more than 2 years after undergoing radiotherapy. Various theories have been proposed to account for this subset of patients. It is possible that these represent tumors with either less biological activity and are thus more slow growing, or are more sensitive to radiotherapy. Alternatively, these patients may harbor lesions other than tumors, although the appearance mimics that of tumors on MR imaging.

The goal of the present study was to evaluate \(^1\text{H}-\text{MR} \) spectroscopy as a means to gain additional information regarding the biological activity of diffuse pontine gliomas. Proton MR spectroscopy can be performed using standard MR imagers combined with a software upgrade; it adds approximately 10 minutes to imaging time. Unlike conventional MR imaging, which demonstrates protons predominantly in water, proton MR spectroscopy can quantify the relative concentration of nonwater, proton-containing metabolites from discreet tissue regions by

Abbreviations used in this paper: CSF = cerebrospinal fluid; MR = magnetic resonance; NAA = \( \text{N}-\text{acetyl-aspartate} \).
suppressing the signals from water and lipids. Various substances within the brain are measured using MR spectroscopy, including the neuronal marker NAA, creatine (a reflection of cellular metabolism), and choline (a constituent of cell membranes). Proton MR spectroscopy has been described in the evaluation of stroke, as well as neoplastic, infectious, and inflammatory diseases of the brain.2,4,11,18,20,21,24 Our hypothesis was that the chemical makeup of such tumors might reflect their biological activity and that MR spectroscopy could thus aid in the evaluation of these lesions.

CLINICAL MATERIALS AND METHODS

A retrospective review was conducted of the brain tumor database at Childrens Hospital Los Angeles of patients treated between January 1991 and January 2000. All cases of diffuse pontine glioma in this database were identified. Charts and imaging studies were reviewed in their entirety.

Patient Population

Forty-two pediatric cases of diffuse pontine glioma were identified. This group included 23 boys and 19 girls who ranged in age from 6 months to 13 years. All patients underwent MR imaging, which led to the diagnosis. Five of these patients (12%) survived longer than expected (>18 months). There were no differences in these patients in terms of demographics, presentation, conventional imaging findings, or treatment compared with the group as a whole.

Informed parental consent was obtained to conduct an additional MR spectroscopy study after completion of all clinically indicated MR imaging studies. The MR imaging/MR spectroscopy protocol, and the review and correlation with clinical data were approved by the local institutional review board.

Magnetic Resonance Spectroscopy Studies

Precontrast and postcontrast MR imaging and 1H-MR spectroscopy images were acquired on a clinical 1.5-tesla General Electric imager in which a standard head coil was used. Single-voxel 1H-spectra of the tumors were acquired using a PRESS sequence (TE 35 msec, TR 1.5 seconds). Proton spectra were processed using the LC-Model software (Stephen Provencher Inc., Oakville, ON, Canada). The unsuppressed water was used as an internal reference. Absolute intensities were obtained. The basis set ware (Stephen Provencher Inc., Oakville, ON, Canada).

RESULTS

We identified 42 children with diffuse pontine glioma (23 boys and 19 girls), who ranged in age from 6 months to 13 years (median age 4.5 years). The duration of symptoms, based on reports provided by their parents, ranged from 1 day to 7 months. In 37 of the 42 patients cranial nerve deficits were observed on initial examination. Long tract signs were present in 29 patients and ataxia in 31 patients.

Magnetic resonance images were obtained in all children prior to therapy. In all cases a diffuse tumor was seen centered in the pons. Cases involving isolated tectal lesions and dorsally exophytic lesions were excluded. All lesions appeared hyperintense on T2-weighted sequences. Ring or patchy enhancement was revealed on imaging prior to therapy.

In the entire group, the mean time from diagnosis to death was 9.5 months. Five (12%) of these patients, however, survived longer than expected (>18 months). There were no differences in patients in terms of demographics, presentation, traditional imaging findings, or treatment compared with the group as a whole. Three of these patients and 17 of the remaining 37 patients underwent CSF evaluation; in no case were the results suggestive of an alternate pathological processes.

High-quality 1H-MR spectroscopy were obtained in all five patients, as well as in 12 of the other 37 patients with typical gliomas. The overall evaluation session, including complete MR imaging and 1H-MR spectroscopy study times, required approximately 1 hour, and no adverse effects were reported.

A spectrum from healthy gray matter obtained in a control and that obtained in a diseased patient with a typical clinical course are shown in Fig. 1. In these tumors the choline level was increased relative to creatine whereas NAA was depleted. Myoinositol relative to creatine was increased (Fig. 1).

The spectral patterns demonstrated by 1H-MR spectroscopy in patients with atypically long survival proved to be different, which most likely represent significant variations in underlying biochemistry. A significantly elevated lipid peak, with a marked decrease in the other measured entities, was observed in two long-term survivors despite a typical MR imaging–based appearance of diffuse pontine glioma (Fig. 2).

In the other three long-term survivors, less dramatic shifts were revealed on MR spectroscopy. In these patients moderately elevated myoinositol and choline levels were displayed (Fig. 3).

DISCUSSION

Five (12%) of the 42 patients with pontine gliomas at our institution lived longer than expected. This rate of atypical long-term survival is well described in the literature.8,10,15 The reasons for these cases of long-term survival remain unknown, partly because of the inhomogeneity apparent in the literature. It is well documented that exophytic and tectal tumors have a significantly different disease course from true diffuse pontine gliomas, as do evenly enhancing pilocytic astrocytomas.2,27 Thus, their inclusion in some series would skew the results to indi-
cate a greater number of long-term survivors. In our series, only patients with truly diffuse pontine gliomas on documented MR imaging were included to avoid this difficulty.

Once selection bias is eliminated and treatment standardized, it is reasonable to assume that atypical long-term survival is based on some innate property of the tumor itself. To attempt to identify such biochemical factors, we performed MR spectroscopy to study these tumors. Magnetic resonance spectroscopy was safely and effectively performed in 17 patients with gliomas. The additional imaging sequences added fewer than 10 minutes to the overall imaging time and were obtained without sequelae.

Although these results are preliminary, they indicate that spectroscopic patterns may exist that indicate tumor behavior. In two of our patients choline, creatine, and NAA levels were low and lipid levels were elevated. Elevated choline/creatine ratios were documented in three patients when compared with normal cerebral tissue, but no significantly elevated choline/NAA ratios were found. Given the small numbers and lack of quantification of these levels, we would consider these qualitative observations. Clearly, more data are needed.

The utility of MR spectroscopy in evaluating pediatric tumors has been recognized by other authors. Warren, et al., demonstrated a relationship between a high choline/NAA ratio and short duration of survival in a heterogeneous group of pediatric brain tumors. They raised the issue as to whether this link may have a biological basis. They cited the fact that choline, a constituent of cell membranes, is increased in states of high membrane turnover, such as in malignant tumors. On the other hand, NAA is seen in normal cerebral tissue and is replaced in neoplasms that destroy such tissue. Neoplasms are thought to replace or destroy the NAA-containing cells, thereby accounting for the decreased NAA. Thus, malignant tumors with a high choline/NAA ratio would show a rapid turnover of cell membranes and decreased number of normal neurons.

Preliminary results suggesting that MR spectroscopy can yield information that differentiates among lesions in the pons may have prognostic significance.

CONCLUSIONS

Advanced neuroimaging modalities play an important
role in the diagnosis and management of diffuse pontine gliomas. Magnetic resonance spectroscopy yields additional information that may aid in the understanding of this devastating disease.

References


Manuscript received June 11, 2003.
Accepted in final form June 20, 2003.
Address reprint requests to: Mark D. Krieger, M.D., 1300 North Vermont Avenue, Suite 1006, Los Angeles, California 90027. email: mkrieger@chla.usc.edu.