Qualitative detection of ceramide and other metabolites in brain tumor by localized correlated spectroscopy

R. Nagarajan[1], W. B. Pope[1], N. Salamon[1], L. M. Liau[2], T. Cloughesy[3], and M. A. Thomas[1]
[1]Radiological Sciences, University of California Los Angeles, Los Angeles, CA, United States, [2]Neurosurgery, University of California Los Angeles, [3]Neurooncology, University of California Los Angeles

Introduction: Glioma is a type of brain tumor that grows from glial cells and is an umbrella term used to describe different types such as astrocytoma, oligodendroglioma, and glioblastoma multiforme (GBM). Gliomas vary in their aggressiveness, or malignancy. Some are slow-growing and are potentially curable. Others are fast-growing, invasive, difficult to treat, and are likely to recur. Lower grade gliomas can degenerate into higher grade tumors, resulting in secondary GBM, in contrast to primary GBM which arise de novo. Proton magnetic resonance spectroscopy (^{1}H MRS) is a noninvasive technique which can play an important role in the diagnosis as well as in the therapeutic management of brain tumors (1). In vivo one-dimensional (1D) MRS is limited by its inability to resolve several J-coupled metabolite resonances and by its ability to detect brain metabolites that occur at low concentrations (around 1mM). In contrast to localized 1D MRS, localized 2D correlated spectroscopy (L-COSY) has improved dispersion along the second spectral dimension resulting in the feasibility of detecting these low concentrated metabolites (2). The goal of this work was to investigate if metabolites such as ceramide (Cer), phosphoethanolamine (PE), taurine (Tau) and 2-hydroxy glutaric acid (2HG) can be detected in GBM by 2D L-COSY and whether this technique can also resolve choline groups, N-acetylaspartate (NAA), glutamine/glutamate (Glx), lactate (Lac), myo-inositol (mI) and creatine (Cr).

Methods: The 2D L-COSY sequences was implemented on a 3T Trio-Tim MRI/MRS scanner (Siemens Medical Systems, Erlangen, Germany) running on the VB15 platforms. Thirteen brain tumor patients (mean age of 54.6 years) have been scanned so far: four primary GBM (grade IV), one secondary GBM, one anaplastic mixed glioma and one anaplastic oligodendroglioma (grade III), and six low grade (grade II) astrocytomas, oligodendroglioma and mixed glioma. The following parameters were used for L-COSY: TR/TE=2.0s/30ms, 6-8 averages per Δt_1 and 100 Δt_1 increments. Most of the tumors were big enough to accommodate the MRS voxel size of 3x3x3 cm^3. The Siemens 12 channel "receive" phased-array coil was used for this study. The entire protocol was approved by the institutional review board (IRB), and informed consent was obtained from each human subject.

Results and Discussion: Figure 1A shows a 2D L-COSY spectrum recorded in a 32 yo primary GBM patient using the 3T MRI/MRS scanner. The axial slice MRI in Fig.1B shows the voxel location used for the 2D MRS. Shown in Fig.2 is a 2D L-COSY spectrum recorded in the left parietal region of a 48 yo low grade astrocytoma patient. A projected 1D MR spectrum from the F_2 dimension is also shown on top of each 2D spectrum. In agreement with the previous 1D MRS reports of high and low grade brain tumors, the diagonal and cross peaks showed significantly reduced NAA and increased total choline (Cho) and Lac (3). In addition to these major metabolites including mI, there were 2D cross peaks due to aspartate (asp), glutathione (GSH), phosphocholine (PCh), glycerylphosphocholine (GPC), Tau and PE. The first major finding was that the 2D L-COSY spectra of GBM showed more significant cross peaks due to PE than the choline groups including PCh, GPC and free choline. The presence of ceramide (sphingosine, a monounsaturated fatty acid) in high grade gliomas was previously reported by Lombardi et al. (4). A second major observation from the present study was the feasibility of detecting ceramide by showing unambiguous cross peaks at (F_2 =5.4, F_1= 2.75 ppm) and (F_2=2.8ppm, F_1= 5.45 ppm). The observation of 2D L-COSY resonance corresponding to ceramide in high grade gliomas, but not in low grade gliomas (grade II astroctyomas, oligodendrogliomas and mixed gliomas), meningiomas or normal human brain, supports the previously noted association of ceramide with increasing tumor grade (4). Currently we are focusing on detecting the methylene and methine resonances from 2HG in order to distinguish this metabolite from the closely positioned Glx resonances.

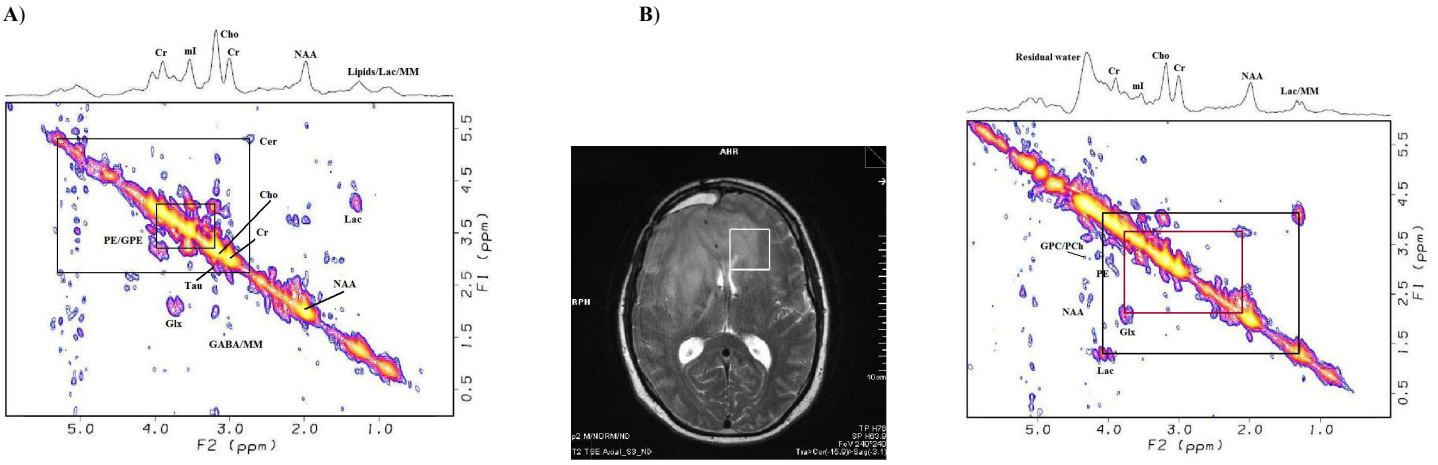

Fig.1. **A**) 2D L-COSY spectrum and **B**) Axial MRI of 32yo patient with GBM showing the MRS voxel. **Fig.2**. 2D L-COSY spectrum of a low grade astrocytoma in a 48 yo patient.

Conclusion: This pilot study demonstrates the advantages of 2D L-COSY for detecting ceramide, PE, Tau, and 2HG more sensitively than other methods, with better separation of GSH, Asp, Lac, etc. mainly due to the added 2nd dimension. Spatially resolved 2D MRS has great potential for the noninvasive biochemical characterization of both high and low grade brain tumors, and 2D L-COSY may provide additional information in cases where the determination of tumor grade by MR imaging alone is difficult.

References

1. Tate AR, Griffiths JR, Martinez-Perez I, et al. NMR Biomed 1998; 11:177–191.
2. Thomas MA, Yue K, Binesh N, et al. Magn. Reson. Med. 2001; 46: 58-67.
3. Li Y, Srinivasan R, Ratiney H, et al. J Magn Reson Imaging. 2008; 28:342-50.
4. Lombardi V, Valko L, Valko M, et al.Cell Mol Neurobiol. 1997; Oct;17(5):521-35.