Lecture #16
Clinical $^1$H Spectroscopy

- Neurospectroscopy in clinical practice and research
- Body applications
- References
Brain Tumors – Key Points*

- Multimodal imaging providing improved diagnostic and prognostic accuracy, fundamental in disease monitoring and assessing response to therapy.
- $^1$H-MRSI provides a valuable clinical tool depicting metabolic changes reflective of cellular density, anaplasia, and mitotic index.
- Cho is elevated in all tumor types due to altered membrane metabolism, and shows correlation with cellular density and indices of cell proliferation. NAA decreases with tumor infiltration and substitution of normal neural and glial cells. The Cho/NAA ratio is a useful parameter particularly in most primary brain tumors, with a higher ratio correlating with higher cell density and generally associated with a poor prognosis.
- While $^1$H-MRS can show different metabolic patterns in different tumor types, it is not used as a primary diagnostic tool.
- Increasing Cho/NAA and Cho/Cr ratios in serial exams of a primary astrocytoma are suggestive of transformation to a higher grade and can be useful in monitoring disease progression or response to therapy.
- $^1$H-MRSI may provide guidance for targeted biopsy, surgery, or therapy.

*Barker, et al.
Tumor vs non-Tumor

52 y.o male: MRI #1 - rule out stroke, MRI #2 - tumor?

9 y.o male: non-enhancing lesion in left hippocampus
68 F who reports fairly abrupt onset of a visual field defect. Pt is referred for MR to r/o PCA stroke

Dx=GBM

SV PRESS, TE=288

Cho (high)

NAA (low)

FLAIR

axT1gd

DWI
44 F with acute onset aphasia, clinical ddx includes demyelination, abscess, glioma and met

Dx: *Strep viridans* abscess
Diagnosis?

Necrotic mass  Abscess with bacterial metabolism

Stagg and Rothman
Tumor vs non-Tumor

Diagnosis: oligoastrocytoma grade II

Multiple sclerosis diagnosed at follow-up
Pediatric Brain Tumors

Medulloblastoma

Low-grade astrocytoma

Pilocytic astrocytoma

Anaplastic astrocytoma

Barker, et al.
Meningioma

Stagg and Rothman
$^1$H MRS
brain tumor
flow chart

Stagg and Rothman
PRESS $^1$H MRSI

Typical clinical parameters: TR/TE=1500/144 ms, 16x16 matrix, 1.5 cm slice, 24 cm FOV, 3.4 cc voxels, 6-8 min acquisition, 3T.
Metabolic and histopathologic heterogeneity in low-grade astrocytoma

MRSI (PRESS: TR/TE = 1200/135 ms; 24 × 24 matrix; FOV = 200 × 200 × 15 mm3)

Stagg and Rothman
MRSI used for early diagnosis of 7 year old with small asymptomatic tumor (medulloblastoma). Note, very high choline in lesion.
Lymphoma
High choline in an oligodendroglioma

Surprisingly at histopathology the diagnosis of low-grade oligodendroglioma was made. The very high Cho signal is likely related to the very high cellular density that was demonstrated on the HE-stained histologic slide. The rate of mitosis and anaplasia was very low in this oligodendroglioma.
Tumor Grading

Ranking gliomas by the Cho/Cr ratio

N = 66

- WHO I pilocytic astrocytoma
- WHO II astrocytoma
- WHO II oligodendroglioma
- WHO III anaplastic astrocytoma
- WHO IV GBM

Barker, et al.
Choline changes between consecutive studies in progressive (red) versus stable (green) brain tumor patients
MRS-Aided Biopsy

42 y.o. male with non-enhancing glioma

T$_2$-weighted FSE

Post-contrast GRE
MRS-Aided Biopsy

42 y.o. male with non-enhancing glioma

T₂-weighted FSE

Choline
51 M s/p surgery and XRT for anaplastic astrocytoma, now with new area of enhancement.

MRS: reduced NAA, increased Cho c/w normal. Dx: tumor recurrence.
34 F previously rx’d with surgery and high dose XRT for GBM
Tumor recurrence vs radiation necrosis?

Cho can transiently increase after XRT, but these findings are worrisome for tumor recurrence.
Response to therapy in lymphoma

$^1$H-MRSI maps of Cho, Cr, NAA, and lipids from a serial exams in a patient with non-Hodgkin lymphoma (A) before, (B) 17 days and (C) 28 days after initiation of radiation therapy, and (D) at 33-month follow-up.
Metabolic Disorders - Key Points*

• MR spectroscopy is a valuable tool to direct biochemistry work-up of patients with inborn errors of metabolism, with MRSI the best method to study the heterogeneous anatomic distribution of metabolic diseases.

• The interpretation of MR spectra and MR images together increases diagnostic accuracy.

• Abnormal MR spectral peaks are diagnostic of a few hereditary metabolic disorders.

• Lactate is elevated in about half of patients with mitochondrial disorders, in most patients with leukoencephalopathies with demyelination or rarefaction of white matter, and in few with organic acidopathies targeting the subcortical gray matter nuclei.

• MRS may be useful to monitor response to therapy when available.

*Barker, et al.
Succinate Dehydrogenase Deficiency

Figure 11.2. A 12-month-old boy with 3 month history of arrest of psychomotor development and tetraparesis. He was diagnosed with mitochondrial encephalopathy due to succinate dehydrogenase deficiency (SDH). MRSI (PRESS: TR/TE = 1200/135 ms; 24 × 24 matrix; FOV = 200 × 200 × 15 mm3) was acquired at the level of the centrum semiovale. Cho, succinate (Succ), lactate (Lac) and NAA maps with two selected spectra are illustrated. The white matter spectrum from the right centrum semiovale (1) showed an abnormally elevated succinate peak at 2.42 ppm, associated with moderate NAA and mild Cr signal losses. Lactate was mildly elevated in white matter voxels. The gray matter spectrum from the adjacent parasagittal parietal cortex showed only minimal succinate accumulation and mild NAA signal loss. The Succ map elegantly demonstrates accumulation selectively in white matter, confirming that the metabolic defect targets white matter and spares gray matter. In the Lac map the bright signal around the brain arises from the lipid signal in the scalp. On the T2-weighted MR images at the level of the centrum semiovale, note the signal hyperintensity in the deep white matter with relative sparing of the subcortical white matter. On the ADC map diffusivity is reduced in the deep periventricular white matter; it was reduced also in the corpus callosum and corticospinal tracts (images not shown).
Figure 11.6. 16-month-old girl who presented with ataxia and severe developmental delay. She was diagnosed with mitochondrial encephalopathy due to complex I respiratory chain defect:

Multivoxel display shows extensive elevation of lactate in the white matter of the centrum semiovale, whereas in the gray matter there is no Lac accumulation and Cho, Cr, and NAA have normal signal intensities.
13 mo F with hypotonia and developmental delay

Dx: creatine deficiency (guanidinoacetate methyltransferase [GAMT] deficiency).

Absence of Cr peak at 3.0 ppm
Creatine deficiency: Treatment Response

Post dietary supplementation

Barker, et al.
Cystathionine B-Synthase deficiency

Figure 11.8A. Ten-year-old female with Cystathionine B-Synthase (CBS) deficiency, hyperhomocysteinemia, and elevated plasma methionine levels. T₂-MRI at presentation shows global elevation of white matter signal intensity, while selected spectra from gray and white matter (MRSI, TR/TE 2300/270 ms, top row) show near-normal metabolite levels, suggesting vasogenic edema rather than demyelination or axonal loss. Short TE white matter spectrum (bottom row) also shows near-normal metabolite levels. (*) indicates unknown resonance at approximately 2.6 ppm, possibly due to homocysteine.
Figure 11.14. Two-year-old girl with severe developmental delay and macrocephaly since the first year of life, muscle hypotonia, dysphagia, and cerebellar ataxia. She was diagnosed with Alexander disease.

MRSI (PRESS: TR/TE = 1500/135 ms; 32 × 32 matrix; FOV = 160 × 160 × 20 mm³) was acquired at the level of the centrum semiovale. The location of four selected spectra is overlaid on the T₂-weighted MR image.

Note increased Cho with decreased NAA and Cr in the spectra from the right and left centrum semiovale (1, 2, 3). Minimal lactate elevation is also detected (1), while the gray matter spectrum (4) is normal. Swelling with diffuse signal hyperintensity throughout the white matter, in the basal ganglia, and subependymal regions is illustrated in the axial T₂-weighted MR images. Note “enhancement” of the periventricular rim (arrow) after i.v. gadolinium administration in the sagittal T₁-weighted MR image, which is a very suggestive finding of infantile AD.
Canavan’s Disease

Figure 11.3. Ten-month-old girl presenting with hypotonia with poor head control, mild spasticity, and macrocephaly, diagnosed with Canavan disease.

MRSI (PRESS; TR/TE = 1200/135 ms; 24×24 matrix; FOV = 200×200×15 mm³) was acquired at the level of the lateral ventricles. Cho, Cr, and NAA maps with three selected spectra are illustrated.

Note abnormal marked elevation of the NAA peak in the right centrum semiovale (spectrum 1) and in the parasagittal parietal lobe (spectrum 3). The elevation of NAA is milder in the left corona radiata where less signal hyperintensity is seen on the T1-weighted MR images (right column).
Traumatic Brain Injury - Key Points*

• TBI is a major cause of morbidity in young adults and children.
• Low levels of NAA and, if seen, increased lactate, in the early stage of injury are prognostic of poor outcome with other common abnormalities being increased levels of choline, myo-inositol, and Glx.
• Metabolic abnormalities are observed with MRS in regions of the brain with normal appearance in conventional MRI.
• MRI and MRS are difficult to perform in acutely ill TBI patients: MRS may be more feasible in mild TBI patients for the purpose of predicting long-term cognitive deficits.
• The role of MRS in guiding TBI therapy is unknown, and the comparative value of MRS compared to other advanced imaging modalities remains to be determined.

*Barker, et al.
Figure 10.9. (A) Graph showing the time course of NAA/Cho and NAA/Cr decline in patients with head injuries who had poor outcomes. The NAA reduction was gradual and non-linear, reaching its lowest point at about 10 days and showing no recovery up to 60 days. (B) Scatter plot demonstrating the association between NAA reduction and 6-month outcome (Glasgow Outcome Score, GOS). Patients with good outcomes exhibited mean ratios >1.50. Conversely, those with poor outcomes were characterized by ratios <1.50, identifying a possible threshold of irreversible neurochemical damage. Note that the metabolite ratios in patients with GOS scores indicating good recovery or moderate disability are not significantly different from those of healthy volunteers. The metabolite ratios of patients with poor outcomes at 6 months were significantly lower than controls (p < 0.01). (Adapted with permission from [114].)
Stroke and Hypoxic Ischemic Encephalopathy – Key Points*

- MRS is highly sensitive to metabolic changes associated with hypoxic or ischemic injury to the brain.
- Lactate is elevated during acute hypoxia or ischemia, and may also increase during “secondary” energy failure after reperfusion.
- NAA decreases with prolonged hypoxia or ischemia.
- In $^{31}$P MRS, high-energy phosphates decrease, inorganic phosphate increases, and pH decreases during acute hypoxia and ischemia.
- Both $^1$H and $^{31}$P MRS offer prognostic information in HIE, which may be complementary to, and sometimes easier to interpret than, conventional or diffusion-weighted MRI in the neonatal brain.
- DWI may be better for evaluating small HIE lesions than MRS.

*Barker, et al.*
18 hr old term infant s/p 30 min arrest
Dx: anoxic injury

*injection solvent for anticonvulsants, center 1.1 ppm
**note the relatively low NAA in the term neonate
Neonatal Encephalopathy

Figure 6.11. Representative thalamic PRESS spectra (8 ml, TR/TE 2000/270 ms) acquired from a control infant and 2 neonates with neonatal encephalopathy. (A) Control. (B) Normal/mild outcome. (C) Severe/fatal outcome. The dashed lines are the spectrum analysis Lorentzian profiles fitted to the peaks. Reproduced with permission from [74].
Acute CNS Injury: Near Drowning

Moats, et al.
JCAT, 19:480, 1995
MRSI with J-editing for Lactate

- MELAS patient (metabolic disorder with multiple strokes)

Hepatic Encephalopathy

Figure 11.7. Hepatic encephalopathy. Example of single-voxel PRESS spectra from parietal white matter (short echo time, TE 35 msec) from a 2-year-child with liver failure and an age-matched control subject. Note the increased signal from Glx (due to increased glutamine) and decreased Cho in the patient. There is also a small decrease in myo-inositol.
Brain Development – Key Points*

• Substantial regional variations in proton brain spectra exist; differences between gray and white matter, anterior–posterior gradients, and differences between the supra- and infra-tentorial brain are common.

• Spectra change rapidly over the first few years of life; at birth, NAA is low, and choline and myo-inositol are high. By about 4 years of age, spectra from most regions have a more “adult-like” appearance.

• In normal development, only subtle age-related changes are found between the ages of 4 and 20 years.

• In normal aging, only subtle age-related changes are found. A recent meta-analysis indicated the most common findings are mildly increased choline and creatine in frontal brain regions of elderly subjects (> 68 years), and stable or slightly decreasing (parietal regions only) NAA.

*Barker, et al.
Figure 4.8. Age-related variations in MRS – the normal developing brain. At birth, spectra of both gray and white matter show low signals from NAA and elevated levels of Cho and ml. As the brain develops, NAA increases and Ch and ml decrease so that by about 4 years of age (in these locations) the spectra are essentially indistinguishable from those in young adults. Reproduced with permission from [17]. Spectra recorded at 1.5T.
Brain Development

Figure 6.7. Representative short echo time single voxel spectra from neonates of 25, 35, and 49 weeks gestational age. Of note is the decrease of ml and increase in NAA with age. A small lactate peak is also clearly visible in the younger neonates. Normative curves showing evolution of NAA, lactate (Lac) and glutamine (Glu) with gestational age from 20 to 100 weeks are shown. The black dots represent NAA, Lac, and Glu values from one infant with methyl malonic aciduria (MMA), clearly showing the deviation from the normal age-related metabolic pattern (elevated Lac, low NAA). Reproduced with permission from [63].
Neurodegenerative Disorders-
Key Points*

- Despite the relatively common occurrence of neurodegenerative diseases, MRS is lightly used likely due lack of sensitivity and overlap of spectral findings.
- MRS usually shows decreased levels of NAA in dementia.
- Dementias associated with gliosis (e.g. Alzheimer’s) also have increased myo-inositol (mI), and mI/NAA ratios may be helpful in the differential diagnosis of different dementias (Alzheimer, vascular, frontotemporal, Lewy body).
- Parkinson’s disease does not seem to be associated with any metabolic disorders, and metabolic changes in Huntington’s disease are unclear.
- Prion diseases are characterized by decreased NAA levels.
- In amyotrophic lateral sclerosis (ALS), NAA decreases may be helpful in establishing a diagnosis.

*Barker, et al. 42
Neurodegenerative Disorders

Figure 9.2. Examples of proton spectra obtained from the posterior cingulate VOI with a TE of 30 ms in a control subject (top), in a patient with MCI (middle), and in a patient with AD (bottom). NAA/Cr ratio is lower in the patient with AD than both the patient with MCI and the control subject. ml/Cr ratios are higher in patients with MCI and AD than the control subject. The ml/Cr ratio is also higher in the patient with AD than the patient with MCI. [Adapted from Kantarci et al., Neuroimag Clin N Am 2003; 13: 197–209, figure 3, with permission.]

Barker, et al.
Prostate Cancer – Key Points* 

• High incidence; a leading causes of death in men.
• The sensitivity and specificity of diagnosing prostate cancer with conventional imaging methods (ultrasound, MRI) is relatively low.
• The normal prostate contains high levels of citrate (Cit) which can be detected in the proton spectrum at 2.6 ppm. Other compounds detectable in vivo include creatine, choline, spermine, and lipids.
• Citrate is a strongly coupled multiple at 1.5 and 3.0 T. For optimum detection, careful attention to pulse sequence parameters (TR, TE) is required. TE 120 ms is commonly used at 1.5 T, and TE 75–100 ms at 3 T.
• Multiple studies have reported that prostate cancer is associated with decreased levels of citrate and increased levels of Cho, compared to both normal prostate and also benign prostatic hyperplasia (BPH).
• MRS and MRSI of the prostate is technically challenging: water- and lipid-suppressed 3D- MRSI is the method of choice for most prostate spectroscopy studies.
• Some studies report that adding MRSI to conventional MRI increases sensitivity and specificity of prostate cancer diagnosis.
• MRSI is traditionally performed with an endorectal surface coil, but acceptable quality data may be obtained at 3 T with external phased-array coils which are more comfortable for patients.

* Barker, et al.
Prostate Anatomy and Metabolism

Prostate gland in the axial plane. PZ, peripheral zone; CZ, central zone; TZ, transitional zone; U, urethra; AFT, anterior fibromuscular tissue; UT, periurethral tissue; ED, ejaculatory duct; NVB, neurovascular bundle; SV, seminal vesicles; B, bladder; P, prostate.

Barker, et al.
Prostate Cancer: $^1$H MRS Exam

**Figure 12.5.** Multiple spatial saturation pulses are used in the (a) axial, (b) coronal, and (c) sagittal plane to conform to the shape of the prostate to minimize off-resonance artifacts in the resultant spectra. The white rectangular box shows the bounding box for the prostate and the hashed lines represent the saturation slabs that are used to shape the prostate.

**Figure 12.6.** Scoring methodology employed by the University of San Francisco researchers for the interpretation of the prostate spectra that takes into consideration the role of polyamines. A score of 1 is considered normal prostate tissue, whereas a score of 5 indicates malignant prostate tissue whose (Cho+Cr)/Cit ratio is greater than four standard deviations from the normal ratio of 0.22 $\pm$ 0.13. From [74], with permission.
MRI/MRSI Data Display

Prostate

T2 weighted FSE image

Corrected T2 image

Overlaid Choline Image + Citrate Image

Overlaid Spectral Grid

Overlaid Choline/Citrate image
Prostate Cancer: Treatment Response

**Figure 12.4.** Metabolite concentrations (a) before and (b) ~3 years after external beam radiation therapy. Note the increase in (Cho+Cr)/Cit ratio in the left peripheral zone. Complete metabolic atrophy is seen after radiation therapy which may be mistaken for failed exam. The quality of the exam can be confirmed by verifying the linewidth of the residual water peak which confirms metabolic atrophy. From [67], with permission.
Prostate Cancer: Research

“New pulse sequences have been proposed that control the J-modulation of citrate to obtain pure absorption spectra from citrate at reasonable echo times.”

Barker, et al.
MSK – Key Points*

- $^{31}$P-MRS detects metabolites central to energy metabolism and is valuable in monitoring therapeutic response in a number of neuromuscular disorders.
- $^1$H-MRS of muscle has a limited clinical role, but is used as a research tool to assess intramyocellular lipid, e.g. insulin resistance and type 2 diabetes mellitus.

$^{31}$P-MRS: Exercise and Recovery

$^1$H-MRS: anterior tibialis

* Barker, et al. 50
Breast Cancer – Key Points*

• MRS of the breast is more technically demanding than that in the brain.
• Cho levels have been reported to be higher in malignant breast cancer than in benign lesions and normal breast tissue.
• Early decreases in Cho signal intensity may be seen in lesions that respond to treatment.
• MRS is limited by sensitivity to lesions at least 1 cm³.
• Inadequate sensitivity may lead to false negatives, and both false positives and negatives may arise due to insufficient water and lipid suppression, or other artifacts.

*Barker, et al.
Breast Cancer

Diagnosis

Treatment Response

Figure 13.5. (A) Total choline levels in treatment responders and non-responders at baseline and after one cycle of chemotherapy. Responders have higher initial Cho levels and show a significantly greater decrease in Cho after treatment compared to non-responders. (B) An example of a decreasing Cho in a responder after 1 and 4 cycles of neoadjuvant chemotherapy (reproduced with permission from [3]).
Next Lecture: Hot Topics