Detection of Opportunistic Infections & Paradoxical Reactions

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MS Treatment

1st line agents (Interferons)

- Relative risk reduction 30%
- Absolute risk reduction 0.3 relapses/y

Baldwin Curr Opin Neurol 2013

Natalizumab

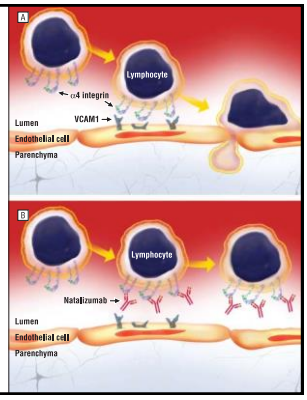
Humanized monoclonal antibody

→

α4-integrin

cellular adhesion molecule

Rudick JAMA Neurol 2013



MS Treatment

Natalizumab

- Relative risk reduction **68%**
- Absolute risk reduction 0.55 relapses/y

Baldwin Curr Opin Neurol 2013

Natalizumab

Treatment effect

- Annual relapse rate ⇓ 68%
- Disability progression (sustained for 6 M) ⇓ 54%
- Gd-lesions in 2nd year ⇓ 92%
- New/enlarging T2-lesions ⇓ 83% (over 2y)

Natalizumab

- Very good effect
- However, 2 PML cases in 2005 (3rd in Crohn)

⇒ Suspension

Safety study: PML risk 1/1000 (95% CI 0.2–2.8 per 1000) mean treatment period 17.9M

- Readmission in 2006

Dilemna

MS Chronic disease

Treatment

PML Acute, deadly disease

Natalizumab

Strategies to establish a PML diagnosis as early as possible using

- Clinical vigilance
- MRI pattern
- CSF analysis

Table 1. Features Visualized on Magnetic Resonance Imaging to Be Considered in the Differential Diagnosis of Multiple Sclerosis and Progressive Multifocal Leukoencephalopathy.[a]

Feature	Multiple Sclerosis	Progressive Multifocal Leukoencephalopathy
Location of new lesions	Mostly focal; may affect entire brain and spinal cord, in white and possibly gray matter; posterior cranial fossa lesions are rarely seen	Diffuse lesions, mainly subcortical and rarely periventricular, located almost exclusively in white matter, although occasional extension to gray matter has been seen; posterior fossa frequently involved (cerebellum)
Borders	Sharp edges; mostly round or finger-like in shape (especially periventricular lesions), confluent with other lesions; U-fibers may be involved	Ill-defined edges; infiltrating; irregular in shape; confined to white matter, sparing gray matter; pushing against the cerebral cortex; U-fibers destroyed
Mode of extension	Initially focal, lesions enlarge within days or weeks and later decrease in size within months	Lesions are diffuse and asymmetric, extending homogeneously; no confluence with other lesions; confined to white-matter tracks, sparing the cortex; continuous progression
Mass effect	Acute lesions show some mass effect	No mass effect even in large lesions (but lesion slightly abuts cerebral cortex)
On T_2-weighted sequence	Acute lesions: hyperintense center, isointense ring, discrete hyperintensity outside the ring structure Subacute and chronic lesions: hyperintense, with no ring structure	Diffuse hyperintensity, slightly increased intensity of newly involved areas compared with old areas, little irregular signal intensity of lesions
On T_1-weighted sequence	Acute lesions: densely hypointense (large lesions) or isointense (small lesions); increasing signal intensity over time in 80 percent; decreasing signal intensity (axonal loss) in about 20 percent	Slightly hypointense at onset, with signal intensity decreasing over time and along the affected area; no reversion of signal intensity
On FLAIR sequence	Hyperintense, sharply delineated	Hyperintensity more obvious, true extension of abnormality more clearly visible than in T_2-weighted images
With enhancement	Acute lesions: dense homogeneous enhancement, sharp edges Subacute lesions: ring enhancement Chronic lesions: no enhancement	Usually no enhancement even in large lesions; in patients with HIV, some peripheral enhancement is possible, especially under therapy
Atrophy	Focal atrophy possible, due to focal white-matter degeneration; no progression	No focal atrophy

MR Criteria

Shortcomings

Criteria based on

- 2 PML (Natalizumab/MS) patients
- PML in HIV patients

➞ Need to establish new recommendations

Challenge in Natalizumab Treated MS Patients

MR

- Identification of early PML signs
- Differentiation early PML from new MS lesions
- Is the PML pattern similar?

PML vs MS

Table 2. Brain MRI Characteristics in PML and RRMS[a]

MRI Pattern	No. (%) PML (n=35)	No. (%) RRMS (n=100)	P Value	Adjusted P Value[b]
Large, confluent, granular T2-weighted lesions	26 (74)	2 (2)	<.0001	.0005
Deep gray matter involvement	11 (31)	7 (7)	<.0001	.0005
Crescent cerebellar lesions	8 (23)	0	<.001	.003
Gadolinium-enhancing lesions	8 (23)	54 (54)	.001	.003
Tumefactive lesions	1 (3)	6 (6)	.07	.084
Periventricular white matter lesions	3 (9)	89 (89)	<.0001	.0005
Transcallosal	3 (9)	3 (3)	.067	.078

Boster Arch Neurol 2009

Basic pattern (PML-MS)

• **Location**	Subcortical (U-fibers)		100%
• **Signal**	T2w/DWI	hyper	100%
	T1w	hypo	94%
• **Border**	GM	sharp	100%
	WM	ill-defined	100%

Yousry Annals Neurol 2012

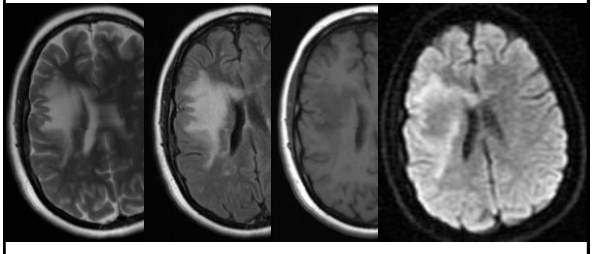
Variations

Basic pattern +

• **>3cm**	93%
• **Peri T2 hyper**	73%
• **>3cm + Peri T2 hyper**	67%

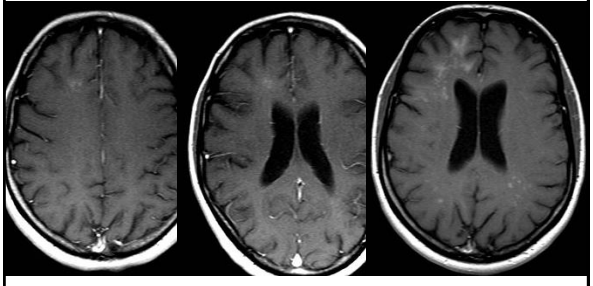
Yousry Annals Neurol 2012

Basic Pattern >3cm/Peri T2



Contrast Enhancement

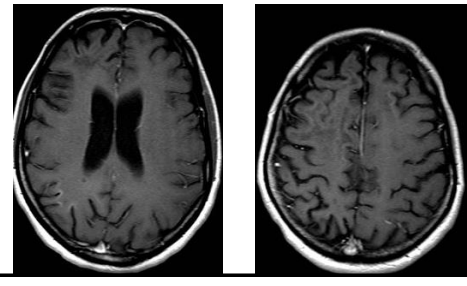
• **PML**	Presym	33%
	Early (≤ 14d)	41%
	FU (>14d)	75%
• **IRIS**	Acute (≤14d)	71%
	Post (>14d)	100%



Pre-sym Early IRIS

T1 Hyperintensity

IRIS-Post-IRIS



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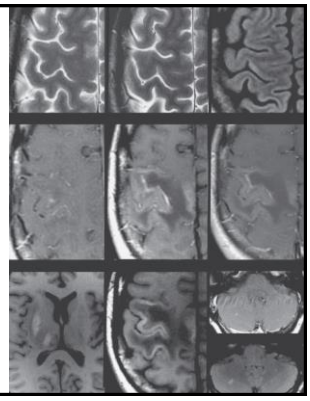


Lindå N Engl J Med 09

DD Problems at Presentation

High lesion load

- MS vs PML

Lesion < 3cm

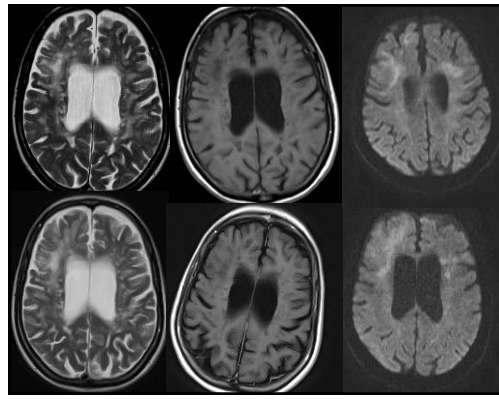
- Filling gyrus
- Band cortex/subcortex

Unusual pattern

1) High lesion load

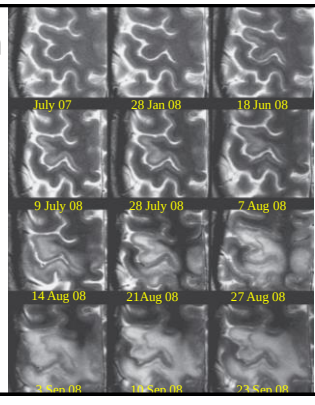
MS vs PML

- T1 hypointensity
- DWI



2) Lesion < 3cm

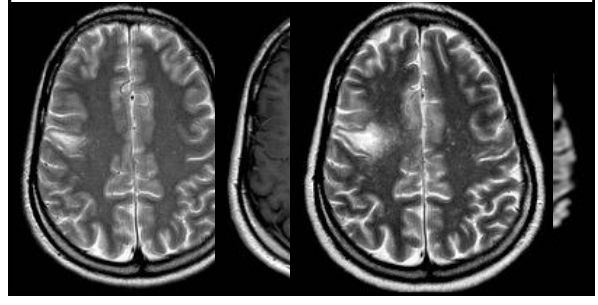
a) Band-like



Lindå N Engl J Med 09

2) Lesion < 3cm

b) Filling Gyrus



Punctate Lesions

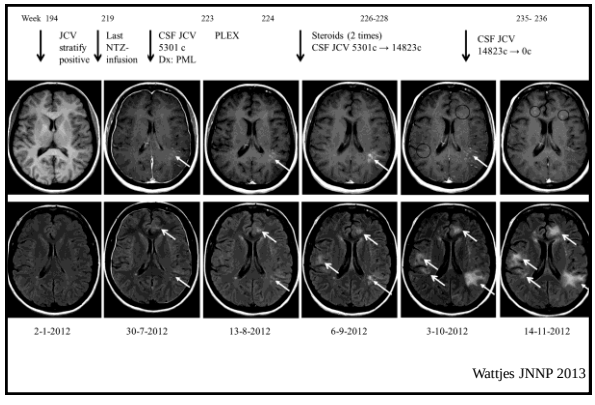
Early PML
- T2/FLAIR 72%
- Enhancement 83%

PML IRIS
- T2/FLAIR 86%
- Enhancement 71%

Punctate Lesions

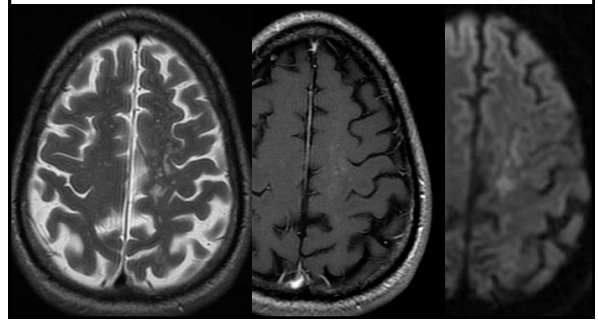
IRIS T lymphocyte infiltration of VR

PL
- Infiltrated VR?
- Sign of early inflammation in Early PML
- PML & IRIS simultaneous?



Wattjes JNNP 2013

3) Unusual Pattern



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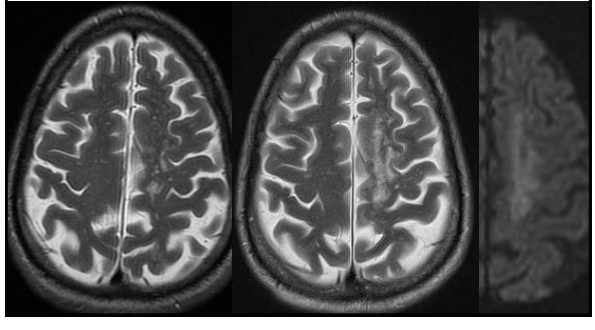

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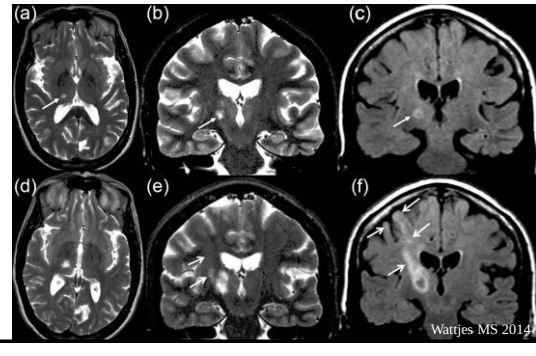
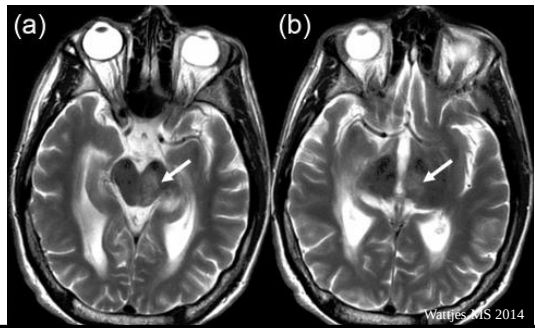


Wattjes MS 2014

3) Unusual Pattern



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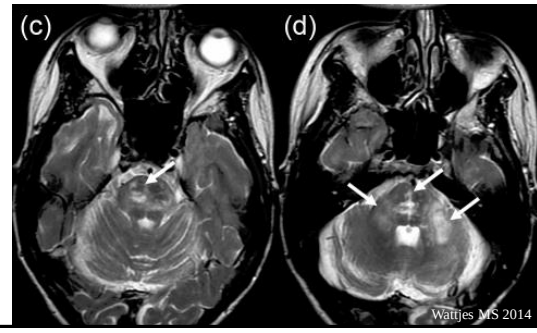

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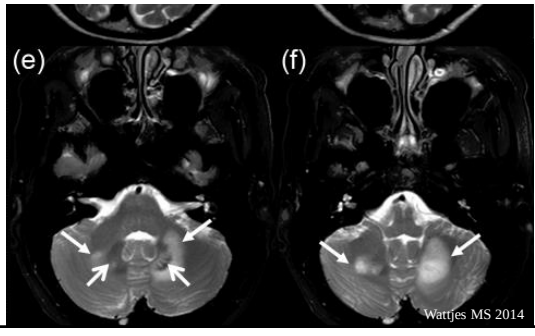
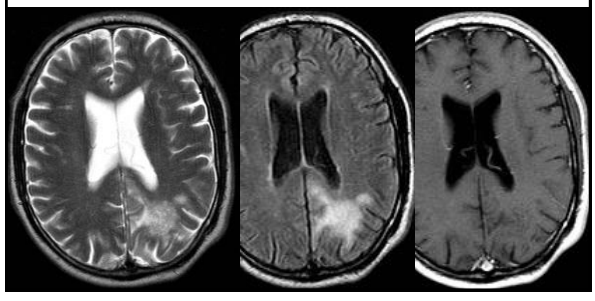
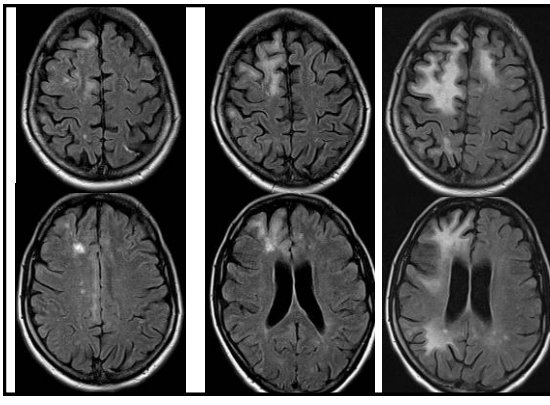


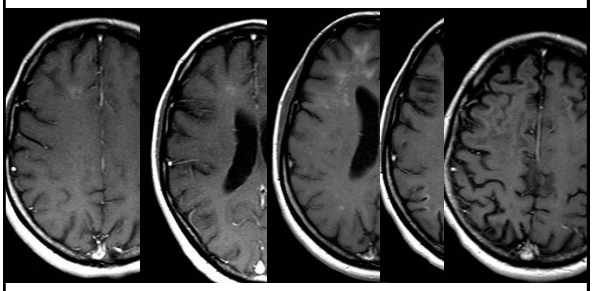
Characteristics Features

Location	**Subcortical U-fibers**; cortex & BG; often bilateral	
Size	**Usually >3cm**	
Borders	GM Sharp	WM ill defined
Progression	Increase in size and new appear	
Mass effect	No	
Signal	T2w	Hyperintense
	T1w	Typically hypointense
Hyperintensity PML-IRIS		
	FLAIR	Hyperintense; >T2W images
	DWI	**Always hyperintense; rim**
Perilesional	**Small, punctate T2-hyperintense** lesions in immediate vicinity of main lesion	
Enhancement	**Frequent punctate** and/or rimlike	
Atrophy	Not in early phase	

PML-IRIS







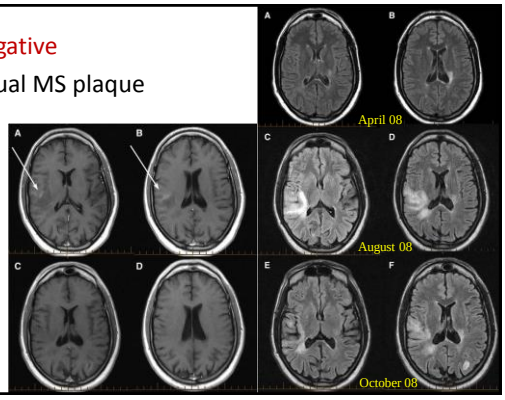
Pre-sym Early IRIS Post-IRIS

However....

- 27 y man, diagnosed MS in 06 → frequent relapses
- April 08 Natalizumab
- August 08: new onset confusion, altered behavior, left hemianesthesia, worsening gait and balance

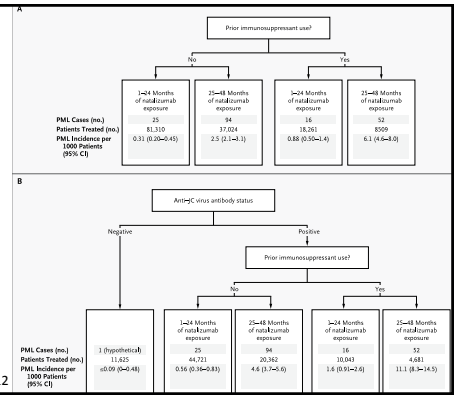
Twyman JNS 10

- JC negative
- Unusual MS plaque



Twyman JNS 10

Risk



Bloomgren NEJM 2012

Risk Factors

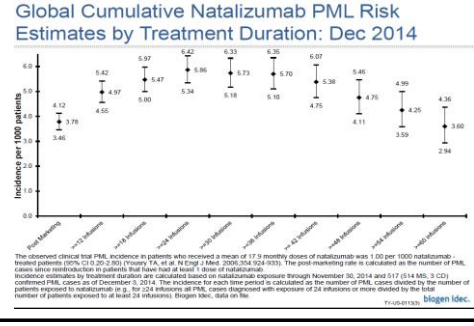
- Anti-JCV serum antibodies
- Prior immunosuppressive use
- Duration of natalizumab treatment (25-49 infusions)

Table 1. Estimated risk of natalizumab related to progressive multifocal leukoencephalopathy according to currently known risk factors

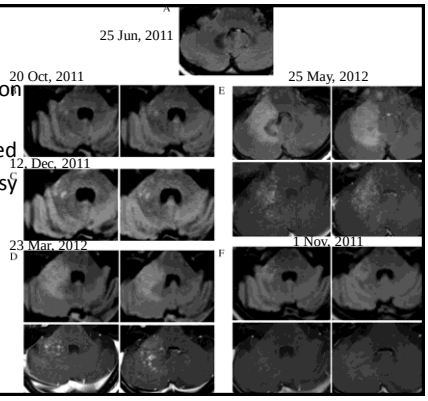
	Prior immunosuppressants?	Overall risk	Risk up to 24-month therapy	Risk after 24-month therapy
JCV antibody negative	No	~1:11 563	~1:51 526	~1:6357
	Yes	~1:4078	~1:18 171	~1:2242
JCV antibody positive	No	~1:289	~1:1288	~1:159
	Yes	~1:102	~1:454	~1:56

Baldwin Curr Opin Neurol 2013

Duration of Exposure

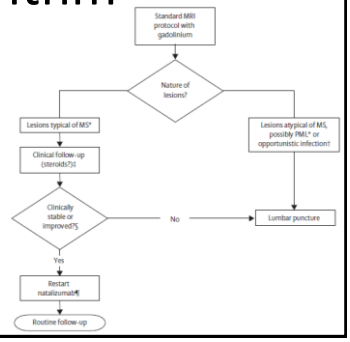


Natalizumab
Oct 2007-Dec 11
47th administration
Jan 12 Breast Ca
Tys stopped
Mar Cog+Mot sy

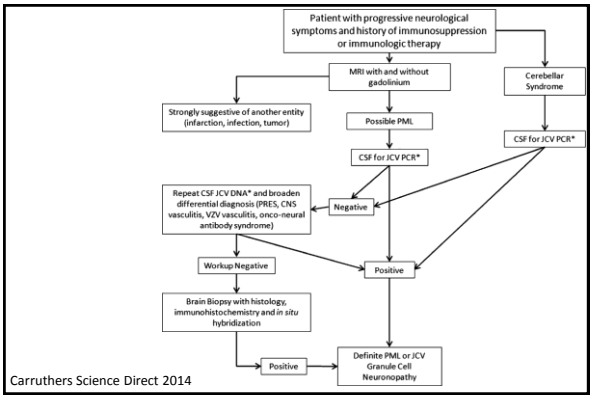


Blinkenberg MSJ 13

MR Algorithm



Kappos Lancet Neurol 2011



Carruthers Science Direct 2014

Recommendation

- Location **Subcortical**
- Grey matter Cortex 50% Deep 28%-57%
- Border GM: sharp WM: ill defined
- MR signal T2 + **DWI** hyper T1 hypo
  T1 shortening IRIS
- Size **> 3cm**
- Contrast 50-80%
- **Punctate** **T2/contrast**
- **IRIS** **T1 Hyperintensity**

Recommendation

- Sequences FLAIR/T2
  DWI
  (T1-Gd)
- Frequency 4-6m
  Clinical suspicion

Summary

PML

- Typical MR pattern
- Early diagnosis crucial, best in silent phase
- MR has a central role in assessing patients treated with Natalizumab