



New Approaches to Neuroimaging of Progressive Multifocal Leukoencephalopathy

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What is Progressive Multifocal Leukoencephalopathy (PML)?

- A demyelinating disease of the CNS caused by reactivation of the JC virus in immunocompromised patients
- PML is typically seen in AIDS patients, transplant recipients, and leukemia patients
- 80% of normal adults have anti-JC antibodies indicating that exposure to JC virus is almost universal
- Diagnosis of PML is by PCR of cerebrospinal fluid (CSF)
 - 70-100% sensitive
 - 92-100% specific
- If the PCR test is negative but clinical suspicion is high a brain biopsy can be used to confirm the diagnosis



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What is the clinical presentation of PML?

- The most common presenting symptoms are:
 - focal or generalized weakness (50-63%)
 - gait disturbance (32-43%)
 - cognitive dysfunction (29-55%)
 - speech disturbance (21-50%)
 - seizures (5-23%)
 - visual disturbance (30-50%)
- In AIDS patients the incidence is 2-4%, typically presenting after the CD4 count falls below 100 cells/ μ l.
- The only effective treatment is highly active anti-retroviral therapy.
- Average survival without treatment is 2.5 months.
- Average survival with HAART is over 2 years but 50% will die within 3 months of diagnosis.



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Patient “C.A.”

- A 38yo HIV+ male presents with 8 weeks of progressive dysarthria, dysphagia, and gait difficulty.
- He was hospitalized in Chicago for 4 weeks and then requested a transfer to Boston to be close to his family.
- Per outside hospital records he was diagnosed with PML and started on highly-active antiretroviral therapy (HAART) 4 weeks prior to his transfer to Boston.
- On exam he was profoundly dysarthric without aphasia, and had a lateral rectus palsy on the right as well as poor finger-to-nose coordination bilaterally.



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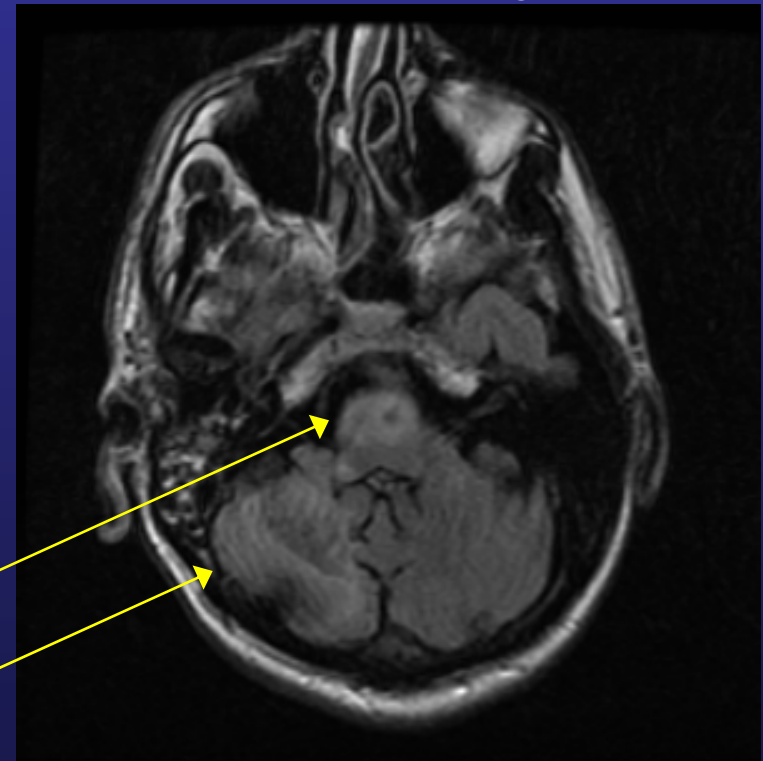
Patient "C.A." (cont.)

FLAIR imaging: there is a hyperintense lesion of the pons bilaterally extending into the right cerebellar hemisphere

bilateral pontine hyperintensity

right cerebellar hyperintensity

Axial FLAIR image



Courtesy of Dr Santosh Kesari, BWH



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Patient "C.A." (cont.)

T1-post: There is a hypointense lesion of the right cerebellar hemisphere that does not extend into the pons

There is no Gadolinium enhancement.

There is no mass effect in the posterior fossa.

axial T1 post-Gadolinium image



right cerebellar hypointensity



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What are the typical findings in PML patients?

| Finding | Frequency |
|----------------------------|-----------|
| Cortical Atrophy | 68.8% |
| Ventricular Dilatation | 50.1% |
| White Matter Lesions | 100.0% |
| Supratentorial Lesions | 93.8% |
| Parietal Involvement | 93.2% |
| Temporal Involvement | 33.3% |
| Infratentorial Lesions | 58.3% |
| Pons Lesions | 82.2% |
| Middle Cerebellar Peduncle | 64.3% |
| Cerebellar white matter | 57.1% |
| Gray Matter Lesions | 56.3% |
| Thalamus | 92.6% |
| Mass effect | 10.4% |

(Post, M.J.D et al, 1999)



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Do neuroimaging findings correlate with survival in PML patients?

- Post et al., 1999: examined 48 patients with biopsy-proven PML in the absence of HAART
 - no imaging findings correlated with survival except for mass effect which was found in only 10% of patients and which indicated a poor prognosis



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What are the typical MR findings in PML patients?

- High intensity white matter lesions on T2/FLAIR with or without matching T1 hypointensities
 - Hyperintense T2 signals represent increased water content corresponding to inflammation, gliosis, edema, demyelination, remyelination, Wallerian degeneration and axonal loss
 - Hypointense T1 signals represent reversible edema, inflammation and demyelination or irreversible tissue damage due to demyelination and axonal loss
- Low intensity T1 lesions help to differentiate PML from HIV encephalopathy
- PML lesions do not enhance with Gadolinium reflecting an intact blood-brain-barrier



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*Differential Diagnosis of T2-bright, T1-dark
Brainstem Lesion without Mass Effect*

- Amyotrophic Lateral Sclerosis
- Low-grade Glioma
- Infarct
- Small Vessel Ischemic Changes
- Lupus Erythematosus
- Multiple Sclerosis
- Central Pontine Myelinolysis
- PML
- Shearing Injury
- Wallerian degeneration

(Reeder and Felson's Gamuts in Radiology, 2003)



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Differential Diagnosis of T2-bright, T1-dark Sub-Cortical Lesions without Mass Effect

- Embolic infarct
- PML
- Shearing injury
- Tuberos Sclerosis

(Reeder and Felson's Gamuts in Radiology, 2003)



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How do the MR findings progress in untreated PML?

data from 15 patients with a mean survival of 2.5 months

| Finding | Frequency |
|--|-----------|
| Worsening of MR findings | 86.7% |
| Increasing Cortical Atrophy | 73.3% |
| Increasing Ventricular Dilatation | 53.3% |
| Parenchymal Lesion Progression | 73.3% |
| New Sites of Involvement | 100.0% |
| Corpus Callosum | 45.4% |
| Gray Matter | 36.4% |
| Posterior Fossa | 36.4% |
| Increasing Size and Confluence of White Matter Lesions | 66.7% |
| Development of Mild Mass Effect | 6.7% |
| No Significant Disease Progression | 13.3% |

(Post, M.J.D et al, 1999)



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Does HAART Treatment affect the MR Findings?

- Study of 2 long-term and 2 short-term survivors of PML with HAART:
 - short-term survivors had more extensive white matter lesions on MR prior to initiating therapy in spite of having a similar level of immunosuppression
 - both short-term and long-term survivors showed increased T1 hypointensity over time probably representing demyelination
 - long-term survivors showed diminished FLAIR signals over time - probably representing necrosis from the demyelination which occurred prior to initiation of HAART
 - short-term survivors showed increased FLAIR signals over time - probably representing progressive destruction

(Thurnher et al., 2001)



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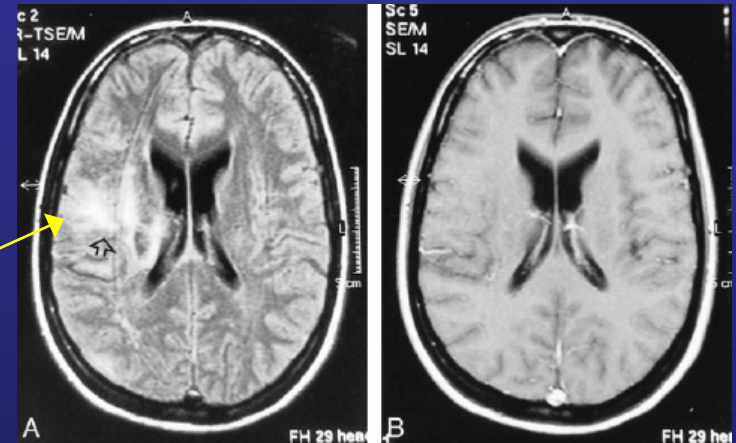
Progression of PML lesions in a long-term survivor (22 months) treated with HAART

Dec 1998: High signal intensity lesion in the white matter of the right centrum semiovale. No mass effect. No enhancement on contrast-enhanced T1WI.

centrum semiovale hyperintensity

axial FLAIR

axial T1+Gd

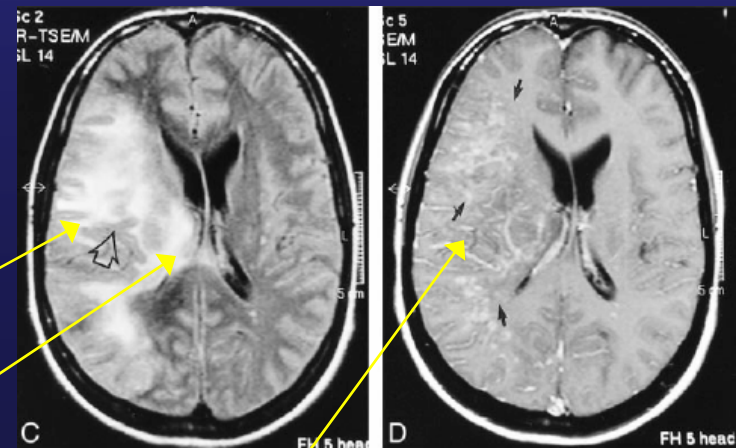


Jan 1999: Progression of white matter abnormalities with mass effect and compression of R ventricle. Diffuse enhancement of white-matter abnormalities on contrast-enhance T1WI.

progression of white matter changes

mass effect in right ventricle

T1 enhancement



(Thurnher et al., 2001)



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Progression of PML lesions in a long-term survivor (22 months) treated with HAART

Feb 2000: Further progression of high-intensity lesions of white matter disease on FLAIR. There is also slight enhancement on contrast-enhanced T1WI with increased hypointensity and regression of mass effect.

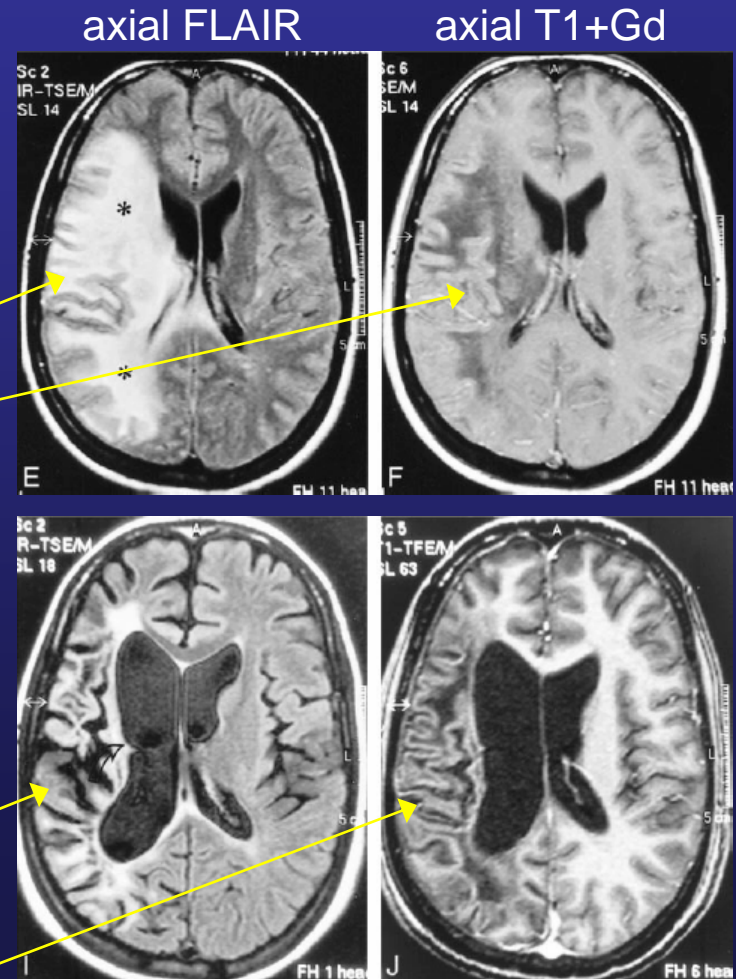
progression of white matter disease

T1 enhancement and hypointensity

Sept 2000: FLAIR image reveals regression of white matter changes (representing leukomalacia) with hypoattenuation on T1-weight images. Note the atrophic changes in the right hemisphere with widening of the sulci and ex-vacuo widening of the right ventricle.

regression of white matter changes

atrophic changes



(Thurnher et al., 2001)



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How can we improve the radiologic diagnosis of PML?

- Diffusion-Weighted Imaging (DWI):

- measures the diffusion of water in living tissues
- diffusion techniques can also be used to image the “anisotropic” (ie non-random) behavior of water molecules which diffuse in specific directions due to the constraints of their environments - ie along axons rather than across myelin membranes
- highly mobile water appears black on DWI
- diffusion-restricted water appears bright on DWI



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What is Diffusion-Weighted Imaging (DWI) used for?

- DWI can to distinguish intracellular (cytotoxic) from extracellular (vasogenic) edema:
 - cytotoxic edema is typical of acute cell damage as in acute ischemia which causes restricted diffusion within 10 minutes of symptom onset - this is a useful tool in acute stroke as normal MR and CT changes are only seen after 4-6 hours
 - vasogenic edema is caused by damage to the blood-brain barrier and is typical of neoplasms, infections and hypertensive encephalopathy, all of which increase diffusion
- PML lesions appear as large areas of restricted diffusion with some increased diffusion at the center of old lesions - this pattern is not typical of other infections



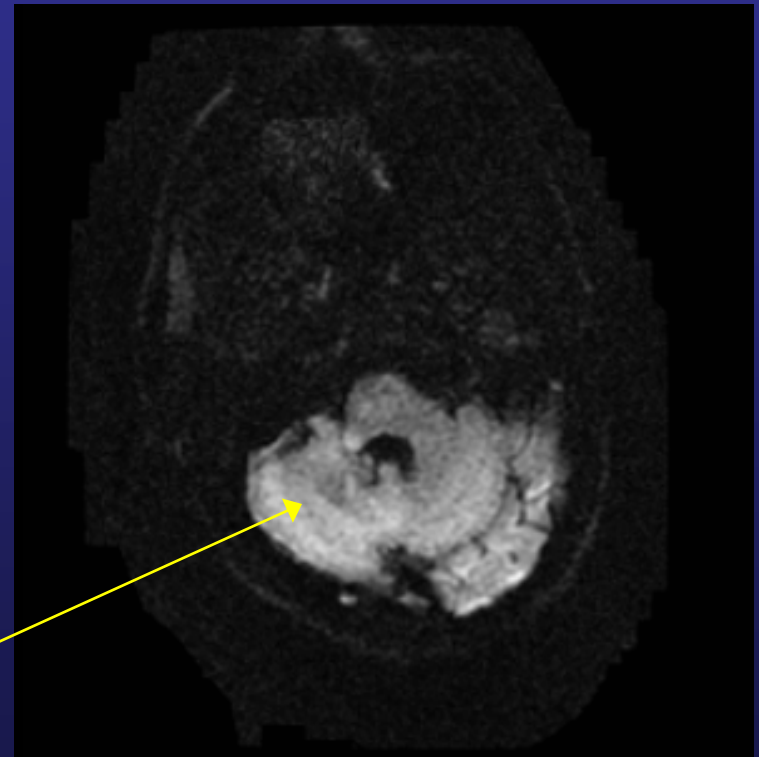
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What is Diffusion-Weighted Imaging (DWI) used for?

On DWI the right cerebellar T2-intense lesion appears hyperintense at the periphery and hypointense centrally.

axial DWI of "C.A."



hypointense DWI lesion with hyperintense periphery



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What is the Apparent Diffusion Coefficient (ADC)?

- Diffusion-weighted images suffer from “shine-through” due to a T2 component to the image
- ADC eliminates “shine-through” by comparing two DW images that are differently sensitized to diffusion but identical in other parameters
 - the images are subtracted to eliminate the effects of T1 and T2 signals and isolate the diffusion data
 - restricted diffusion (as in cytotoxic edema) appears “bright” on DWI and “dark” on ADC
 - increased diffusion (as in vasogenic edema) appears “dark” on DWI and “bright” on ADC



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What do PML lesions look like on ADC?

- In ADC characteristic focal PML lesions display:
 - a center of increased diffusion indicating vasogenic edema due to completed tissue injury (ADC hyperintense, DWI hypointense)
 - a peripheral rim of reduced diffusion indicating cytotoxic edema due to progressive injury (ADC hypointense, DWI hyperintense)

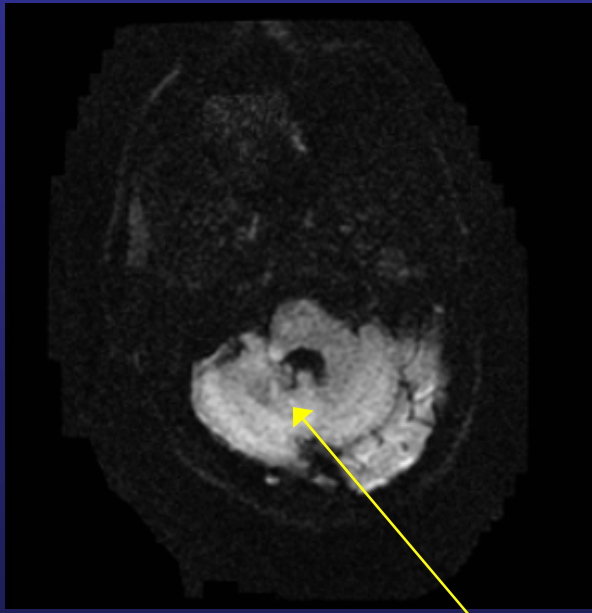


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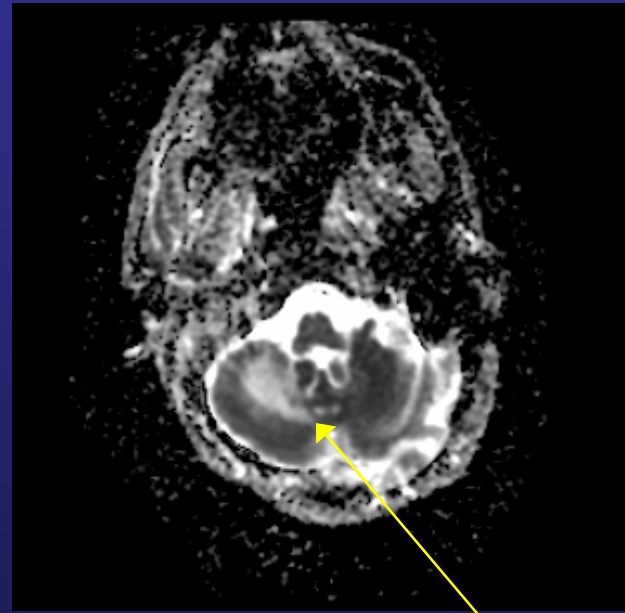
What do PML lesions look like on ADC?

axial DWI of "C.A."



The PML lesion is DWI hypointense with a hyperintense peripheral rim.

axial ADC of "C.A."



The PML lesion is ADC hyperintense with a hypointense peripheral rim.



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Are there any techniques that can be used to assess the prognosis of PML patients?

- MR Spectroscopy:

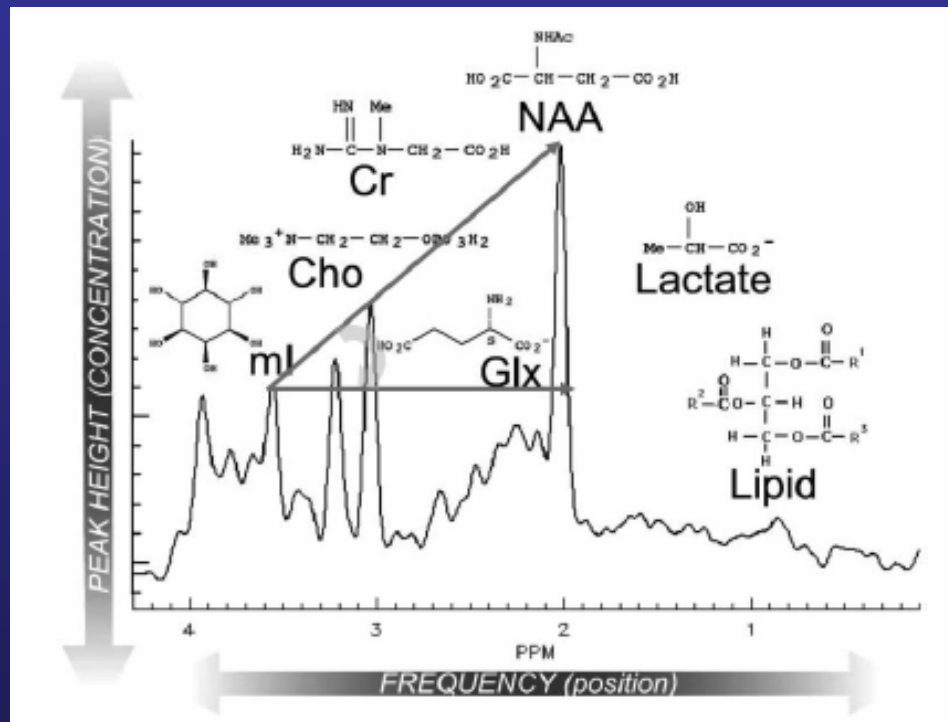
- a technique which combines the spatial resolution of magnetic resonance imaging (MRI) with the spectroscopic information of nuclear magnetic resonance (NMR)
- can be performed with a standard MRI scanner
- the radio frequency spectrum is acquired as the proton spins are returning to their normal alignment in the magnetic field after disruption by a radio frequency pulse
- the radio frequencies emitted by the relaxing spins are characteristic of different molecules and can be recorded and provide a molecular “signature” for the tissue



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What is MR Spectroscopy?



A representative MR spectroscopy scan of normal human brain tissue. The curved arrow represents Hunter's angle (HA) which connects the peaks for myoinositol (ml), Creatinine (Cr), Choline (Cho) and N-acetylaspartate (NAA) and which is normally 45° in human brain tissue.

(Lin et al., 2005)



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What are the peaks in MR Spectroscopy?

•Order of peaks =

“Lying, Lazy, No Good Crooks Collected My Insurance”

- Lipid: not detected in healthy brain - indicates necrosis
- Lactate: not detected in healthy brain - indicates hypoxia
- n-acetylaspartate: neuronal amino acid - indicates viable neurons
- Glutamate/Glutamine: neurotransmitters involved in the Krebs cycle - indicate hypoxia
- Creatine: a constant
- Choline: umbrella term for myelin components - indicates alterations in membrane turnover as seen in tumor or MS
- Myoinositol: a brain osmolyte and glial marker - indicates tumor, MS, dementia, hyponatremia, and hepatic encephalopathy as well as gliosis and inflammation



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What are the findings for PML on MR Spectroscopy?

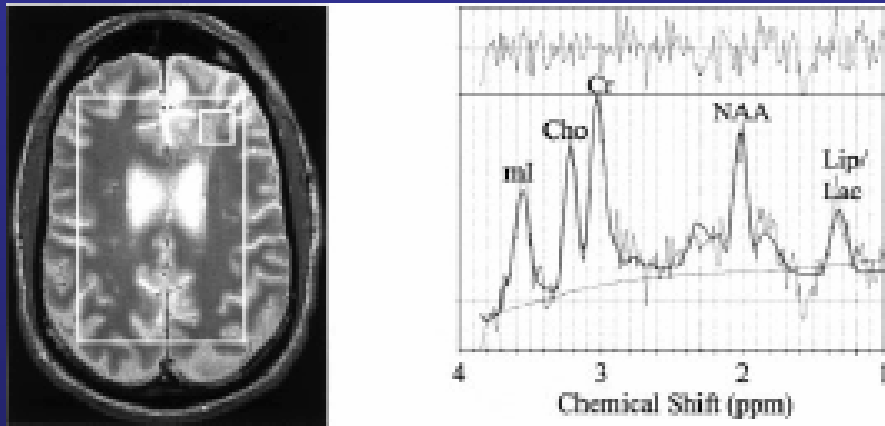
- MR spectra of acute PML lesions in patients who are long-term progressors differ from those of long-term survivors:
 - survivors show a higher ratio of ml:Cr than progressors suggesting increased inflammation in survivors
 - there is no significant difference in NAA:Cr ratios or Cho:Cr ratios between survivors and progressors
 - survivors were also found to have JCV-specific CD8+ T cells in peripheral blood



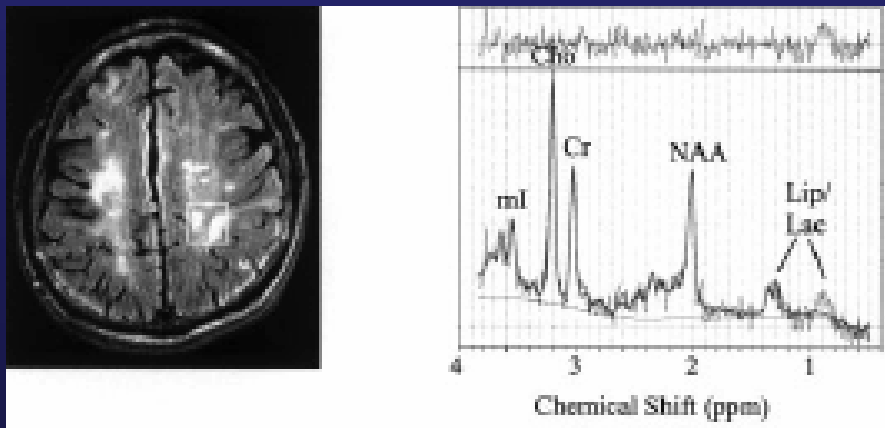
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What are the findings for PML on MR Spectroscopy?



MR Spectroscopy of a PML survivor showing a high ml:Cr ratio. The spectrum corresponds to the small white box on the MR image.



MR Spectroscopy of a PML progressor showing a low ml:Cr ratio. The spectrum corresponds to the small white box on the MR image.



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An example of real-life MR spectroscopy...

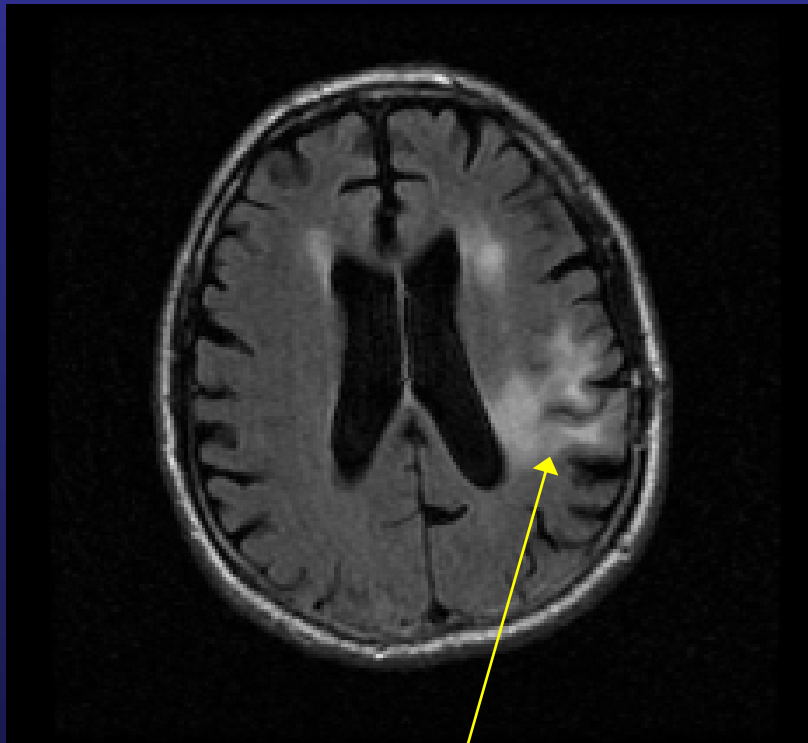


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Patient "F.G."

axial T2WI



hyperintense parietal lesion

A 70 yo M diagnosed with CLL 3 years prior who presented with clumsiness of the right hand

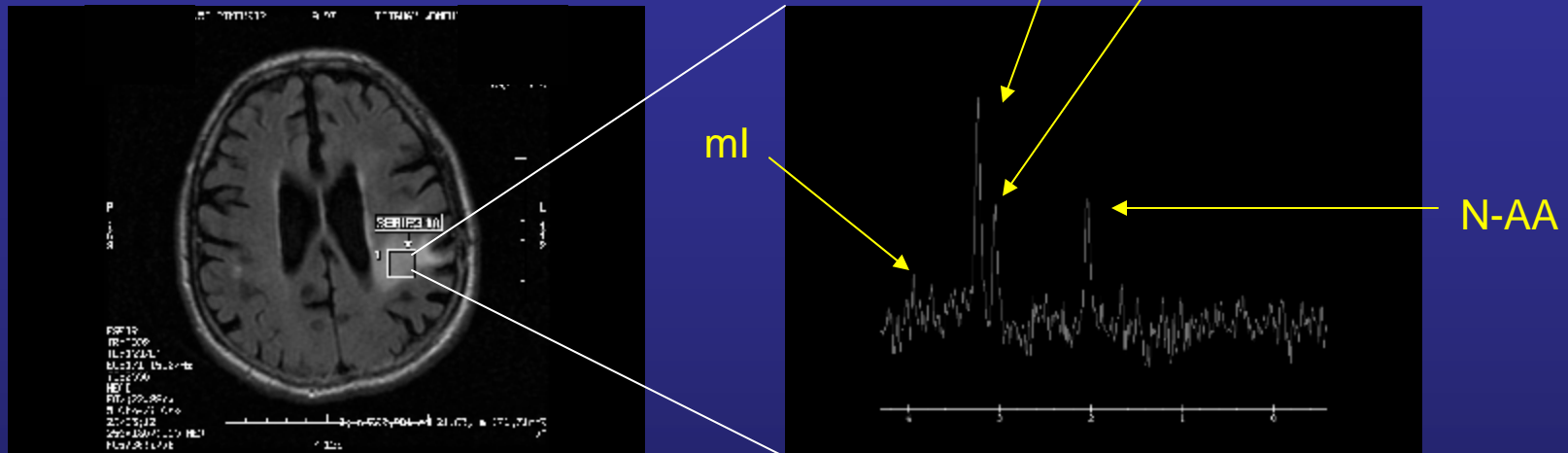
T2WI: multiple foci of abnormal T2 intensity in the left hemisphere, primarily in the left parietal lobe including the post-central gyrus, and also in the corona radiata anteriorly.



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Patient "F.G." (cont)



- MR Spectroscopy of the left parietal lobe of F.G. demonstrating an increased choline to NAA ratio

- NAA is an axonal marker while Cho is a cell membrane marker that is elevated in the context of demyelination thus an elevated choline to NAA ratio is a non-specific marker of demyelination and is observed in PML and MS lesions as well as in neoplastic processes

-n.b. - the ml/Cr ratio was not measured but the ml peak is noticeably small



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Conclusions

- PML lesions are hyperintense on T2WI and FLAIR, and may be iso- or hypointense on T1WI
- On diffusion-weighted imaging PML lesions have a core of increased diffusion (representing vasogenic edema) surrounded by a rim of decreased diffusion (representing cytotoxic edema) which differentiates them from other neurologic infectious processes.
- On MR spectroscopy a high myoinositol to creatinine ratio is characteristic of PML lesions in PML survivors which may prove to be a tool for estimating PML prognosis.



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