Neuroradiology: Using MR Spectroscopy and Perfusion Imaging to Increase Specificity of Diagnosis

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Learning Objective
- Improve accuracy in neuroradiology interpretation for difficult cases where anatomic imaging alone does not suffice

Topics
- Common applications of proton MR spectroscopy (MRS) and MR perfusion (MRP)
- Technical aspects
- Principles
- Avoiding interpretation pitfalls
- High-impact controversies in neuroimaging

Summary of Learning Points
- Imaging cannot be interpreted in isolation
- MRS and MRP are not perfect, but when used in conjunction with conventional imaging and clinical history they can be powerful tools
- Techniques have been around for a long time
  - Routine practice in many academic institutions and increasing in the community
  - Demand is present as it is being seen in the clinical literature in multiple specialties
  - Takes time and experience so better to embrace and be an early adapter

Benefits
- Narrow differential diagnoses
  - Ischemia, Infection, Inflammation, Metabolic, Neoplastic
  - Low grade, high grade, metastatic
  - Functional imaging often more sensitive and/or precedes conventional imaging1,2
- Diagnostic work-up
  - Optimal biopsy site
- Treatment guidance
  - Ischemic penumbra
  - Tumor follow-up
    - Residual or Progressive disease
    - Pseudoprogression
    - Radiation necrosis
    - Pseudoresponse
    - High grade transformation
**MRS technical**

- Voxel
  - Single voxel – quick, SNR, more accurate
  - Voxel size and location
  - Multivoxel (MRSI) – spatial distribution
- Echo time
  - Short TE (20–40ms)
    - ↑ SNR
    - More metabolite peaks (lip, glx, myo, some macromolecules)
  - Intermediate to long TE (135 – 288ms)
    - More simple spectra
    - Lactate inverted at 135-144ms
- Field strength
  - 3T ↑SNR, spectral resolution, and ↓ acquisition time

**Metabolites**

Major:
- Lipids (Lip) – [0.9-1.3] Cell breakdown
- Lactate (Lac) – [1.3] Anaerobic metabolism
- N-acetylaspartate (NAA) – [2.0] Neuronal marker
- Creatine (Cr) – [3.0] Energy metabolism
- Choline (Cho) – [3.2] Cell membrane turnover
- Myoinositol (Myo) – [3.5] Glial cell marker

Minor, but relatively specific:
- Alanine (Ala) – [1.48] Meningiomas
- Glutamate/Glutamine/GABA (Glx) – [2.05-2.5] Meningiomas, hepatic encephalopathy
- Acetate [1.9] and Succinate [2.4] - Microorganism anaerobic metabolism
- Amino acids such as valine, leucine, and isoleucine – [0.9] products of proteolytic enzymes

**MRS Principles**

- ↑ Cho (Cho/Cr; Cho/NAA) = neoplasm, gliosis, inflammation
- ↑↑ Cho = high grade neoplasm
- ↑ Lipid-lactate = cell breakdown; anaerobic metabolism
- ↑ Cho in perilesional region = infiltrating neoplasm
- ↓↓ NAA = high grade neoplasm or secondary process
- ↑ Myo = low grade neoplasm, gliomatosis, MS, AD, FTD, HIV
- Infection
  - Succinate (2.4) and acetate (1.9)
  - Valine, leucine, and isoleucine (0.9)

**MR perfusion technical**

- Techniques
  - Dynamic Susceptibility Contrast Enhanced (DSC)
  - Dynamic Contrast Enhanced (DCE)
  - CT perfusion (CTP)
  - Arterial Spin Label (ASL)
- Parameters
  - Cerebral blood volume (CBV)
  - Mean Transmit Time (MTT)
  - Cerebral Blood Flow (CBF)
  - Tmax
  - Transfer constant (kTrans)

**Spectra**

- X axis – chemical shift of metabolites in ppm from right to left
- Y axis – relative amplitude

**DSC source cine**
**MRP Tumor Principles**

- Tumors
  - Contrast enhancement = BBB breakdown
  - First pass perfusion (CBV) = neoangiogenesis/vascularity
  - ↑ CBV
    - Tumor (lymphoma exception)
    - Higher grade
    - Recurrent or residual neoplasm
    - High grade transformation

**MRP Stroke Principles**

- Ischemic core – tissue irreversibly injured that will proceed to infarction despite immediate reperfusion
- Ischemic penumbra – salvageable tissue at high risk to proceed to infarction without early reperfusion
- PWI – DWI mismatch = ischemic penumbra
  - Hypoperfused Tissue (Tmax > 6 sec) – Ischemic core (diffusion restriction) = ischemic penumbra

**CTP Principles**

- CTP = Hypoperfused tissue (↑MTT) – Ischemic core (↓CBV) = ischemic penumbra (Wintermark et al, Stroke 2006)
  - Hypoperfused tissue:
    - rMTT > 145%
    - Tmax > 6 sec
    - TTP > 4 sec
    - CBF < 20ml/100g/min
  - Ischemic core:
    - CBV < 2ml/100g
    - CBF < 10-20ml/100g/min

**Case 1:** h/o Afib woke up (0430?) with aphasia and right sided weakness p/w NIHSS 8
Q1. At least 8 hrs from ictus and clinically improving:
What would you do next?
A. Get the NIR team ready for endovascular tx
B. Call for an ICU bed to monitor post IV tPA
C. Tell the ER the pt can go home
D. Advise clinical correlation, sign off report, and block any calls from neurology
E. None of the above.

What happened?
- Outside IV tPA window (>4.5hrs)
- Debate between CTP results
- Pushing time limits of endovascular tx
- Decision was made not to take to angio
- HTN tx with neosynephrine gtt
- Continued to improve with 6 mos f/u – 90% speech; weakness nearly resolved; mild residual dypraxia, neglect, and dysesthesias

6 mos f/u MRI:

Determination of tissue viability based on imaging has the potential to individualize thrombolytic therapy and extend the therapeutic time window for some acute stroke patients. Although perfusion imaging has been incorporated into acute stroke imaging algorithms at some institutions, its clinical utility has not been proved.
CTP in Kaiser San Diego

- Wake-up strokes and/or unknown onset
- Utilize increase sensitivity for ischemia in patients unable to get MRI
- Cerebrovascular reserve in chronic stenoses
- Tumor imaging

Case 1

Q2. Diagnosis please:

A. Evolving hematoma
B. Subacute infarct
C. Atypical abscess
D. Glioblastoma
E. Tumefactive plaque

KEY POINTS

\[
\text{Cho/Cr > 1.7 and/or Cho/NAA > 2} \quad \text{~ high grade neoplasm}
\]

\[
\text{rCBV > 2} \quad \text{~ high grade neoplasm}
\]

\[
\text{Lipid/lactate} \quad \text{~ high grade neoplasm}
\]

\[
\text{↑ Cho or ↑ rCBV in perilesional region} \quad \text{~ primary neoplasm}
\]

Case 2 MRP and MRS

\[
\text{↑ rCBV 4x at periphery and nodule}
\]

Case 3: Gr II Oligo–astrocytoma

6 mos later – confirmation of recurrence/high grade transformation

KEY POINTS

Enhancement with ↑ rCBV = tumor recurrence/progression

\[
\text{nl/↓ rCBV = XRT necrosis}
\]

\[
\text{↑/↑ NAA, Cho, Cr and +/- lactate} \quad \text{~ XRT necrosis}
\]
Q3. Diagnosis please:
A. Sarcoidosis
B. Subacute infarct
C. Capnon
D. Kikuchi’s
E. Histoplasmosis
F. Atypical meningioma
G. Breast cancer met

KEY POINTS
Infarction ➔ ↓ rCBV
Lactate (1.3 ppm) ➔ anaerobic metabolism
Succinate (2.4 ppm) ➔ Infection
Trehalose (3.6–3.8 ppm) = Fungal

Law et al. AJNR 2003; 24

Fig 1: Non-enhancing tumor
Fig 2: Rim-enhancing tumor with blood products

Tumor Grading

Case 4: Stroke code

Q4. Diagnosis please:
A. MCA stroke
B. Herpes encephalitis
C. Oligodendroglioma
D. Glioblastoma
E. Lymphoma

Case 4: Cortical restricted diffusion one week prior

Case 4 SVS
**Case 5**

![Image of Case 5](image1)

**Tumor grading exceptions**
- Low grade tumors with possible aggressive features on MRP and/or MRS:
  - Oligodendroglioma
  - Central neurocytomas
  - Pilocytic and pilomyxoid astrocytomas
  - Dysplastic cerebellar gangliocytomas

**Case 6**

![Image of Case 6](image2)

**Case 6 MRP and MRS**

![Image of Case 6 MRP and MRS](image3)

**Q5. Diagnosis please:**
- A. Glioblastoma
- B. Anaplastic oligodendroglioma
- C. Grade II oligodendroglioma
- D. Lymphoma
- E. Demyelinating disease

**Q6. Diagnosis please:**
- A. Metastatic disease
- B. Lymphoma
- C. Glioblastoma
- D. Demyelinating disease
- E. Abscess
- F. Evolving hematoma
- G. Evolving infarct
Balo’s Concentric Sclerosis

- Rare variant of MS
- Lesions consist of rings of demyelination alternating with rings of intact myelin
- Traditionally a rapidly fatal disease, but now thought to have three subtypes:
  - Self-limited, monophasic illness
  - Relapsing–remitting demyelination
  - Primary rapidly progressive

Q7. Diagnosis please:

A. Demyelinating disease
B. Susac’s syndrome
C. Lymphoma
D. Metastatic disease
E. Multifocal glioblastoma
F. Abscesses

**KEY POINTS**
- Active TDL can have aggressive appearing A140-150
- Subtle signs on conventional imaging most often helpful

Q8. Diagnosis please:

A. Demyelinating dz
B. Lymphoma
C. Metastases
D. Glioblastoma
E. Abscesses

**KEY POINTS**
- Very low ADC in the central cavity favors abscess whereas lower degrees of restricted diffusion peripherally are typically found in neoplasms.
- 1HCho can be seen in infection too.
- Succinate (2.4ppm) peak can be subtle and easily missed
Case 9: 66yo with AMS

Q9. Diagnosis please:
A. PRES
B. HSV
C. CLIPPERS
D. CADASIL
E. MELAS
F. GBM
G. DNET

KEY POINTS
Disease is not excluded in the absence of typical AI findings
Cortex is not ideal for AI because of field inhomogeneity
Basal ganglia is suboptimal d/t susceptibility from mineralization
Older patient age group favors high grade neoplasm

Case 10: H/o lung CA with normal brain MRI one year prior.

Case 10: SVS

Case 10: 2D MRSI

Case 10: Metabolite maps
Case 10: MRP

Q10. Diagnosis please:
A. Lung CA met
B. Tuberculoma
C. Neurocystercosis
D. Bacterial abscess
E. I don’t know

KEY POINTS
MRSI has the advantage of showing distribution of metabolites
Bayes' theorem: Posttest odds = Pretest Odds x Likelihood Ratio

Case 11: Metastatic lung CA with weakness and thrombocytopenia s/p fall

Case 11: MRP and MRS

Case 11: MRS cont.

Q11. Diagnosis please:
A. Small cell metastasis
B. Subacute infarct with petechial hemorrhage
C. Hemorrhagic contusion

KEY POINTS
Diffusion restriction can be seen in highly cellular tumors
Preserved NAA in metastatic brain tumors is likely due to sampling adjacent normal brain
Case 12: Metastatic melanoma

9/13: 5mos post stereotactic XRT

10/13: 6 mos post XRT
MRP and MRS

11/13 CTP: 7 mos post XRT

1/14: 9 mos post XRT

Key points

- Post-radiation effects/XRT necrosis may show increase in lesion size, thick enhancement, vasogenic edema, and mass effect
- AI is very helpful in this setting, particularly MRP
- When there is question of false negative results due to susceptibility artifacts, DCE MRP and CTP are alternatives
Glioblastoma is the most common primary malignant neoplasm in adults and is associated with a very poor prognosis. Current standard care:
- Maximal surgical resection
- Radiotherapy
- Concomitant and adjuvant temozolomide (TMZ)

EORTC/NCIC trial: RT vs RT+TMZ
- Median survival 12.1 mos vs 14.6 mos
- 5 year survival 1.9% vs 9.8%
- No negative impact on QOL

Bevacizumab, an anti-VEGF agent, received FDA approval for recurrent glioblastoma in 2009

Because of the relatively recent standardization of treatment, certain imaging patterns have become better appreciated. Pseudoprogression – Radiographic worsening from the first few weeks to up to 6 months after RT followed by improvement or stabilization without further tx.
- Most often asymptomatic or mild sx
- Seen in 38% in RT alone and 53% in RT+TMZ
- Associated with methylated MGMT promoter with both being positive px factors

Malignant glioma tx
- Glioblastoma is the most common primary malignant neoplasm in adults and is associated with a very poor prognosis.

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Pseudoprogression

- Rapid decrease in contrast enhancement after the administration of antiangiogenics
  - Frequently associated with clinical improvement, but with modest improvement in overall survival
  - “Pseudo” because radiographic response primarily from decreased permeability and edema with smaller component of antitumoral effect
  - Increase to 46% 6-mos progression free survival in recurrent GBM (vs 21% with TMZ alone)

Pseudoresponse

- Increase/new enhancement at initial or satellite sites, often linear or wispy
- Increase in T2 signal and gyral swelling
- INCREASE/NEW areas of diffusion restriction
- Advanced imaging:
  - MRS tumor spectra in area of NEW signal abnormality
  - DSC/DCE normalizes on antiangiogenics so less sensitive, but if it does not decrease or actually increases then worrisome

Imaging patterns of antiangiogenic tx failure

- Increase/new enhancement at initial or satellite sites, often linear or wispy
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6/12 s/p bevacizumab and carboplatin


6/13 Restart of bevacizumab and carboplatin

12/13 Progression confirmed on MRS

10/12 New restricted diffusion called ischemic change.

3/11 ER visit for neuro changes

Case 16: 64yo h/o stroke and TIA p/w aphasia on 11/10

Ddx: subacute PCA infarct vs HSV or encephalitis. NL LP, tx acyclovir. Clinic f/u few weeks later, reported improvement, but told residual sx may take some time to completely resolve.

Interval 50% debulk. RT+TMZ on 6/11, but changed to bevacizumab and carboplatin soon after for new nodule. Relatively stable for over a year.
3/13: Imaging and clinical progression

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