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IMAGING

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Janet Cochrane Miller, D.Phil., Author Raul N. Uppot, M.D., Editor

# Magnetic Resonance Spectroscopy in the Brain

- Magnetic resonance spectroscopy (MRS) is a technique that detects metabolites, such as n-acetyl aspartate, choline-containing compounds, creatine/phosphocreatine, and lactate
- Measurements of metabolite ratios provide diagnostic information that adds to that obtained by MRI alone
- MRS can be valuable in
  - The diagnosis of leukodystrophies and mitochondrial disorders
  - Providing prognostic information in neonatal hypoxia/ischemia
  - Differentiating among brain tumors, staging, and identifying a suitable biopsy site
  - Differentiating between tumor progression and radiation necrosis
- In most cases, single voxel MRS is used to obtain chemical information from a region of interest measuring 2x2x2 cm; in multivoxel MR spectroscopic imaging (MSRI), the voxel size is 1x1x1 cm

Standard clinical MR images depend on magnetic resonance signals of hydrogen nuclei, which are present in very high concentrations in water and, to a lesser extent in lipids. Although other hydrogen-containing metabolites are present, their concentrations are too low to contribute significantly to the MR signal unless the water signal is suppressed. This can be achieved using a chemical-selective saturation radiofrequency pulse.

Because protons are shielded by their valence electrons, every proton group experiences a slightly different magnetic field and therefore resonates at different frequencies, measured as the chemical shift away from a reference standard in parts per million (ppm). These differences can be demonstrated by MR spectroscopy (MRS) as spectra whose peaks are attributable to particular metabolites. The appearance of the spectra depends on the settings on the scanner (Figure 1). For example, short TE spectra display peaks attributable to a wide variety of metabolites, including lipids and macromolecules, glutamate and glutamine, and myo-inositol (Figure 1A). Long echo time (TE) MRS, which is insensitive to lipids and macromolecules, is better at differentiating alanine and lactate (Figure 1B). Both long and short TE spectra show n-acetyl aspartate (NAA), choline-containing compounds (Cho), and creatine/phosphocreatine (Cr).

Metabolic information obtained by MRS can be helpful in diagnosis. NAA is only found in neurons and is a marker for neuronal density and viability. Phosphocreatine acts as a reservoir for the generation of ATP, which means that the Cr peak serves as a marker for energy-dependent systems. The Cho peak contains contributions from glycerophosphocholine, phosphocholine, and choline. Pathological changes in membrane turnover or rapid cell division increase the relative size of the Cho peak. Lactate (Lac) is not normally seen in the adult brain and its presence can be detected in cases of cerebral infarction, high-grade malignancy or mitochondrial disorders. These and other important metabolites detectable by MRS are shown in Table 1. Table 2 shows the changes in metabolites seen in a variety of different diseases.

**Table 1. Some Important Metabolites Seen in MRS**

| Metabolite | Major resonance (ppm) | Significance | Visible only at short TE |
|---|---|---|---|
| **Lipids (Lip)** | 0.8 - 1.4 | Breakdown of tissue | Y |
| **Lactate (Lac)** | 1.3 | Marker of anaerobic glycolysis | N |
| **NAA** | 2.0 | Marker of neuronal health | N |
| **Glutamate & Glutamine (Glx)** | 2.1 - 2.6 | Excitatory neurotransmitter | Y |
| **Cho** | 3.2 | Marker of membrane metabolism, cell proliferation | N |
| **Cr** | 3.0 (and 3.9) | Marker of cellular energetics | N |
| **Myo-inositol (MI)** | 3.5 | Osmolytic marker; proposed glial marker | Y |

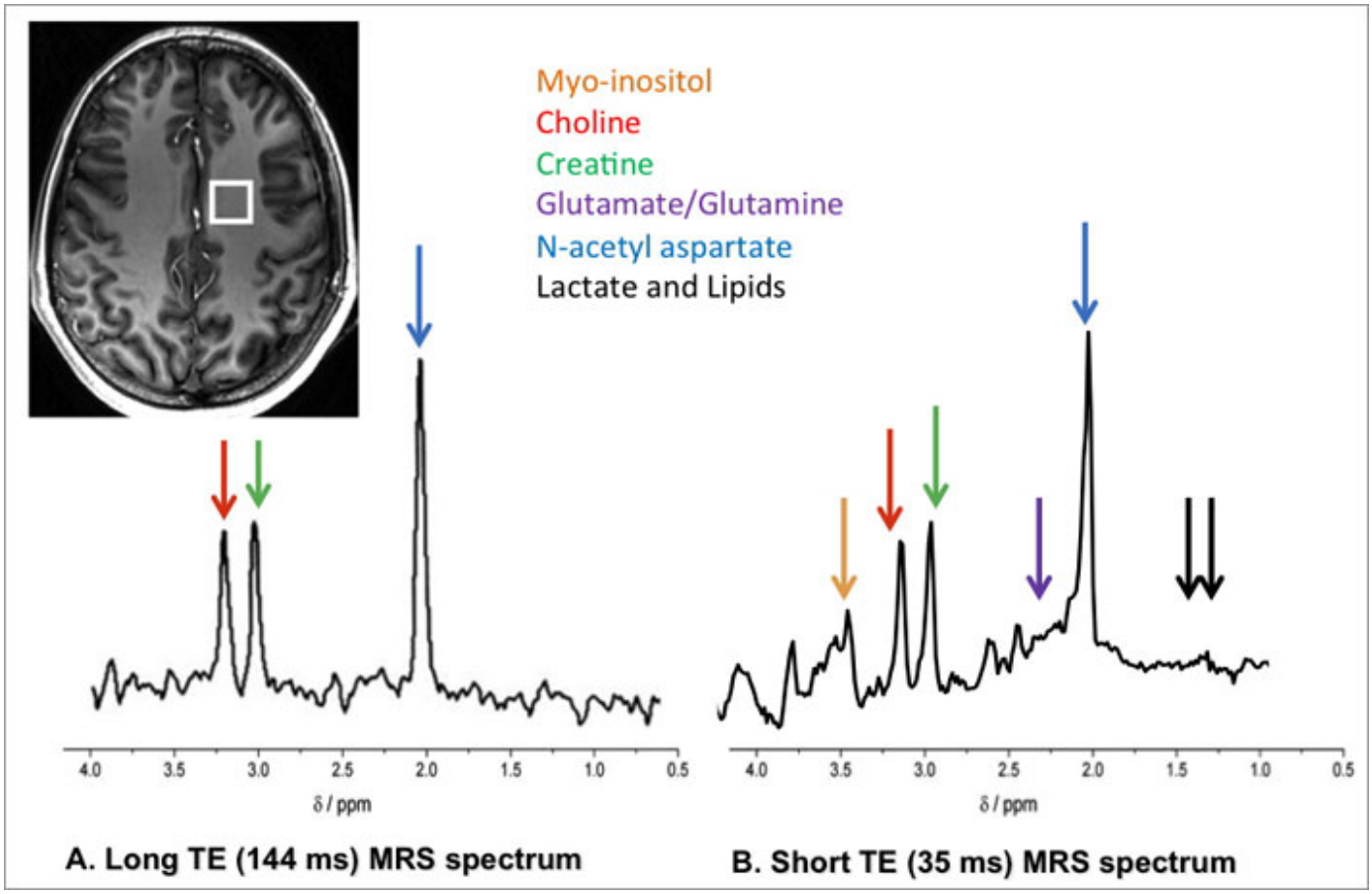


**Figure 1. MRS of white matter in a normal brain. (A)** Long TE spectra have less baseline distortion and are easy to process and analyze but show fewer metabolites than short TE spectra. Also, the lactate peaks are inverted, which makes them easier to differentiate them from lipids. **(B)** Short TE demonstrates peaks attributable to more metabolites, including lipids, glutamine and glutamate, and myo-inositol.

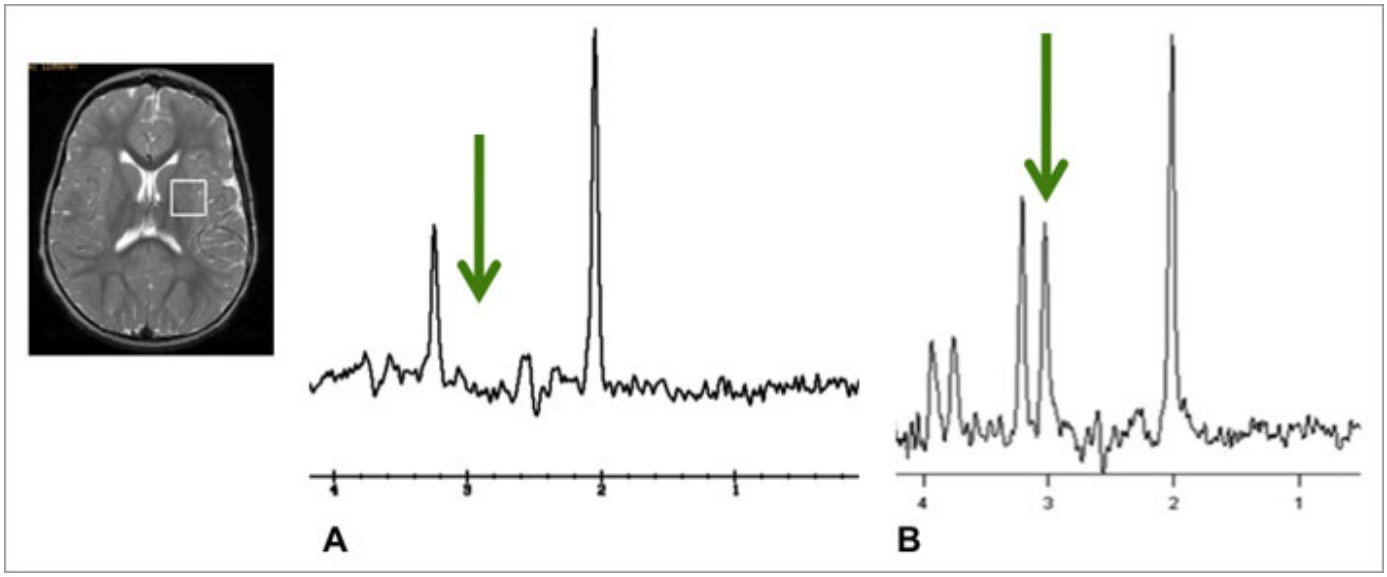


**Figure 2. (A)** MRS of a 2.5 y/o child with mental retardation, seizures and speech delay shows the absence of creatine, indicating a metabolic disorder. **(B)** Subsequent MRS after oral supplementation of creatine monohydrate corrects the deficiency, indicating that the disorder is due to the inability to synthesize creatine.

The area under the peak is proportional to the metabolite concentration. However, absolute quantification requires comparison to an external reference standard. Moreover, there are large inherent errors in estimates of absolute concentrations of metabolites. Thus, metabolite ratios, which are much more reproducible, are commonly used.

## Pediatric Leukodystrophies

A number of inborn errors of metabolism result in neurological disorders that are associated with white matter abnormalities. MRS can provide more specific information than MRI and can help in the diagnosis of many of these diseases.

For example, disorders that affect the metabolism of creatine can be diagnosed by MRS because there is an almost complete absence of the Cr signal in these patients while all other metabolites retain their normal pattern (Figure 2A). This abnormality can be observed when MRI does not show any pathology. Two of these diseases are caused by mutations in enzymes that are involved in creatine synthesis and can be treated by oral supplementation with creatine. The third is an X-linked disease that prevents the uptake of creatine into cells because of a mutation affecting the creatine transporter, which is not improved by oral creatine supplements. While MRS cannot distinguish among the three diseases in untreated patients, follow-up imaging after the commencement of creatine supplements restores the MRS to a more normal profile if the problem is due to a deficiency in creatine synthesis (Figure 2B). Failure to respond indicates that the metabolic error is due to creatine transport deficiency, which cannot be treated effectively at this time.

Canavan disease, or spongiform leukodystrophy, results from a deficiency of aspartocylase, an enzyme that hydrolyzes NAA to acetate and aspartate. In its absence, NAA accumulates in the brain. MRS is diagnostic for this condition because the abnormally high NAA peak (Figure 3) is almost exclusively seen in Canavan disease.

Another example is X-linked adrenoleukodystrophy, which results from a deficiency in acyl-CoA synthase, an enzyme that is essential for the breakdown of long-chain fatty acids. In its absence, inflammatory demyelination occurs, which is detectable by MRS because of decreased NAA and myo-inositol, and increased Cho and Cr. These abnormalities may appear while standard MR images appear normal, although a hyperintense signal in the white matter is characteristic as the disease progresses.

**Table 2. Changes in Metabolites**

| Disease | Metabolic Changes |
|---|---|
| Brain tumors | Cho↑, NAA↓, Cr↓, Lac and Lip↑ |
| Stroke | Lac↑, NAA↓, Glx↑, Cr↓, Cho↓ |
| Epilepsy | NAA↓, Lac↑ |
| Multiple sclerosis | NAA↓, Cho↑, (Cr↓) |
| HIV/AIDS | NAA↓, Cho↑, MI↑ |
| Traumatic Brain Injury | NAA↓, Cho↑, Lac↑ |
| Hepatic Encephalopathy | Cho↓, MI↓, Glx↑ |
| Hypoxic Ischemic Injury | Lac↑, NAA↓, Glx↑, Cr↓ |
| **Neurodegenerative diseases** | |
| Alzheimer | NAA↓, MI↑ |
| Parkinson | NAA↓ (Striatum) |
| Huntington | NAA↓, Cho↑ (Basal ganglia) |
| ALS | NAA↓ (Motor cortex, Brain stem) |
| **Pediatric Disorders** | |
| Canavan's disease | NAA↑ |
| Phenylketonuria | Phenylalanine (7.3 ppm )↑ |
| Nonketotic hyperglycinemia | Glycine (3.5 ppm)↑ |
| Maple syrup urine disease | Branched chain amino acids and oxo acids (0.9 1 ppm)↑ |
| Creatine deficiency | Absence of Cr |
| MELAS | NAA↓ / no NAA, Lac↑ |
| Leigh disease | Lac↑, Cho↑, NAA↓ |
| Alexander's disease | MI↑, Cho↑, Lac↑, NAA↓ |
| X-linked adrenoleukodystrophy | MI↑, Cho↑, Gln↑, Lac↑, Glu↓, NAA↓ |

## Neonatal Hypoxic/Ischemic Encephalopathy

MRS or MR spectroscopic imaging (MRSI) has proven valuable in evaluating neonates with hypoxic/ischemic injury (HII). In these patients, increased levels of lactate and a decrease in the ratio of NAA/lac, Cr/lac, and Cho/lac have been shown to be significantly different in neonates with HII who had poor outcomes at 1 year compared to those with normal or mild outcomes, as determined by a neurological assessment. Therefore, MRS can provide important prognostic information, which can help guide medical interventions and advise families on likely outcomes.

The presence of lactate, a marker for anaerobic metabolism should raise clinical suspicion of a mitochondrial disorder such as MELAS (Figure 4), Complex 1 deficiency and Leigh Disease.

## Brain Tumors

MRS can be valuable of the initial evaluation of brain tumors because of the different patterns of metabolites seen in tumors and because the abnormalities become more severe in advanced disease. Astrocytomas show a relative reduction in NAA and Cr, while Cho increases relative to other metabolites in the progression from normal white

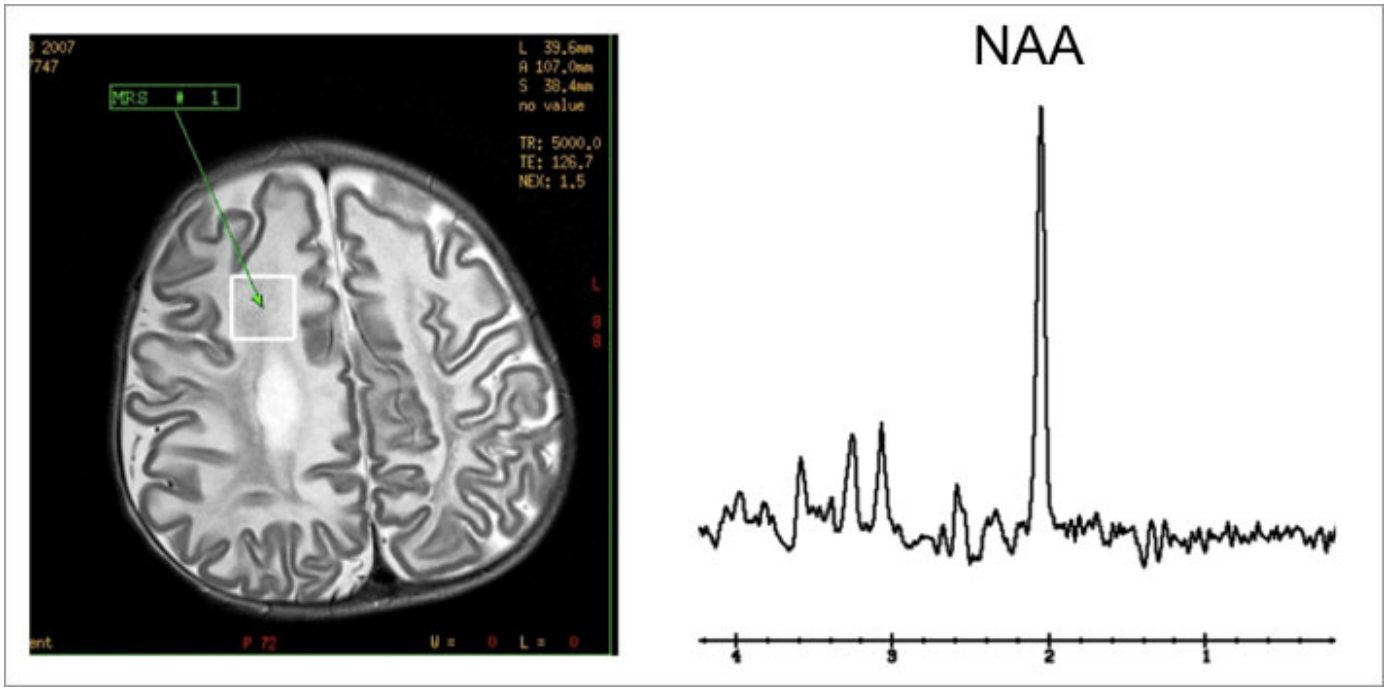


**Figure 3.** MRS of a child with Canavan disease. The NAA peak is abnormally high due to the inability to catabolize NAA.

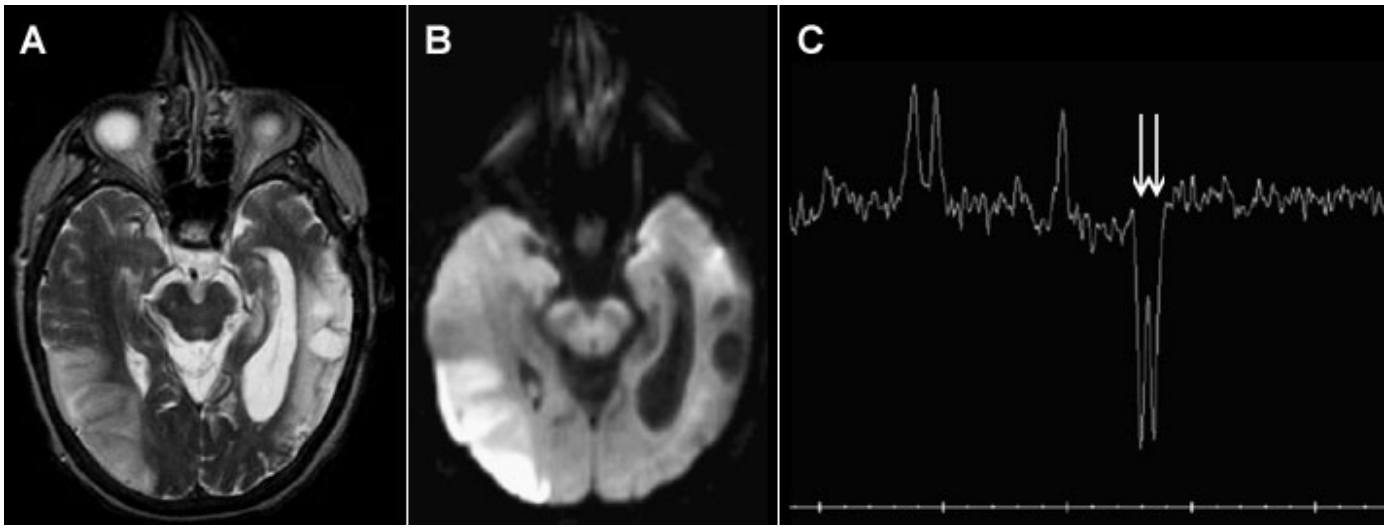


**Figure 4.** Patient with known diagnosis of MELAS (Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes) presenting with new onset of visual symptoms. **(A)** 1.5T brain MRI demonstrates areas of A. T2 hyperintensity and **(B)** abnormal restricted diffusion, likely related to stroke-like areas of cytotoxic edema. **(C)** MR spectroscopy (TE=144 ms) from the right occipital abnormality shows an inverted doublet at 1.3 ppm (arrows) consistent with a lactate peak.

matter to Grade III astrocytoma. In glioblastoma multiforme, some areas of the tumor may demonstrate a decrease in Cho, probably due to intratumoral necrosis. Abnormalities in the levels of alanine, lactate, and mobile lipids are also helpful in determining the grade of a glioma.

The spectra of metastases are similar to those of astrocytomas and lymphomas, with low NAA, low Cr, and high Cho levels. However, one study has shown that the pattern of lipid/macromolecules signals differ in metastases and astrocytomas.

MRSI can be very helpful in selecting a brain tumor biopsy site because the degree of metabolic abnormalities is more marked in areas with greater infiltration of cancer cells (Figure 5). In MSRI, data are gathered from several 1x1x1 cm voxels whereas single voxel MRS, the voxel size is typically 2x2x2 cm.

MRS is useful in follow-up imaging after treatment, where the differentiation between tumor recurrence and radiation necrosis is often difficult in conventional MRI. However, in some cases, the metabolic profiles are readily distinguished by MRS since a Cho/Cr ratio of >3 is associated with tumor progression and a ratio of <2 suggests tumor necrosis.

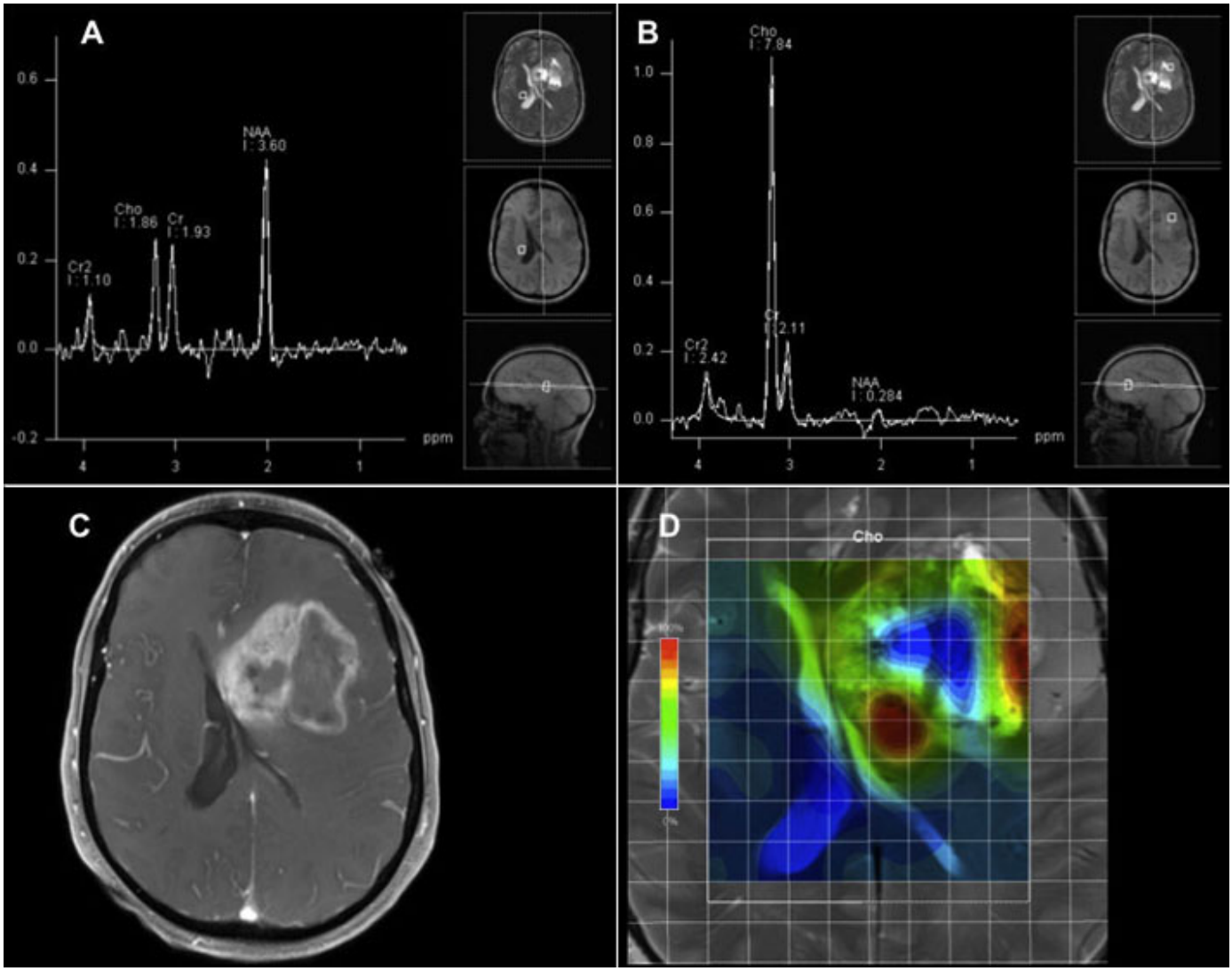


**Figure 5.** Patient with glioblastoma with oligodendroglioma component, WHO grade IV of IV. **(A)** MRS spectrum from region of brain not affected by the tumor. **(B)** Spectrum from a voxel within the tumor, showing elevated choline. **(C)** T1 MR image and **(D)** color-rendered MRS image showing variations in the levels of choline within the tumor.

## Pitfalls of MRS

MRS is a challenging technique and should only be used when spectral data will provide clinical information that is not obtained by other imaging techniques. The technique is very sensitive to inhomogeneities in the magnetic field and requires careful manual adjustment to ensure field uniformity. Artifacts can arise from braces on teeth or proximity to sinuses. If any bone is included in the voxel, it can cause artifacts due to the lipid signal arising from bone marrow. Because of the smaller voxel size and limitations in the length of time of image acquisition, MRSI data is noisier than single voxel MRS. MRS is also very sensitive to motion. To overcome these limitations of MRS, researchers and clinicians have 1) moved studies to higher field strengths to gain signal-to-noise ratio and to detect additional metabolites more reliably; 2) implemented faster MRSI sequences to overcome low spatial resolution and lengthy data acquisitions, and 3) applied motion corrected MRS acquisitions.

## Scheduling

Appointments can be scheduled by calling **617-724-9729** or through the Radiology Order Entry system, http://mghroe/. MRS is available at the main campus, the Mass General / North Shore Center for Outpatient Care, and at the Mass General Imaging Centers in Chelsea and Waltham.

## Further Information

For more information about MR Spectroscopy in the brain, please contact Eva-Maria Ratai, PhD, Neuroradiology, Mass General Hospital, (pager 30173 during office hours).

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