Differentiation of choroid plexus tumors by advanced magnetic resonance spectroscopy

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Object. The management of pediatric intraventricular tumors is highly dependent on identification of the tumor type. Choroid plexus papillomas, a common intraventricular tumor in children, can be difficult to distinguish radiographically from choroid plexus carcinomas and other common pediatric central nervous system (CNS) tumors. In this study to overcome the limitations of current noninvasive imaging modalities, the authors use novel magnetic resonance (MR) spectroscopy techniques in vivo to elucidate the identifying biochemical features of choroid plexus tumors that may facilitate diagnosis and treatment.

Methods. Based on an Internal Review Board–approved protocol, six children with newly diagnosed, untreated intraventricular brain tumors were identified. On retrospective review, this series included three choroid plexus papillomas and three choroid plexus carcinomas. Single-voxel proton MR spectroscopy with a short echo time was performed, and absolute metabolite concentrations (in mmol/kg) were determined using fully automated quantitation. These results were compared with MR spectroscopy profiles obtained in 54 other untreated CNS neoplasms in children.

The myo-inositol (mI) level was significantly higher in choroid plexus papillomas (> 10 mmol/kg), uniquely distinguishing these tumors from choroid plexus carcinomas and all other tumors. Choroid plexus carcinomas, on the other hand, had significantly elevated levels of choline when compared with choroid plexus papillomas.

Conclusions. In this study the authors find that mI is a biochemical constituent that uniquely identifies choroid plexus papillomas and can be used as a noninvasive means of diagnosis and for follow-up evaluations in patients with this disease.

**KEY WORDS** • choroid plexus papilloma • choroid plexus carcinoma • pediatric brain tumor • magnetic resonance spectroscopy

Choroid plexus tumors range from the histologically and clinically benign choroid plexus papilloma to the histologically and clinically malignant choroid plexus carcinoma. Overall, these are relatively rare CNS lesions, accounting for less than 1% of all intracranial tumors.

Nevertheless, they are more commonly seen in children, accounting for up to 6% of all primary CNS neoplasms in a pediatric population. Indeed, this is a disease of the very young, with 70% of these tumors seen in children less than 2 years of age.

Papillomas account for two thirds of choroid plexus tumors, and are generally benign, even when invasion is seen. Resection is curative in these cases. In contrast, carcinomas are malignant lesions, with overall survival rates of 40 to 50%. Surgical removal gives the best chance of cure, and adjuvant therapy is generally recommended. Nevertheless, there is evidence to indicate that these lesions are extremely vascular, making surgery difficult in very young patients.

The management of choroid plexus tumors would be greatly facilitated by an accurate, noninvasive, preoperative diagnosis. Traditional imaging techniques have oftentimes been inadequate in differentiating these tumors. A non-invasive diagnosis would aid in surgical planning; specifically, surgical approaches and adjuvant therapy, such as preoperative embolization, could be planned to address the hypervascularity of choroid plexus carcinomas. Approaches could also be determined to address the invasiveness of these tumors. Additionally, preoperative imaging could be requested to determine metastases in the case of choroid plexus carcinomas. For follow-up evaluations, noninvasive diagnosis could differentiate residual or recurrent disease from posttreatment effects. An added benefit would be to provide a basis for stratifying patients in clinical research trials.

To aid in the preoperative evaluation of choroid plexus tumors, we have used novel MR spectroscopy techniques to evaluate six such lesions in children. The goal of this study was to identify unique biochemical signatures that may
facilitate diagnosis and treatment. With this study, we add to the prior work in the field by presenting a quantitative analysis of the biochemical constituents of these tumors.

CLINICAL MATERIAL AND METHODS

Based on an Internal Review Board–approved protocol, MR spectroscopy studies obtained in six children with newly diagnosed, untreated intraventricular brain tumors were reviewed. Patients 5 years old and younger were anesthetized with 100 to 200 g/min/kg propofol throughout the acquisition of MR images. All tumors were resected within 3 days of the MR examination, and the specimens were reviewed by two independent neuropathologists.

On retrospective review, this series included three choroid plexus papillomas and three choroid plexus carcinomas. The criteria of the World Health Organization were used to classify the tumors. Briefly, choroid plexus papillomas displayed microscopic features of normal choroid plexus, with villi lined by simple epithelium of uniform size and shape. No cellular atypia or mitotic figures were seen. In the patients in this series, no stromal invasion was seen. Choroid plexus carcinomas showed invasion of the adjacent neural tissue, with a diffuse and poorly defined pattern of growth, loss of regular papillary architecture, and evidence of cellular malignancy.

These results were also compared with MR spectroscopy studies performed in 54 other children with newly diagnosed, untreated CNS lesions. This group included 14 medulloblastomas, five anaplastic astrocytomas, three astrocytomas, 17 pilocytic astrocytomas, four anaplastic ependymomas, five ependymomas, and six pineal region germi

Acquisition and Analyses of MR Spectroscopy Studies

The MR imaging was performed with a 1.5-tesla clinical imaging unit (General Electric Medical Systems, Milwauk ee, WI). Standard clinical images in three orthogonal planes were acquired according to established protocols, which included precontrast T1-weighted MR imaging, T2-weighted fast–spin echo imaging, and fluid-attenuated inversion-recovery imaging. The T1-weighted images were obtained in at least two planes after intravenous administration of 0.1 mmol per kg of body weight of Gd-based contrast material (Magnevist; Schering, Berlin, Germany, or Omniscan; Nycomed, Oslo, Norway).

Single-voxel proton (1H) MR spectra of the tumors were acquired using a point-resolved spectroscopy sequence with a short 35-msec TE, a 1.5-second TR, and 128 signal averages. Using the unsuppressed water signal of tissue as an internal reference, this technique allowed absolute quantification (in mmol/kg tissue) of NAA, Cr, Cho, mI, Lac, and Tau. The regions of interest were carefully selected to exclude any partial volume with surrounding normal-appearing tissue. Proton spectra were processed using commercially available software (LCModel Version 6; Stephen Provencher, Inc., Oakville, Ontario, Canada). Processing of MR spectra was completely automated and did not require user interaction. Absolute concentrations of Tau, Cr, Cho, NAA, mI, Glx, and Lac, and concentration ratios relative to Cho were analyzed for this report.

Statistical Analysis

Unpaired two-tailed Student t-tests with unequal variance were used for the following statistical comparisons: choroid plexus papillomas with choroid plexus carcinoma; choroid plexus papillomas with all other tumors; and choroid plexus carcinoma with all other tumors. Metabolite concentrations relative to Cho were evaluated.

RESULTS

The MR spectroscopy images were obtained in six children with newly diagnosed intraventricular brain tumors. These images were obtained at the same time as the preoperative diagnostic MR images, and added a mean of 10 minutes to the procedure time. (Concentrations of metabolites are displayed in square brackets.)

As shown in Table 1, three patients had newly diagnosed choroid plexus papillomas. This group included three boys between 6 and 17 years of age (mean age 9 years). On spectroscopic analysis, there was a significant peak of mI in choroid plexus papillomas (> 15 mmol/kg), and elevated [mI]/[Cho] and [Glx]/[Cho] ratios, distinguishing these tumors from choroid plexus carcinomas, all other tumors, and controls (p < 0.01) (Table 2). An MR spectroscopy study obtained at a long echo time of 144 msec confirmed the assignment of mI. Glycine coresonates with mI at 3.56 ppm, and can thus be confused with mI on analysis. Glycine is expected to have a residual signal in MR spectroscopy obtained with a long echo time, and this was not observed.; Fig. 1) Also seen were lowered mean [Cho] (p < 0.001), [Cr] (p < 0.01), [Lac] (p < 0.001), and [Glx] (p < 0.05) when compared with other tumors. Nevertheless, these results did not reach significance when compared with choroid plexus carcinomas.

Choroid plexus carcinomas exhibited a distinct pattern that clearly distinguished them from papillomas. The most important distinguishing feature was the lack of mI elevation. Despite the small number of patients studied, choroid plexus papillomas appear to be readily distinguishable from choroid plexus carcinomas. In the latter lesions, the mean [mI] and [Glx]/[Cho] were 20 and 30%, respectively, of those measured in choroid plexus papillomas (Table 2). Choroid plexus carcinomas exhibited low [NAA] (p < 0.001) and [Glx] (p < 0.001) when compared with other tumors. As in choroid plexus papillomas, the mean [Cr] was also reduced (p < 0.01). Although the mean [Cho] of choroid plexus carcinomas was high when compared with all other tumors, it did not reach significance because of the small number of patients studied. Among concentration ratios, low [NAA]/[Cho] (p < 0.001), low [Cr]/[Cho] (p < 0.001), and low [NAA]/[Cr] (p < 0.001) were the most

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>No. of Patients</th>
<th>S/I Ratio</th>
<th>F/M Ratio</th>
<th>Age in Yrs (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>choroid plexus papilloma</td>
<td>3</td>
<td>2:1</td>
<td>0.3</td>
<td>9.2 ± 6.5</td>
</tr>
<tr>
<td>choroid plexus carcinoma</td>
<td>3</td>
<td>3:0</td>
<td>1.2</td>
<td>1.1 ± 1.4</td>
</tr>
<tr>
<td>other</td>
<td>54</td>
<td>26:28</td>
<td>24:30</td>
<td>7.4 ± 5.1</td>
</tr>
</tbody>
</table>

* I = infratentorial; S = supratentorial; SD = standard deviation.
Choroid plexus carcinomas were distinguished by an elevated level of Cho, which reached statistical significance when combined in a ratio with Glx and Tau. Other research indicates that Cho is a marker of malignancy. Warren, et al.,33 and Lazareff, et al.,3 have found that a relative elevation of Cho with respect to NAA is predictive of outcome in children with recurrent primary brain tumors. Other authors have also found this change in tumors typically found in adults.24,11

The ability to distinguish between papillomas and carcinomas is important in the preoperative evaluation of children with intraventricular tumors. In both types of tumors, aggressive resection yields the best prognosis.7,13,15–17,19 Nevertheless, carcinomas can be more difficult to excise because of their invasive nature. In fact, some studies cite total excision rates of one third to two thirds for choroid plexus carcinomas.3,6,17 Thus, preoperative diagnosis can help the surgeon plan an aggressive resection in these cases, while being cautious to avoid damaging the invaded substrate.

Additionally, carcinomas present more of a problem with vascularity, and thus blood loss, than do papillomas. This danger is especially important to appreciate in very young children, in whom acute blood loss can be life threatening in a short time. A surgeon expecting a carcinoma can thus tailor the approach to address tumor vascularity early and minimize blood loss. Additionally, he or she can prepare for a transfusion early.

Noninvasive MR spectroscopy diagnosis can also be beneficial in following these patients postoperatively. Often times in such patients, the follow-up neuroimaging studies demonstrate residual enhancement. The knowledge of a significant differentiators of choroid plexus carcinomas from other tumors. The [ml]/[Cho] (p < 0.05), and [Glx]/[Cho] (p < 0.01) were also significantly reduced.

**TABLE 2**

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Choroid Plexus (Papilloma)</th>
<th>Choroid Plexus (Carcinoma)</th>
<th>All Other Tumors (54 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[NAA]/[Cho]</td>
<td>1.3 ± 0.5</td>
<td>0.1 ± 0.0</td>
<td>0.6 ± 0.6†</td>
</tr>
<tr>
<td>[Cr]/[Cho]</td>
<td>0.7 ± 0.3</td>
<td>0.3 ± 0.2</td>
<td>1.2 ± 0.9†</td>
</tr>
<tr>
<td>[ml]/[Cho]</td>
<td>11.9 ± 3.7‡±</td>
<td>0.9 ± 0.6</td>
<td>2.6 ± 1.9§§</td>
</tr>
<tr>
<td>[Glx]/[Cho]</td>
<td>3.8 ± 0.5**</td>
<td>1.2 ± 0.7</td>
<td>4.3 ± 2.0§</td>
</tr>
<tr>
<td>[Tau]/[Cho]</td>
<td>0.5 ± 0.6‡±</td>
<td>0.6 ± 0.3</td>
<td>0.7 ± 0.6</td>
</tr>
<tr>
<td>[Lac]/[Cho]</td>
<td>0.4 ± 0.4</td>
<td>0.4 ± 0.4</td>
<td>1.3 ± 1.5††§§</td>
</tr>
</tbody>
</table>

*Values are given as the mean ± SD.
† p < 0.001 for choroid plexus carcinoma compared with all other.
‡ p < 0.01.
§ p < 0.05.
|| p < 0.001 for choroid plexus papilloma compared with all other.
** p < 0.01 for choroid plexus papilloma compared with choroid plexus carcinoma.
†† p < 0.05.
‡‡ p < 0.05.
§§ p < 0.05.

**DISCUSSION**

In this study the authors examined a group of six children in whom newly diagnosed, untreated intraventricular brain tumors were investigated using MR spectroscopy. This group includes three patients with choroid plexus papillomas and three with choroid plexus carcinomas. We found a biochemical signature that uniquely distinguished the choroid plexus papillomas from the choroid plexus carcinomas and all other tumors. This analysis was facilitated by the development of a novel method of MR spectroscopy evaluation that provides quantitative analysis of the biochemical constituents of these tumors. Other authors have reported the absolute quantification of metabolite concentration by using external standards,2 but we used the imaged water signal of tissue as an internal standard. We have described this technique before in the analysis of untreated pediatric brain tumors.3

Choroid plexus papillomas were identified by a distinct biochemical constituent: strikingly elevated ml. This is consistent with an MR spectroscopy study obtained in a single patient with choroid plexus papilloma and reported by Tzika, et al.32 In this series, absolute ml levels and the ml/Cr ratio separated these lesions from choroid plexus papillomas and other tumors. The role of ml in the brain is not well elucidated, and bears further study.

![Fig. 1. Diagnostic MR spectra of a choroid plexus papilloma (A, left) and a choroid plexus carcinoma (B, left) acquired using a short echo time, and T2-weighted (A, right) and T2-weighted MR images (B, right) acquired after addition of contrast material, indicating the regions of interest. Choroid plexus papillomas show a prominent ml peak, whereas Cr is hardly detectable. In contrast, the more malignant choroid plexus carcinoma shows a prominent Cho peak, whereas ml is not elevated. The Cr is below the level of detectability in the spectrum shown in panel B. The signal from lipids and macromolecules resonating between 0.9 and 1.7 ppm was not analyzed in this report.](image)
biochemical signature that distinguishes tumor from postoperative changes can help practitioners tailor the treatment to the disease.

Clearly, patient numbers are an issue in this study, and additional cases are needed to confirm the reproducibility of our results. Nevertheless, we believe that the striking differences seen, and the statistical significance of these differences, are a preliminary validation of these results. In this series we have not provided an ex vivo analysis of the tissue to verify the presence of the biochemical constituents identified, but in other studies researchers have validated the accuracy of MR spectroscopy used in this fashion.\(^3\) We have advanced the field by using quantitative analysis to provide a noninvasive method for determining histological features in childhood brain tumors. We hope that future work will lead to prognostic information based on these quantitative data.

**CONCLUSIONS**

In this study we identified biochemical constituents that uniquely differentiate choroid plexus tumors in children. These markers can be used as a noninvasive means of diagnosis and for follow-up review in patients with this disease.

**References**


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