Localized $^{31}$P magnetic resonance spectroscopy of large pediatric brain tumors

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Fourteen children aged 1 week to 16 years, with a variety of large or superficial brain tumors, underwent localized in vivo $^{31}$P magnetic resonance spectroscopy of their tumor. Quantitative spectral analysis was performed by measuring the area under individual peaks using a computer algorithm. In eight patients with histologically benign tumors the spectra were considered to be qualitatively indistinguishable from normal brain. The phosphocreatine/inorganic phosphate ratio (PCr/Pi) averaged 2.0. Five patients had histologically malignant tumors; qualitatively, four of these were considered to have abnormal spectra, showing a decrease in the PCr peak. The PCr/Pi ratio for this group averaged 0.85, which was significantly lower than that seen in the benign tumor group ($p < 0.05$). No difference between the two groups was seen in adenosine triphosphate or phosphomonoesters. It is concluded that a specific metabolic "fingerprint" for childhood brain tumors may not exist, but that some malignant tumors show a pattern suggestive of ischemia.

KEY WORDS • magnetic resonance spectroscopy • brain neoplasm • phosphocreatine

PHOSPHOROUS nuclear magnetic resonance spectroscopy ($^{31}$P MRS) has recently been shown to have potential as a noninvasive monitor of mobile phosphorus-containing compounds in vivo. The technique has been applied to the brain in both animals and humans, but most investigators have examined widespread brain insults, such as global ischemia, hypoxia, hyperthermia, seizures, and increased intracranial pressure (ICP). This is because, until recently, spatial resolution of the technique has been poor. The introduction of surface coils by Ackerman, et al., in 1980 allowed high-quality spectra to be obtained from localized volumes of tissue near the body surface, roughly equal in diameter to that of the surface coil. More recently, depth-resolved spectroscopy as described by Bottomley, et al., has become possible, making it feasible to obtain spectra from selective areas within the brain substance, such as tumors.

Studies of the phosphate metabolism of tumors in vivo have largely been limited to animal models. Recent reports have described $^{31}$P MRS in large human tumors as well, including sarcomas (MA Shinkwin, et al.: unpublished data), neuroblastoma, and various adult brain tumors. The aim of these studies has been: 1) to find a metabolic "fingerprint" for malignancy, and thus confirm the potential of this technique for diagnosis; and 2) to identify alterations in phosphorous compounds which might be predictive of response of a given malignancy to certain forms of therapy.

The present study was undertaken to determine whether localized $^{31}$P MRS could provide a better understanding of tumor metabolism in a heterogeneous group of childhood brain tumors. Only children harboring extremely large or superficial masses were studied to ensure that the spectra obtained were largely derived from neoplastic tissue.

Clinical Material and Methods

Fourteen children ranging in age from 1 week to 16 years were studied. Twelve of the patients had newly diagnosed brain tumors and had not undergone surgery or other treatment prior to spectroscopy; the other two patients (both with malignant tumors) had previously undergone surgery and irradiation, and were studied at the time of tumor recurrence. All patients underwent surgical excision or biopsy within 1 week after $^{31}$P MRS, and histological confirmation of the diagnosis was obtained.

Magnetic resonance proton (MR) imaging was obtained at the time of spectroscopy to localize the tumor for surface-coil placement and depth of depth-resolved spectroscopy slices, and also to determine radiological
characteristics of the tumor that could later be correlated with spectral data. In most instances, computerized tomography was performed as well. The tumors were either superficial (and thus accessible to a surface coil) or extremely large. Tumor sizes ranged from 10 to 585 cu cm, with a median size of 147 cu cm.

Before MRS/MR imaging was undertaken, informed consent was obtained from each child’s parent or guardian. Younger children required sedation with chloral hydrate (60 mg/kg), given orally. The entire MRS/MR imaging sequence took less than 1 hour. The MRS/MR examinations were performed using a 1.5-tesla, 56-cm clear-bore scanner equipped with the standard research accessory for spectroscopy.* Magnetic resonance imaging was performed on a 1.5-tesla proton imaging unit with the following parameters: T₁-weighted images were performed with a short (600-msec) time to repetition (TR) and a short (20-msec) time to echo (TE). Proton density-weighted images were performed with a long TR (3000 msec) and a short TE (30 msec), while T₂-weighted images were performed as a second echo with the same TR (3000 msec) and a long TE (80 msec). Slice thickness was 5 mm, with an interscan slice gap of 2.5 mm. Matrix size was 256 × 128, with a 20-cm field of view. Sagittal T₁-weighted images of the entire brain took approximately 2½ minutes to obtain, while axial proton density- and T₂-weighted images of the entire brain took 10½ minutes. Depending upon the location of the tumor, coronal or sagittal images with long TR’s and multiple TE’s were obtained.

All images were examined by one radiologist (R.A.Z.) with attention to tumor size and the presence and extent of necrosis, calcification, and cyst. Tumor volume was estimated by measuring length (L), breadth (B), and depth (D) of the tumor based on the formula for volume of an ellipsoid:

\[
\text{Volume} = \frac{\pi}{6} (L \times B \times D) \text{ cu cm.}
\]

The 3¹P spectroscopy was performed using a 5-cm surface coil, doubly tuned for protons and phosphorus (25.85 MHz). The magnetic field homogeneity was adjusted by shimming on the proton signal. For depth-resolved spectroscopy, a slice-selective 90° radiofrequency pulse (2000 Hz sweep width with 10 Hz line broadening) was used in the presence of a slice-selective gradient to excite a tissue slice of approximately 125 cu cm volume with a repetition time of 4 seconds (2000 points). In most cases, depth-resolved spectroscopy slices were obtained in the sagittal plane, and were approximately 2.5 cm thick. In some cases of very large and superficial tumors, unlocalized spectra were obtained by using an overlying surface coil.

Spectra were processed off-line using a program specifically for the analysis of in vivo spectra. Spectra were fit using an automated program previously described by one of us (R.E.L.)¹⁵ that involves the use of an iterative Lorenzian estimation centered at each peak position in the spectrum and requires no subjective user interaction. Areas for each peak were then calculated and correlated with clinical data. The pH was determined from the chemical shift in parts/million of inorganic phosphate relative to phosphocreatine (PCr).²⁰

Results

The normal ³¹P spectrum of human brain consists of seven peaks: phosphohonoester/sugar phosphate (PME), inorganic phosphate (Pi), phosphodiesters (PDE), PCr, and the γ, α, and β peaks of adenosine triphosphate (ATP). Because the ATP signal also receives contributions from nicotinamide adenine dinucleotide, oxidized form/reduced form (NAD+/NADH), and adenosine diphosphate (ADP) contributes to both the γ and α peaks, the β-ATP is used as the reference for quantitation of ATP and also to normalize other peak integrals in the form of ratios. The relative amounts of PCr, AT, and Pi provide information on the bioenergetic state of the tissue observed: a decrease in the PCr/Pi ratio denotes tissue ischemia.³ The measurement of PME and PDE yields information on cell membrane and myelin turnover.² Both PME and PDE are reportedly increased in tumor tissue²⁰,²¹,²⁷ and in the immature brain undergoing myelination.²⁴,²⁶,²⁷

Evaluable spectra were obtained in 13 of the 14 patients. In the one exception, a patient with a glioblastoma, an adequate spectrum could not be obtained because of intravenous gadolinium given 48 hours previously. On the basis of standard histological features, the tumors in our patients were classified as histologically malignant in five patients and benign or low-grade in eight patients. Tables 1 and 2 describe the patient characteristics and the type, size, and location of the tumor in these two groups. A wide variety of histological types were encountered in both groups.

The eight patients with benign tumors (Table 1) averaged 8 years 9 months in age (range 8 months to 16 years). These patients presented with focal neurological signs; only one (Case 2) had overt symptoms of increased ICP with an enlarged head. No patient demonstrated features of necrosis within the tumor, either on radiological studies or histologically. Qualitative evaluation of the ³¹P spectra revealed an increase in the PME peak in Case 1, as would be expected due to his young age (8 months, Fig. 1), and an increase in the α-ATP peak in Case 2 of uncertain significance. The remainder of the studies were considered to be indistinguishable from those obtained from normal brain tissue. Numerical data for peak areas are presented in Tables 1 and 3. The PCr/Pi ratio averaged 2.0 (range 1.0 to 4.0), and the PME/β-ATP ratio averaged 1.9 (range 1.4 to 3.7). Intracellular pH as determined from the chemical shift of the Pi peak averaged 7.1 ± 0.04 (± standard error of the mean).

The five patients who harbored malignancies were

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* Signa scanner manufactured by General Electric Medical Systems, Milwaukee, Wisconsin.
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**TABLE 1**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Histological Type</th>
<th>Tumor Location</th>
<th>Necrosis</th>
<th>Calculated pH</th>
<th>PCr/Pi</th>
<th>PCr/β-ATP</th>
<th>Pi/β-ATP</th>
<th>PME/β-ATP</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>7, M</td>
<td>astrocytoma</td>
<td>temporal</td>
<td>no</td>
<td>7.3</td>
<td>2.2</td>
<td>0.73</td>
<td>0.33</td>
<td>1.4</td>
</tr>
<tr>
<td>2</td>
<td>13, F</td>
<td>choroid plexus papilloma</td>
<td>lat. ventricle</td>
<td>no</td>
<td>7.0</td>
<td>4.0</td>
<td>1.0</td>
<td>0.25</td>
<td>1.6</td>
</tr>
<tr>
<td>3</td>
<td>8, M</td>
<td>subependymoma</td>
<td>pineal</td>
<td>no</td>
<td>7.0</td>
<td>—</td>
<td>—</td>
<td>0.3</td>
<td>3.7</td>
</tr>
<tr>
<td>4</td>
<td>14, F</td>
<td>astrocytoma</td>
<td>cerebellum</td>
<td>no</td>
<td>7.3</td>
<td>2.4</td>
<td>1.5</td>
<td>0.6</td>
<td>2.0</td>
</tr>
<tr>
<td>5</td>
<td>13, M</td>
<td>meningioma</td>
<td>parietal</td>
<td>no</td>
<td>7.0</td>
<td>1.5</td>
<td>1.7</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>6</td>
<td>3, F</td>
<td>ependymoma</td>
<td>parietal</td>
<td>no</td>
<td>7.0</td>
<td>1.6</td>
<td>1.6</td>
<td>1.9</td>
<td>2.2</td>
</tr>
<tr>
<td>7</td>
<td>14, M</td>
<td>astrocytoma</td>
<td>temporal</td>
<td>no</td>
<td>7.0</td>
<td>1.0</td>
<td>1.4</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>8</td>
<td>16, F</td>
<td>ganglioglioma</td>
<td>parietal</td>
<td>no</td>
<td>7.1</td>
<td>1.6</td>
<td>2.1</td>
<td>1.3</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Mean ± SEM:

Tumor age: 83 ± 9 yrs
Tumor size: 87 ± 4 cm³
Necrosis: 0 ± 0
Calcification: 8.5 ± 1.9

**TABLE 2**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, Sex</th>
<th>Histological Type</th>
<th>Tumor Location</th>
<th>Necrosis</th>
<th>Calculated pH</th>
<th>PCr/Pi</th>
<th>PCr/β-ATP</th>
<th>Pi/β-ATP</th>
<th>PME/β-ATP</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>2 yrs, F</td>
<td>ependymoblastoma</td>
<td>parietal</td>
<td>yes</td>
<td>7.3</td>
<td>0.70</td>
<td>1.3</td>
<td>2.0</td>
<td>1.6</td>
</tr>
<tr>
<td>10</td>
<td>16 yrs, M</td>
<td>malignant oligodendroglioma</td>
<td>temporal</td>
<td>yes</td>
<td>6.5</td>
<td>decreased</td>
<td>—</td>
<td>—</td>
<td>3.0</td>
</tr>
<tr>
<td>11</td>
<td>2 yrs, M</td>
<td>medulloblastoma</td>
<td>cerebellum</td>
<td>no</td>
<td>7.1</td>
<td>0.70</td>
<td>0.75</td>
<td>1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>12</td>
<td>21 yrs, F</td>
<td>chondrosarcoma</td>
<td>frontal</td>
<td>no</td>
<td>7.0</td>
<td>1.4</td>
<td>2.1</td>
<td>1.5</td>
<td>2.3</td>
</tr>
<tr>
<td>13</td>
<td>1 wk, M</td>
<td>malignant teratoma</td>
<td>intraventricular</td>
<td>no</td>
<td>7.4</td>
<td>0.67</td>
<td>0.5</td>
<td>1.0</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Mean ± SEM:

Tumor age: 82 ± 1 yrs
Tumor size: 90 ± 7 cm³
Necrosis: 1.0 ± 0.2
Calcification: 8.5 ± 1.9

*PCr = phosphocreatine; Pi = inorganic phosphate; β-ATP = beta peak of adenosine triphosphate; PME = phosphomonoester/sugar phosphate; SEM = standard error of the mean.

Discussion

The 31P MRS technique is rapid, noninvasive, and apparently risk-free and provides a method by which tumor metabolism can be examined in vivo. Surface-coil localization is appropriate for large or superficial...
FIG. 1. 31P spectrum in Case 1 obtained by placing a 5-cm surface coil over this large superficial low-grade astrocytoma. The peaks are well resolved. This was considered a normal spectrum for an 8-month-old child. PME = phosphomonoster/sugar phosphate; Pi = inorganic phosphate; PDE = phosphodiester; PCr = phosphocreatine; ATP = adenosine triphosphate.

FIG. 2. 31P spectrum obtained from Case 13, a 1-week-old infant with a massive intraventricular malignant teratoma who presented with signs of intracranial hypertension. For abbreviations see Fig. 1. The PCr peak is reduced in height and the Pi peak is increased.

FIG. 3. Spectrum obtained from Case 12. For abbreviations see Fig. 1. The PCr peak is reduced and the Pi peak is increased.

recently, 31P MRS has been used to study a variety of human neuroectodermal tumors and mammary adenocarcinomas transplanted subcutaneously into animals, and a decrease in PCr was found with preservation of the PME and ATP peaks.

Studies of human tumors in situ have been sparse because of the difficulty of localizing the tumor with surface-coil techniques. Maris, et al.,17 reported an increase in the PME peak in childhood neuroblastoma, and noted that this neuroectodermal-derived tumor is the only human tissue other than immature brain for which the in vivo PME/β-ATP ratio is higher than 1. It was suggested that the elevated PME (corresponding to phosphoryl ethanolamine and phosphoryl choline) might be related to the need for increased phospholipid synthesis in these tissues. In our studies, both malignant and benign tumors averaged PME/β-ATP greater than 1, but the significance of this is uncertain without established normal values in children.

Thomsen, et al.,23 reported 31P MRS in eight large brain tumors in adults and found no significant abnormalities in the PCr/Pi ratio. Their tumors were largely low-grade, however, and their results would be supported by our benign group of patients. It is obvious, even with localized 31P MRS, that some signal derives from surrounding brain tissue in all but the largest tumors. Our benign tumors tended to be smaller (average 87.5 cu cm) than the malignant tumors (average 244 cu cm), and it is possible that metabolic abnormalities may have been hidden by an overwhelming contribution from surrounding normal brain. Even with large malignancies, it is unclear how much of the ischemic change derived from the tumor itself and how much may have been due to generalized increased ICP, which has been shown to produce similar abnormalities in animals.22

If it is possible to determine hypoxia within a tumor using 31P MRS, this technique might perhaps have value in predicting the responsiveness of a particular neoplasm to radiation therapy. It is known that a larger
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dose of radiation is needed to achieve the same degree of biological damage to hypoxic tissue as for normoxic tissue. The exact mechanism of this “oxygen effect” is not fully understood but presumably, in the absence of oxygen free radicals produced by ionizing, radiation cannot cause permanent tissue damage. Hypoxic tumors are thus potential targets for radiation sensitizing agents.

Finally, it is worth noting that MR imaging contrast agents, such as gadolinium, may interfere with 31P MRS by shortening the relaxation time. In one of the patients, satisfactory spectra could not be obtained even 48 hours after gadolinium administration. For future protocols, spectroscopy will be included in the precontrast portion of the imaging session.

In summary, it is concluded that MRS can be performed with acceptable quality in children as a supplement to MR studies. A specific metabolic “fingerprint” for childhood brain tumors does not appear to exist; however, some malignant tumors show a pattern suggestive of ischemia, manifested as a decrease in the PCr/PI ratio.

References

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