Differentiating Diffuse Brainstem Neoplasms using Proton Magnetic Resonance Spectroscopy

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Introduction
Proton magnetic resonance spectroscopy (MRS) has demonstrated excellent efficacy in the diagnosis of brain tumor [1-2]. The non-invasive nature of MRS is critical in cases where brain biopsies carry a risk of particular morbidity. In diffuse brainstem lesions, this is the case [3]. Identification of neoplastic lesions through spectroscopy is typically done through a spectral “signature” of high choline to either creatine (Cho/Cr) or N-acetyl aspartate (Cho/NAA) [4,5]. Recalculating the published data and using a receiver operator characteristic (ROC) of > 1.0 for both Cho/Cr and Cho/NAA, discrimination can be achieved between neoplastic and non-neoplastic lesions [4,5]. This operates under the assumption that the “normal” Cho ratios are < 1.0 in the region where the spectra was obtained. The concentrations of choline and creatine differ in grey and white matter [6] and therefore regional differences must be taken into account. In this study, we intend to characterize the metabolite ratios in the brainstem region for normal controls and suspected brain tumors.

Methods
15 normal controls (ages 25-64, mean=43 years) were examined using PRESS-localized short-echo (TR=2s, TE=0.03s) MRS in the brainstem as indicated in Fig 1a. In the controls, a voxel size of 4.5cc was used to maximize area covered in the brainstem. Seven patients with suspected brain lesions in the brainstem identified on previous MRI scans (Fig 2a) were also examined using the same MRS technique. Voxel sizes of lesions ranged from 2-4.5cc which were optimized to reduce partial volume of the lesion. All spectra were then post-processed to obtain metabolite ratios for NAA/Cr, Cho/Cr, and mI/Cr. Absolute creatine concentration was calculated using methods previously described and recalculated for PRESS[6]. Patients were then followed-up for 1 month to 2 years in order to confirm the benign nature of the lesions.

Results
Despite magnetic field inhomogeneity in the brainstem, 12 of 15 control spectra were technically successful. Metabolite ratios and creatine concentration are shown in Table 1. All normal spectra demonstrated a greater than 1.0 Cho/Cr ratio but less than 1.0 Cho/NAA ratio as demonstrated in Fig 1b. Of the seven suspected brain tumors, only one proved to be neoplastic despite the fact that in all cases, Cho/Cr > 1.0. The spectral signature of the malignant tumor not only reflects the high Cho/Cr but it also shows increased lipid and/or lactate as shown in Fig 2b. The NAA resonance is obscured by the third lipid resonance at 2.1 ppm. Had there been evidence of NAA, there would be a narrow resonance at 2.0ppm. In addition, as reported in previous publications, the absolute creatine concentration is decreased in the tumor[7]. The remaining seven lesions demonstrated a similar spectral pattern to the control data and at this current time show no evidence of growth or worsening patient symptoms.

Discussion/Conclusion
Our results show a significantly higher Cho/Cr ratio (1.29±0.33) in normal brainstem tissue when compared to grey (Cho/Cr = 0.60) and white matter (Cho/Cr = 0.82) ratios for this age group[8]. An explanation for the increased Cho/Cr ratios could possibly be due to a lower concentration of total creatine in the brainstem, thus artificially increasing Cho/Cr. This can be ruled out by the absolute creatine concentrations measured in the brainstem (7.01±0.82 mmol/kg tissue) which is very comparable to published grey and white matter Cr concentrations (8.04 and 6.33 mmol/kg tissue, respectively)[9]. The high choline found in this region is most likely due to the high density of axons packed into the brainstem. This is reflected in the increased choline ratio when comparing grey matter to white matter. Non-neoplastic lesions also demonstrated this high Cho/Cr but not a high Cho/NAA due to the persistence of neurons and axons. The potential for misdiagnosis or false positives is high if relying on just using a Cho/Cr ratio to diagnose tumor. This is especially important as in all 7 cases of suspected lesion MRI was not able to differentiate between tumor and non-tumor. Reduced NAA/Cr and/or the presence of lipid and lactate are strong indicators of brain tumor in the region of interest, allowing confident diagnosis of brain tumor, even in the midbrain.

References

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<th>n</th>
<th>NAA/Cr</th>
<th>Cho/Cr</th>
<th>mI/Cr</th>
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<td>12</td>
<td>1.87±0.38</td>
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<td>Non-neoplastic</td>
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<td>1.42±0.13</td>
<td>1.05±0.33</td>
<td>0.72±0.14</td>
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Table 1. Midbrain Metabolites ([ ] indicates absolute concentration)