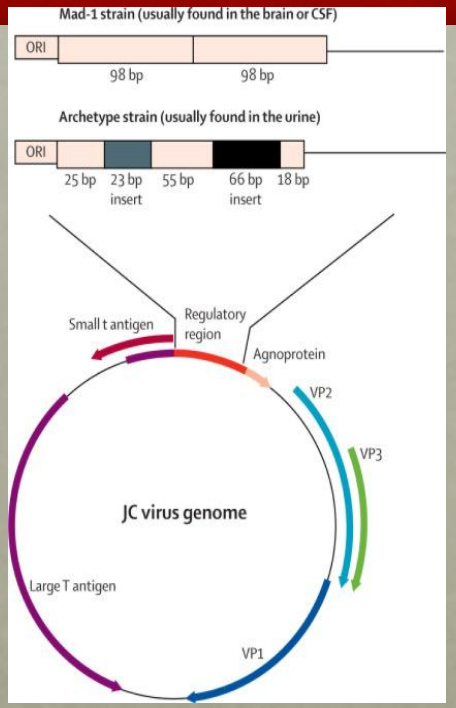
PROGRESSIV MULTIFOKAL LEUKOENCEFALOPATI (PML)

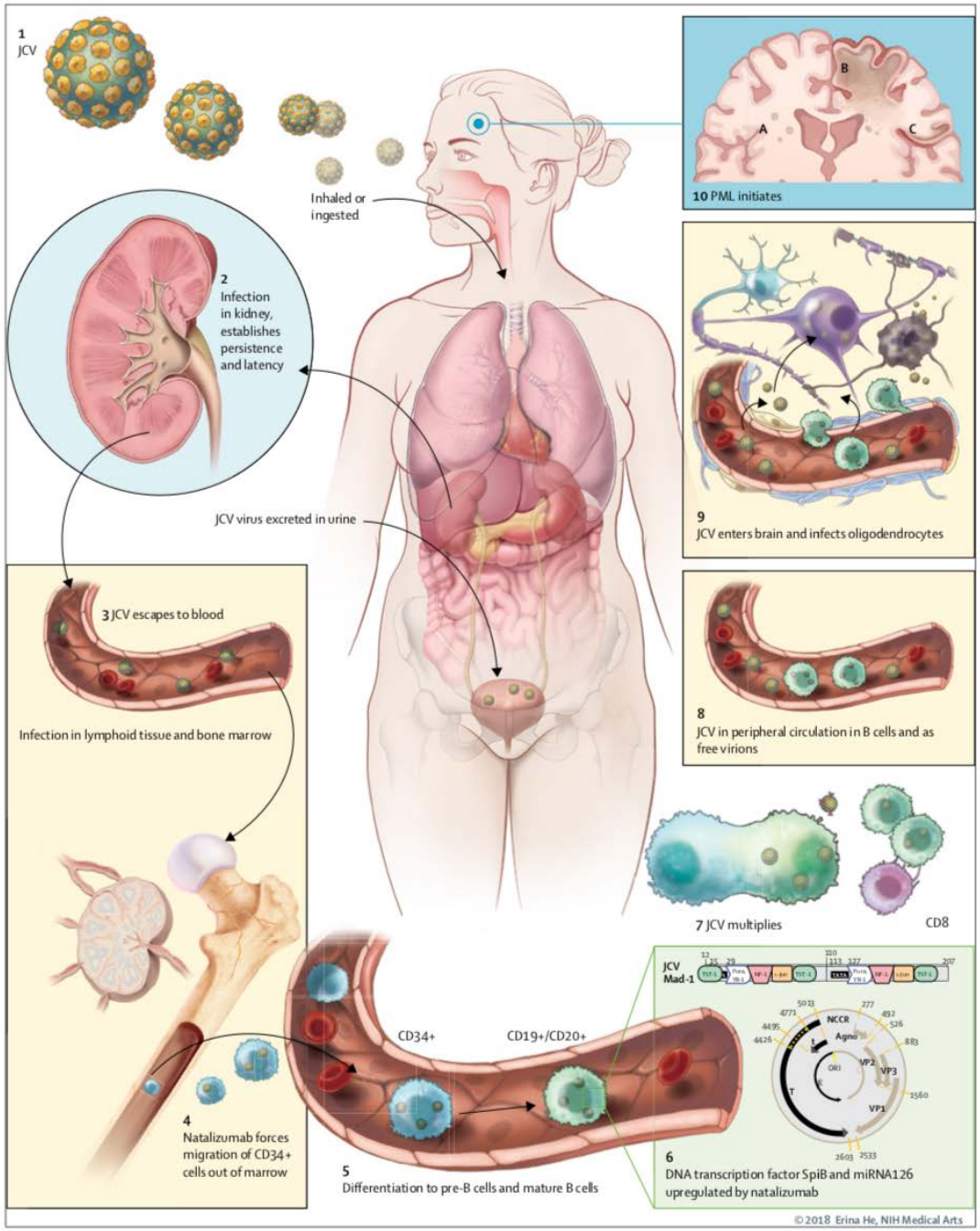
En opportunistisk infektion i CNS

Anders Svenningsson
Neurosektionen
Danderyds Sjukhus

John Cunningham Virus



- Först beskriven 1971
- Neurotropt polyomavirus
- Infekterar oligodendrocyter och astrocyter
- Omfattar inte
  - Synnerv
  - Ryggmärg
- Tre stadier av infektionen
  - Primär (assymptomatisk) under barndomen
  - Latent infektion (njure, benmärg, hjärna)
  - Reaktivering
- Antikroppar mot JC-virus finns hos 50-60% av friska individer, vilket indikerar att de flesta utsatts för viruset



Major et al; Lancet Neurol 2018;17:467-80

JC Virus Associerade Sjukdomar

- Klassisk PML
- “Inflammatorisk PML”
- JC virus encephalit/encephalopati
- JC virus meningit
- JC virus granular cell neuronopati

Epidemiologi

- Ovanligt!
- Personer med nedsatt cellulär immunitet
  - 0,07 % av hematologiska maligniteter [1]
  - 0,8 % levertransplanterade [2]
  - Ca 1 per 1000 posttransplanterade året efter hjärt- eller lungtransplantation [3]
  - Ca 2 per 100 000 patientår vid SLE [4]

1. Power et al. Neurology 2000; 54(3):743
2. Martinez et al. Mod Pathol 1993; 6(1):25
3. Marteen et al. Ann Neurol 2011; 70(2):305
4. Amend et al. Neurology 2010; 75(15)1326

PML drabbar immundefekta

- 80% AIDS
- 20% andra tillstånd
  - BMT, kemoterapi
  - Maligniteter
  - Immunsupprimerande behandling (ALLA former)

BMT=bone marrow transplantation; IC=interstitial cystitis; RA=rheumatoid arthritis.

PML-risk vid några monoklonala antikroppar

- Natalizumab (Tysabri®): Ca 1/1000
- Efalizumab (Raptiva®): Ca 1/1000
- Rituximab (Mabthera®): Ca 1/30 000
- Infliximab (Remicade®): Ca 1/30 000

MS-BEH PML RISK

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Review article

Classifying PML risk with disease modifying therapies

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ARTICLE INFO

Keywords:
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Multiple sclerosis
Progressive multifocal leukoencephalopathy
Natalizumab
Fingolimod
Dimethyl fumarate
Rituximab

ABSTRACT

Objective: To catalogue the risk of PML with the currently available disease modifying therapies (DMTs) for multiple sclerosis (MS).

Background: All DMTs perturb the immune system in some fashion. Natalizumab, a highly effective DMT, has been associated with a significant risk of PML. Fingolimod and dimethyl fumarate have also been unquestionably associated with a risk of PML in the MS population. Concerns about PML risk with other DMTs have arisen due to their mechanism of action and pharmacological parallel to other agents with known PML risk. A method of contextualizing PML risk for DMTs is warranted.

Methods: Classification of PML risk was predicated on three criteria:: 1) whether the underlying condition being treated predisposes to PML in the absence of the drug; 2) the latency from initiation of the drug to the development of PML; and 3) the frequency with which PML is observed.

Results: Among the DMTs, natalizumab occupies a place of its own with respect to PML risk. Significantly lesser degrees of risk exist for fingolimod and dimethyl fumarate. Whether PML will be observed with other DMTs in use for MS, such as, rituximab, teriflunomide, and alemtuzumab, remains uncertain.

Discussion: A logical classification for stratifying DMT PML risk is important for both the physician and patient in contextualizing risk/benefit ratios. As additional experience accumulates regarding PML and the DMTs, this early effort will undoubtedly require revisiting.

Table 1
A PML risk stratification table for disease modifying therapies.

Therapeutic Agent	Treated condition predisposes to PML?	Latency from time of drug initiation to PML	Frequency/ Incidence of PML	Year drug introduced into U.S. and European markets	Patients/patient-year (PY) exposure#
Class I – high potential risk of PML	**No**	**Yes**	**High**		
Natalizumab	MS and Crohn's disease	None < 8 months; > 85% of cases > 24 months	1/100–1/1000	U.S.- approved 2004; withdrawn Feb 2005; reintroduced Jun 2006 EUR – Apr 2006	161,300 patients ~527,159 PY (September 30, 2016)
Class II – low potential risk of PML	**No**	**Yes**	**Low/infrequent**		
Dimethyl fumarate	MS and psoriasis	18–54 months	~1/50,000	U.S. – Mar 2013 Europe – Feb 2014	224,542 patients 308,732 PY
Fingolimod	MS	18–54 months*	~1/18,000	U.S.- Sep 2010 EUR-Mar 2011	160,000 patients 368,000 PY
Class III – no or very low potential risk of PML	**Yes**	**No**	**Very low or evident only with related drug**		
Alemtuzumab	Hematological malignancies, transplantation		Unknown; no cases with MS	U.S. – Nov 2014 EUR – Sep 2013	~11,000 patients ~6000 PY
Rituximab	Lymphoproliferative disorders, rheumatoid arthritis, ANCA-associated vasculitis, SLE		1/30,000	MS – unapproved indication	No data
Mitoxantrone	Non-Hodgkins lymphoma and leukemia			U.S.-Oct 2000 EUR-divergent dates	No data
Teriflunomide	No PML observed with teriflunomide but with related leflunomide			U.S.-Sep 2012 EUR-Aug 2013	68,952 patients 96,909 PY
Daclizumab	No PML observed with MS or as prophylaxis for renal transplant			U.S.-May 2016 EUR-Jul 2016	1516 patients 3744 PY

Legend PY - Patient year exposure.
U.S. – United States.
EUR - Europe.
- Data on file with respective manufacturer as of submission date.

Förekommer det hos immunkompetenta?

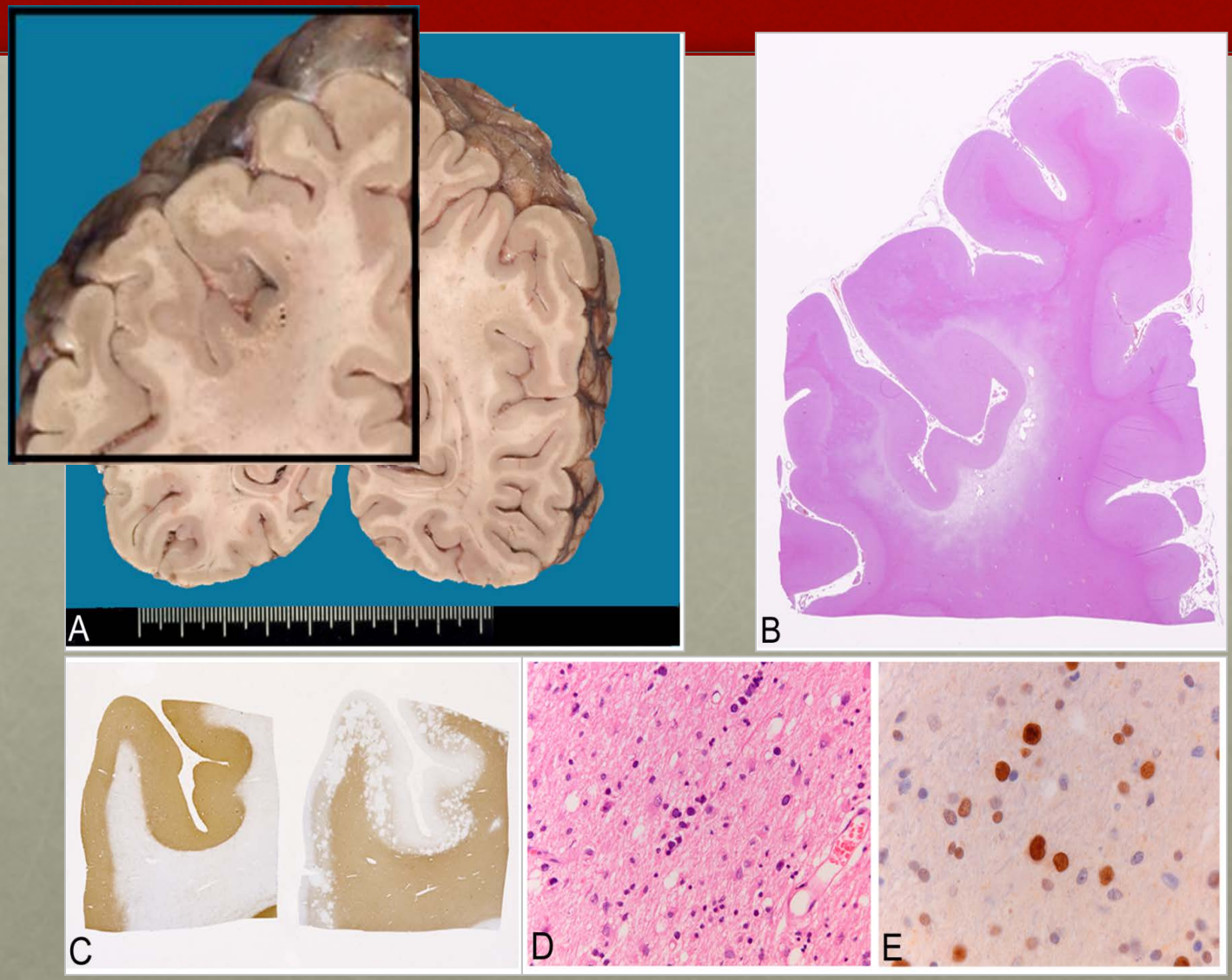
- Mycket ovanligt!
- I litteraturen finns beskrivet ca 40 fall utan uppenbara immundefekter, av dessa hade 9 levercirrhos, 5 njursvikt, 2 var gravida kvinnor, 2 dermatomyosit.
- Detta ger 22 utan underliggande diagnoser som är förknippade med immunnedsättning, men 7 av dessa hade låga CD4+ T-celler
- Detta ger 15 utan något som pekar på nedsatt immunförsvar

PML, presenterande symptom

PML symptom	% PML fall med symptom
Kognitiva/beteendemässiga	49%
Motoriska (eg: hemipares)	37%
Tal (eg: dysartri, afasi)	31%
Visuella (eg: hemianopsi)	26%
Cerebellära (eg: ataxia)	17%
Kramper (eg: fokala motoriska, generaliserade)	17%
Sensoriska (eg: parestesier)	3%

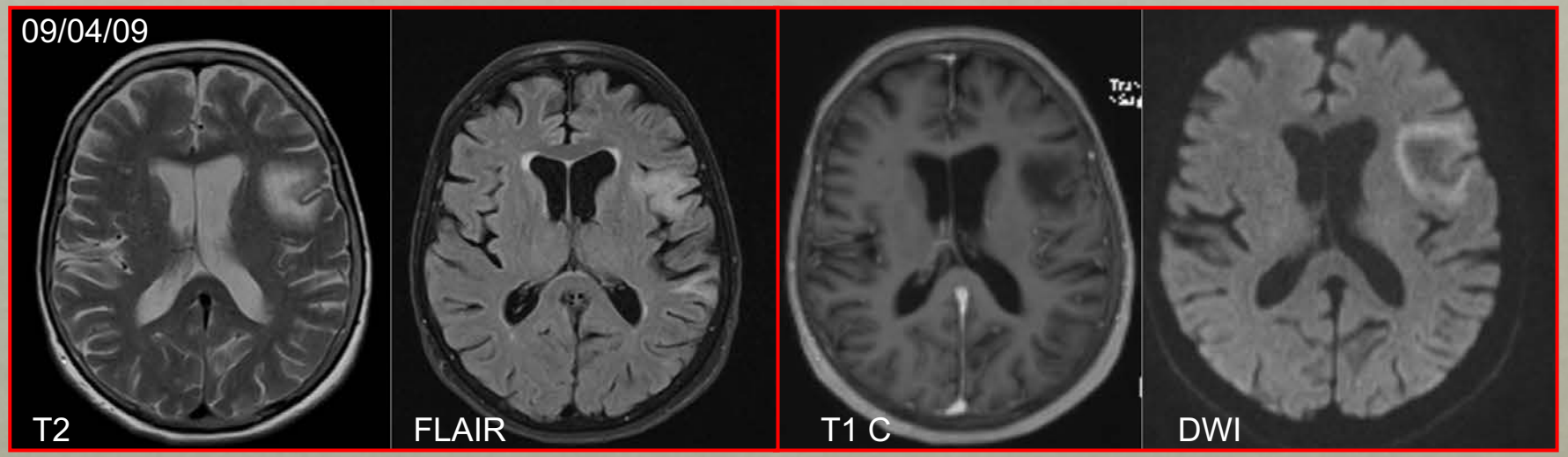
Symtomutveckling typiskt över veckor - månader

Klassisk PML

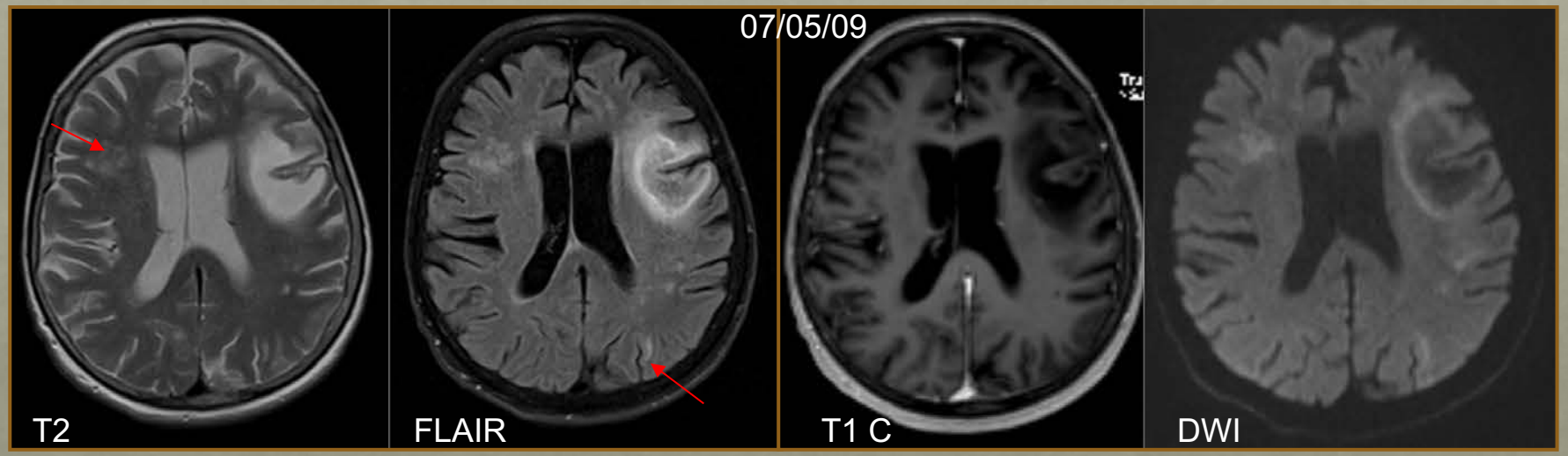


Courtesy of VUMC University Medical Centre.

Klassisk PML: Sjukdomsprogress



Progression with enlargement of previous lesions and new lesions ipsi and contralateral

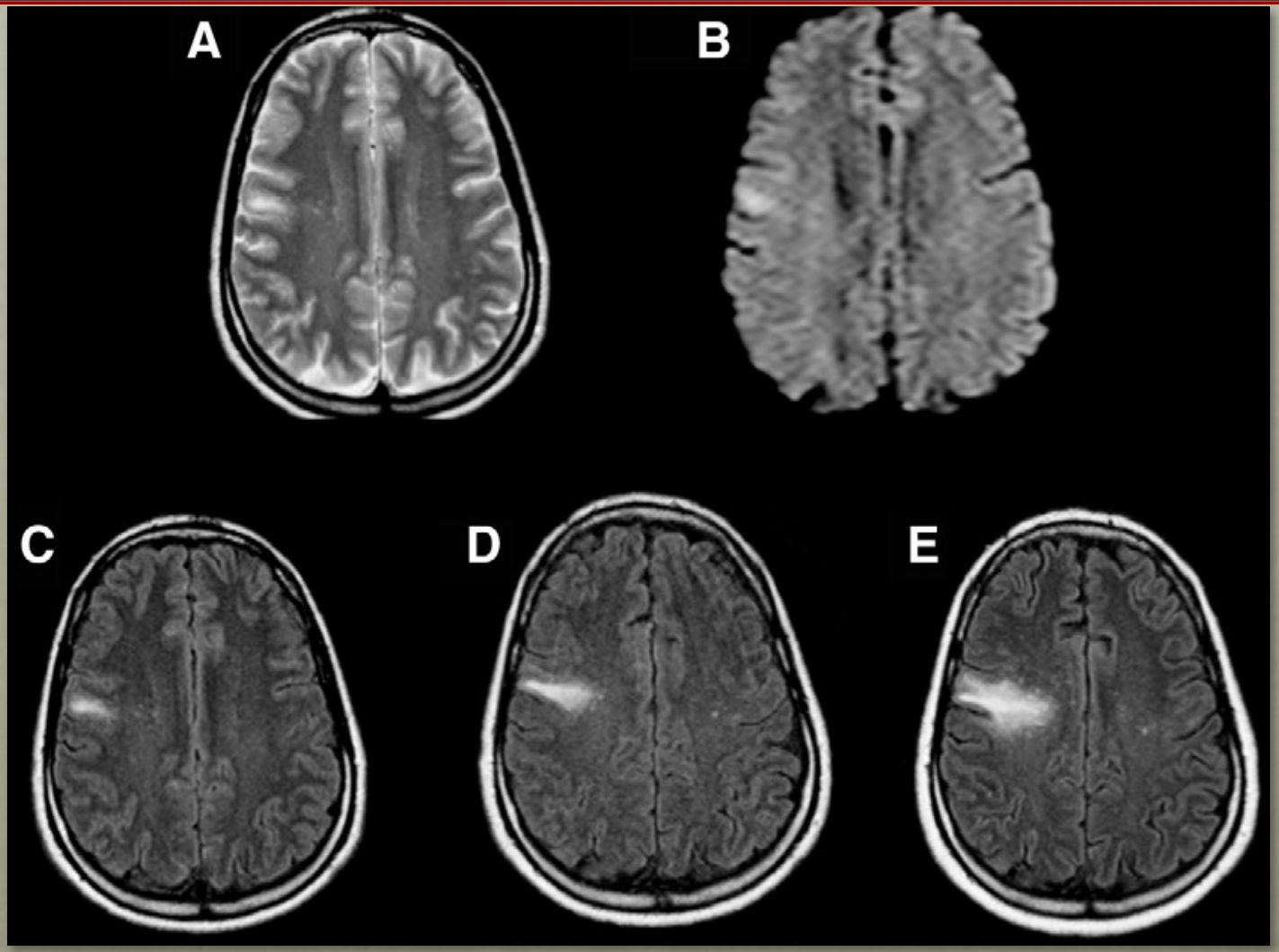


Tysabri-associerad PML

- FLAIR är den känsligaste sekvensen för PML lesion detektion
- Alla lesioner är hyperintensa på DWI
- Kontrastladdning i ca 40% av fallen
- Idag över 600 fall bland Tysabribehandlade
  - 2 – 4 ‰ per års risk efter ca 2 års behandling om JCV+
- PML presentation
  - Unilobär (40%)
  - Multilobär i angränsande lober (20%)
  - Disseminerad (40%)

Richert ND et al. *Mult Scler.* 2012;18:(S4)27.

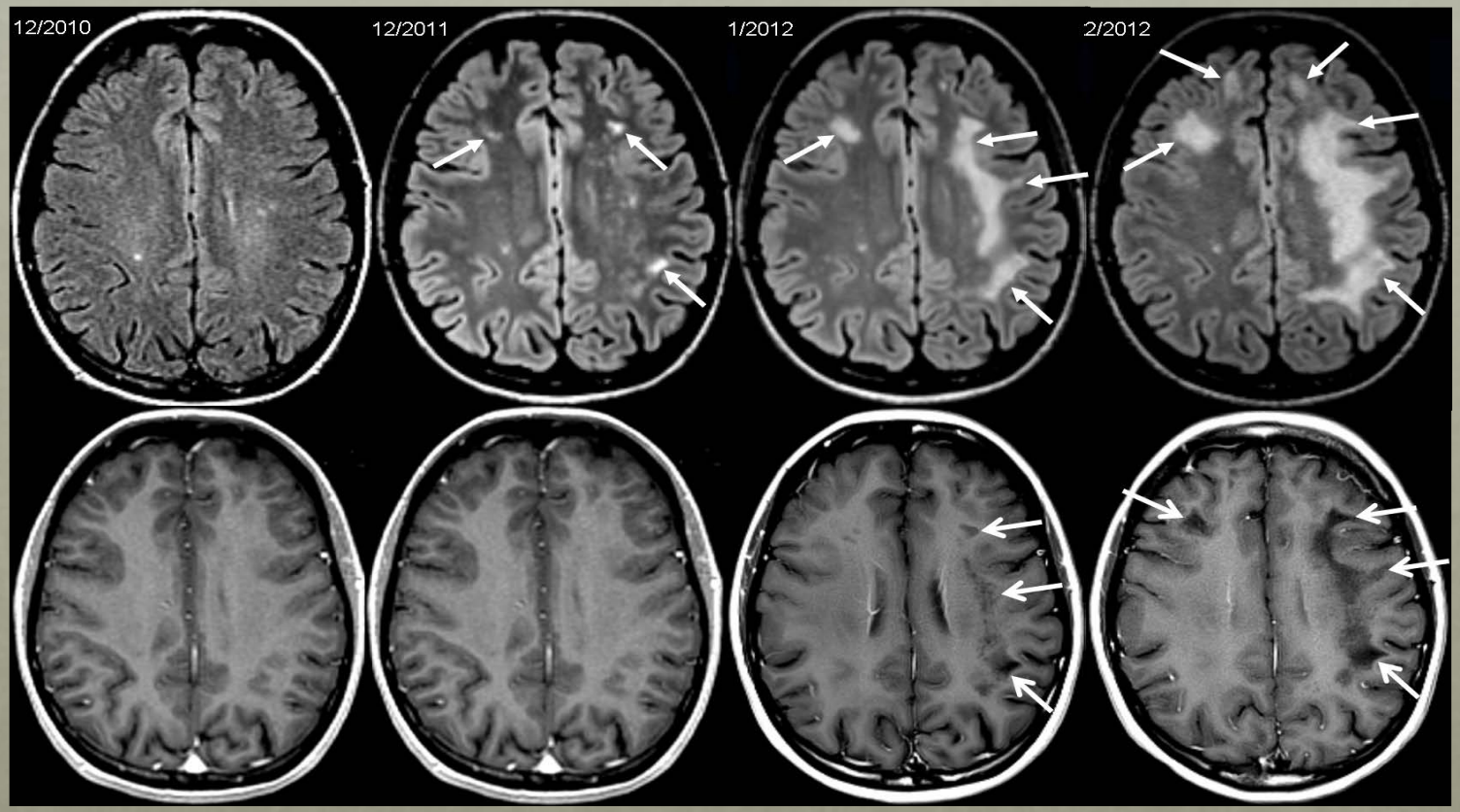
Tysabri-associerad PML



Yousry TA et al. *Ann Neurol.* 2012;72:779-787.

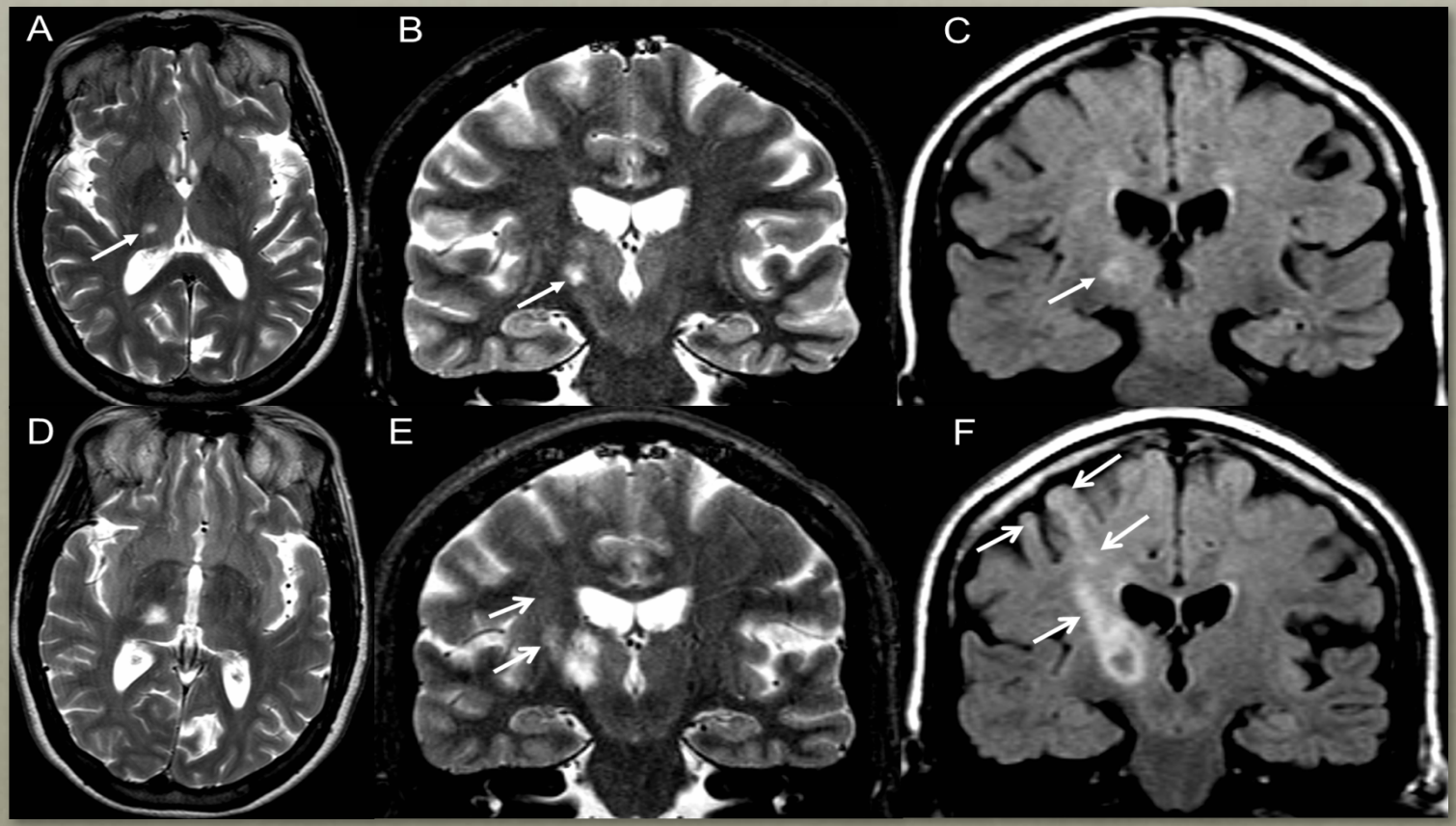
Natalizumab-associerad PML

White matter onset and spreading



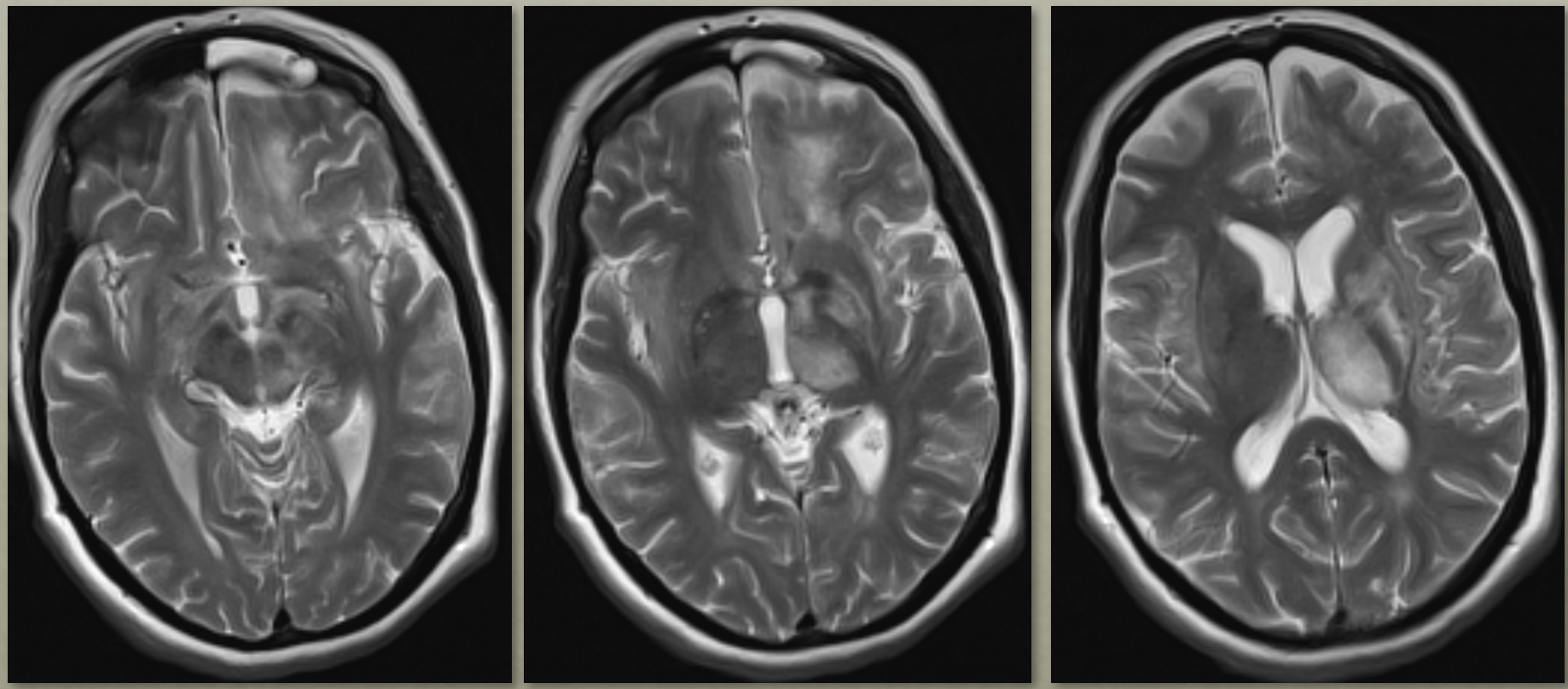
Natalizumab-associerad PML

Deep gray matter involvement

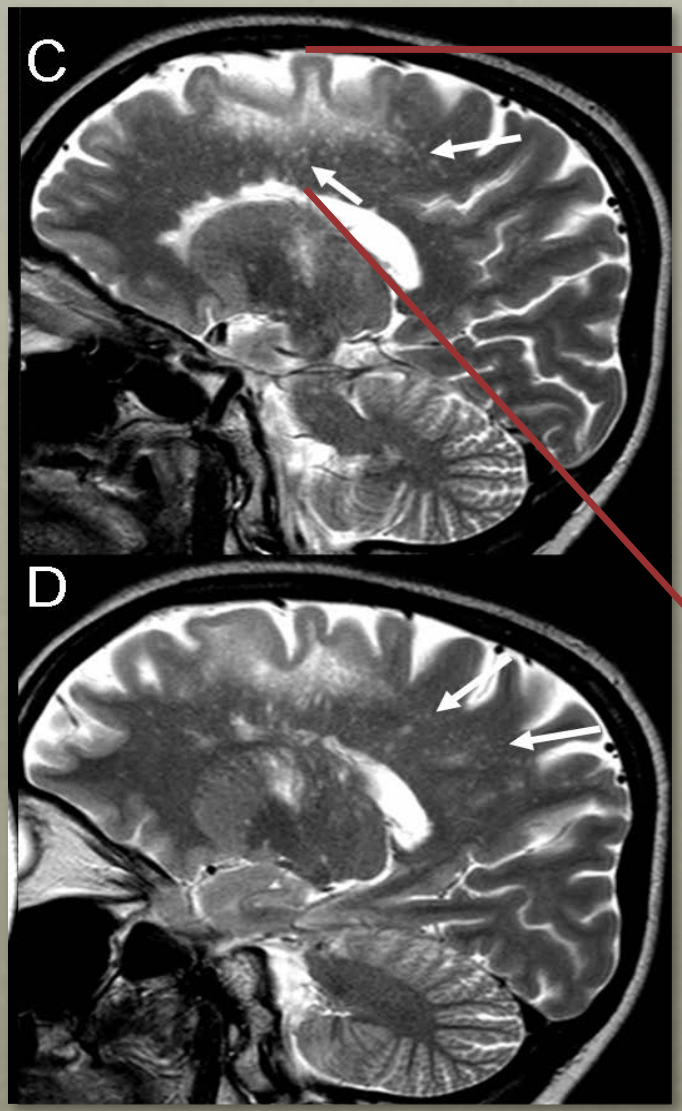


Natalizumab-associerad PML

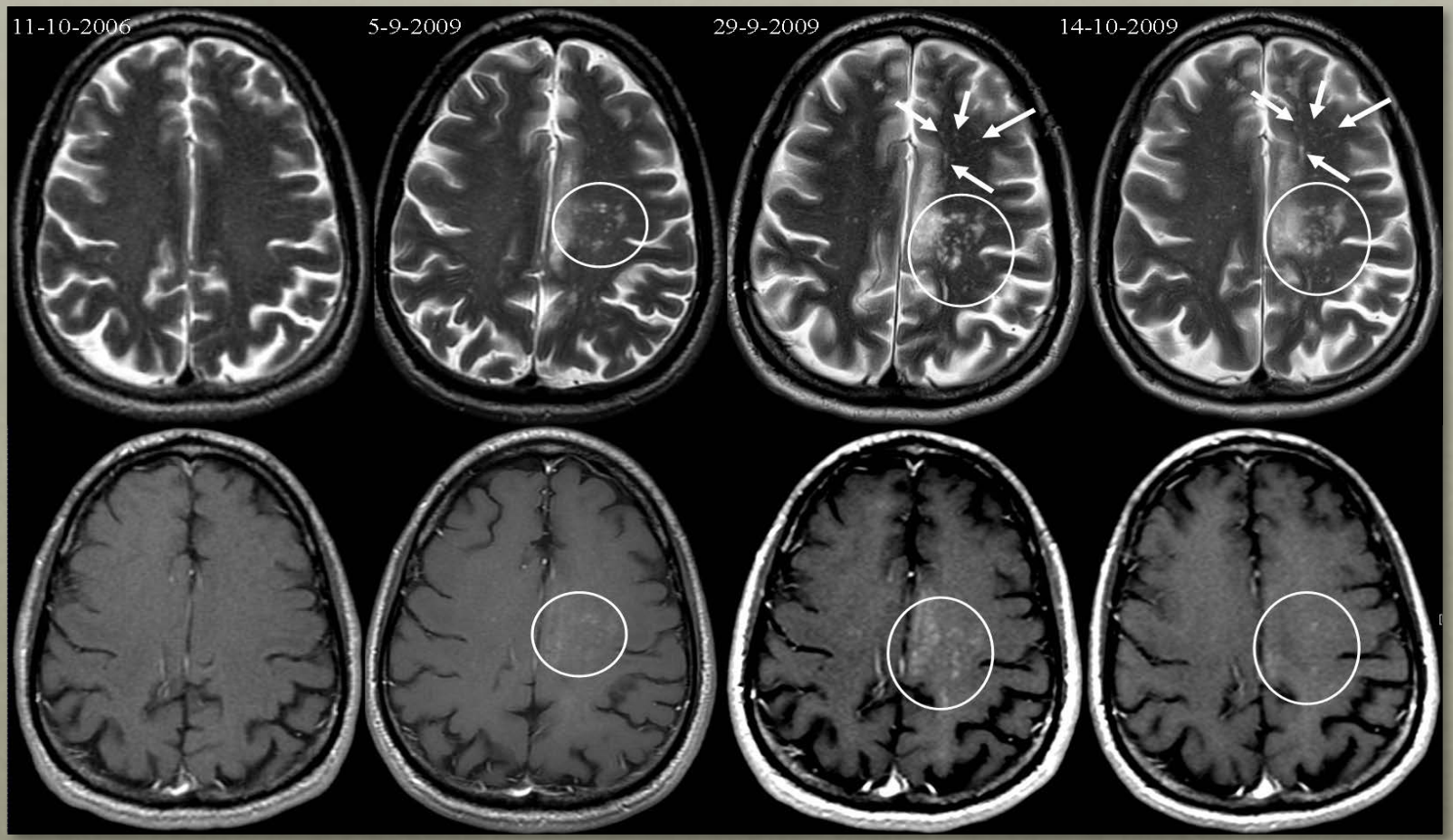
Deep gray matter involvement



Punktata lesioner

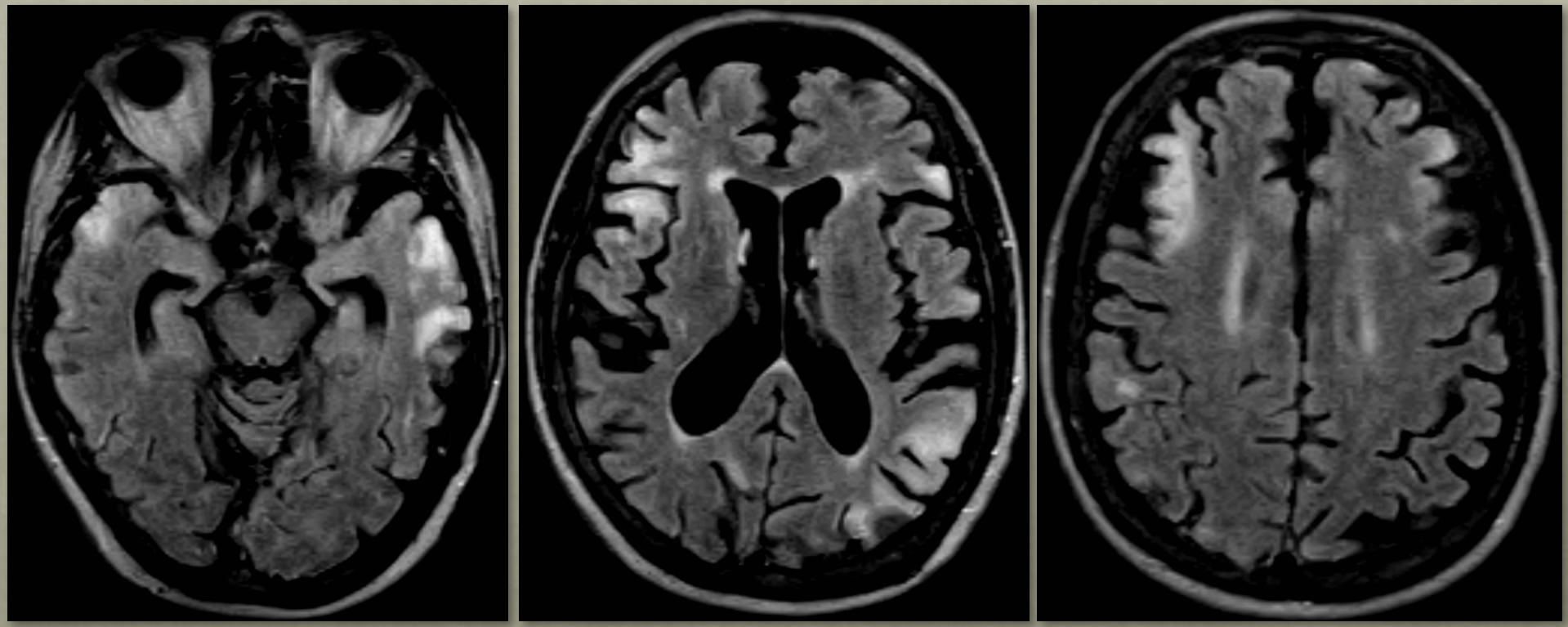


PML: Perivaskulär Inflammation



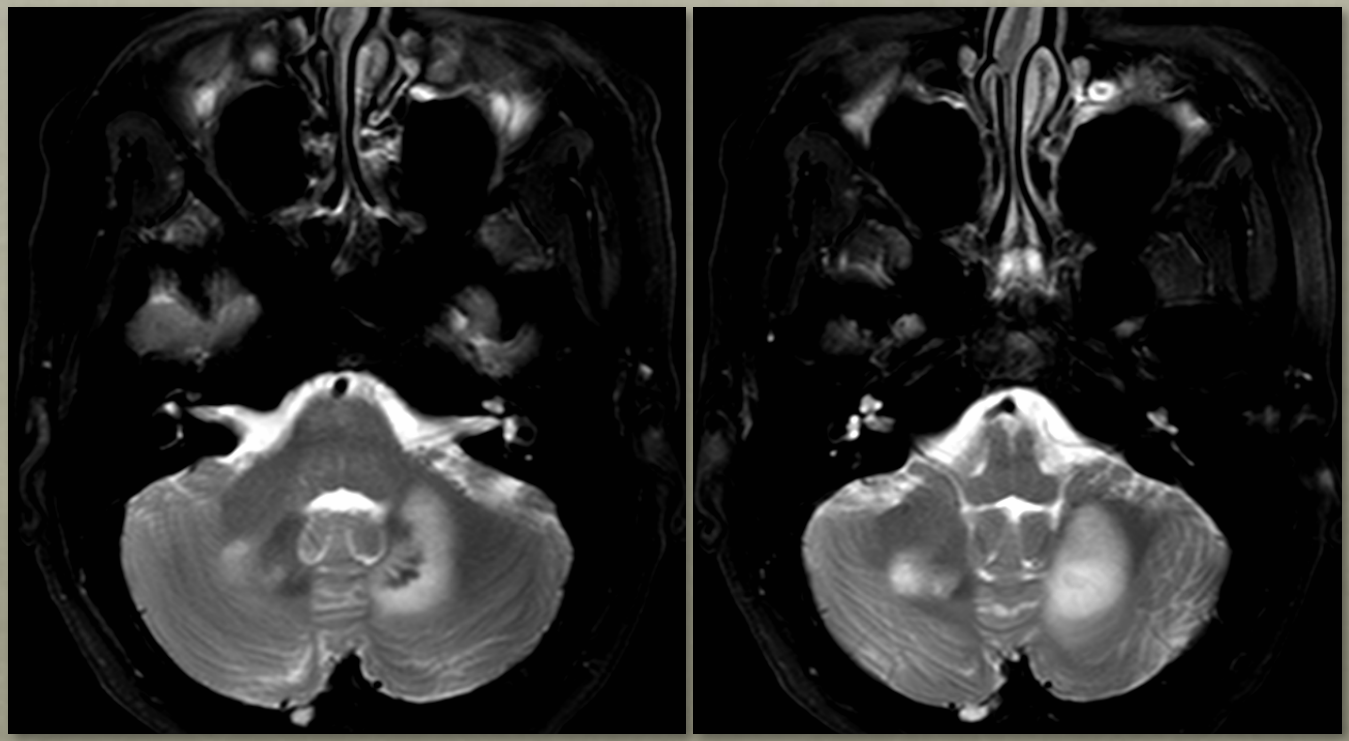
Natalizumab-Associerad PML

Kortikal fenotyp



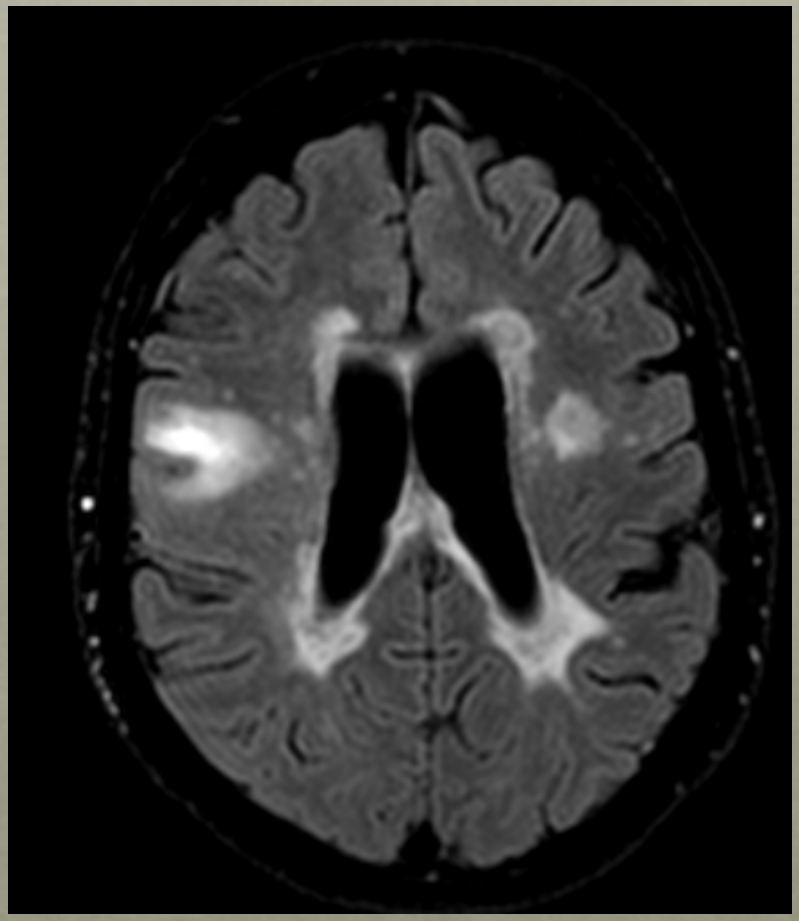
Natalizumab-Associated PML

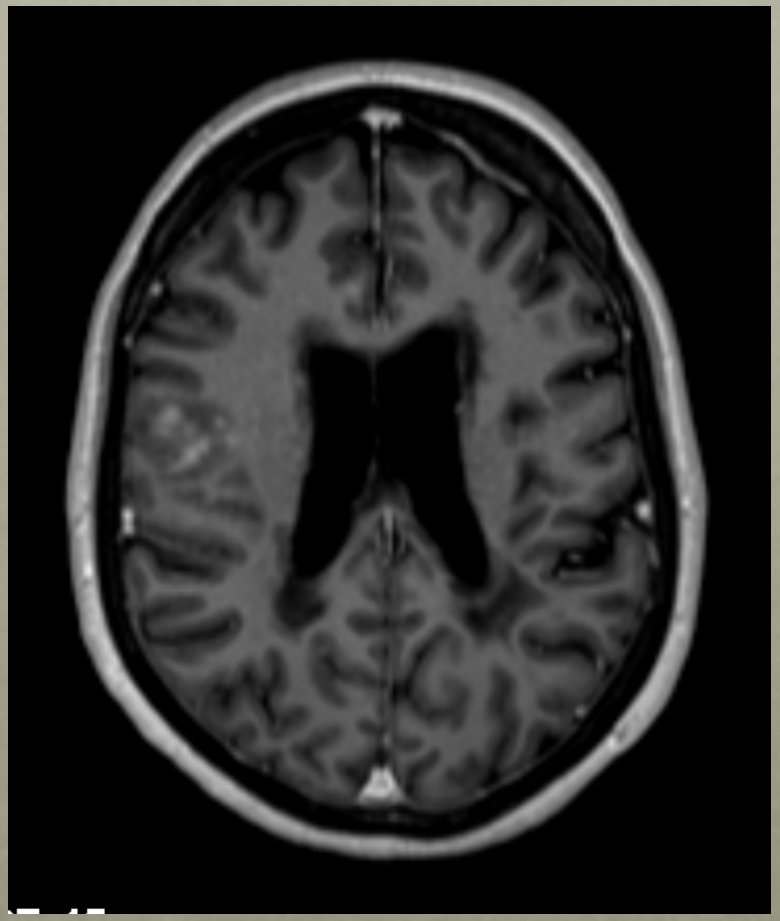
Posterior fossa engagemang



Pat AB -73

2011-11-30





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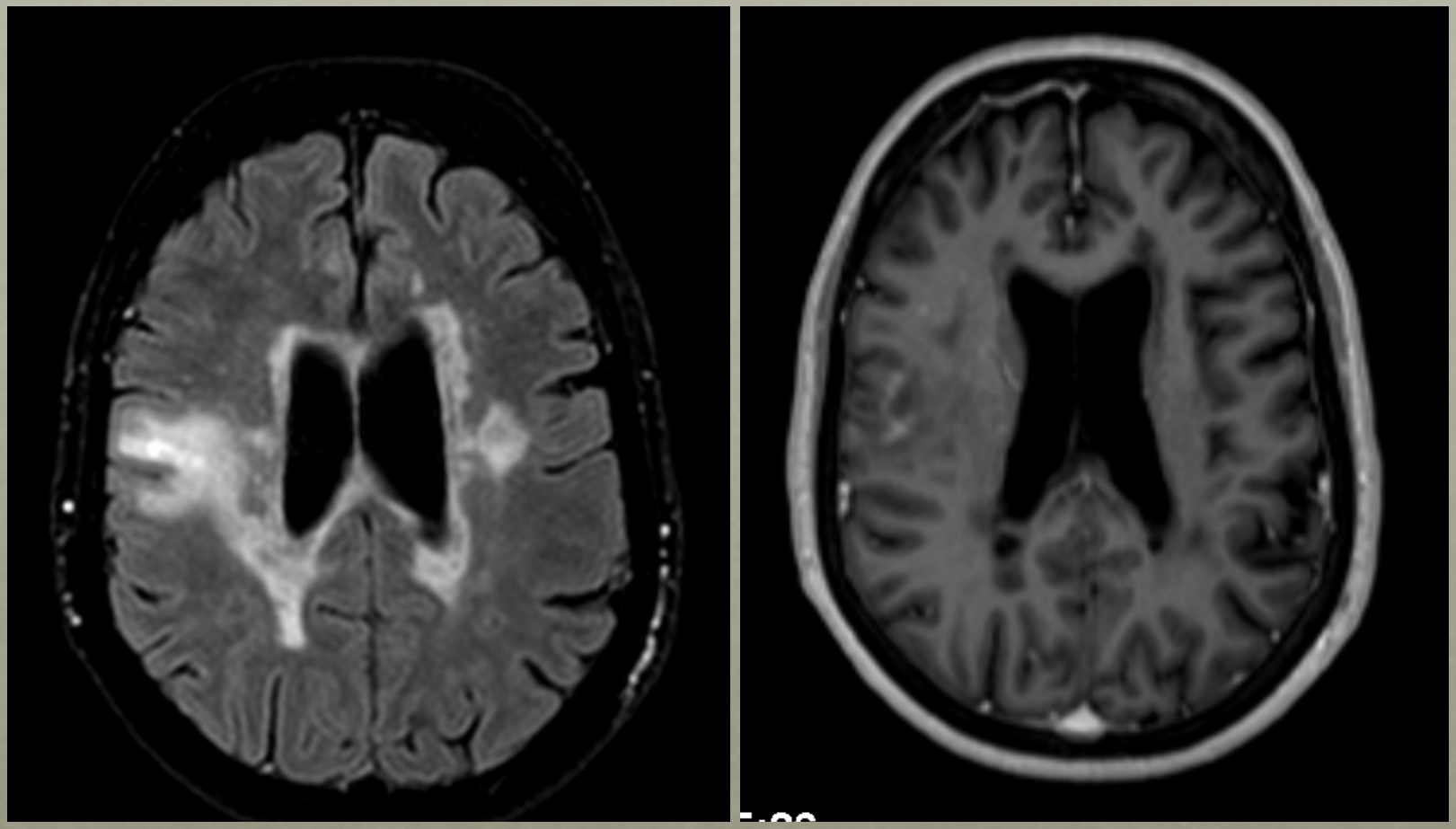

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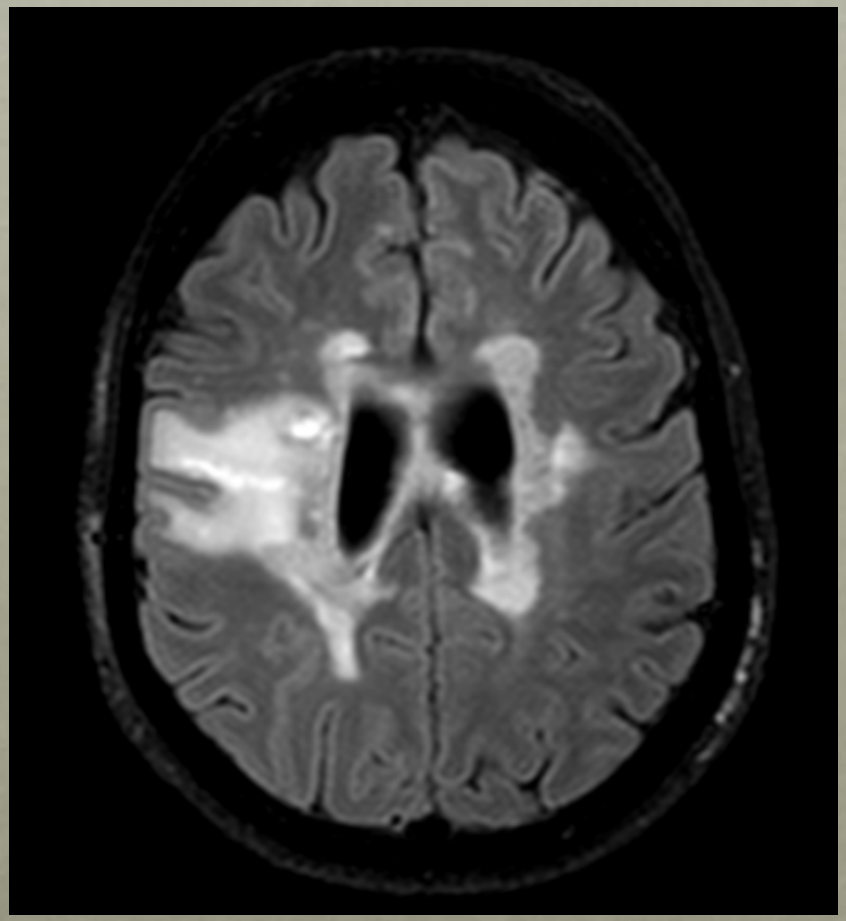

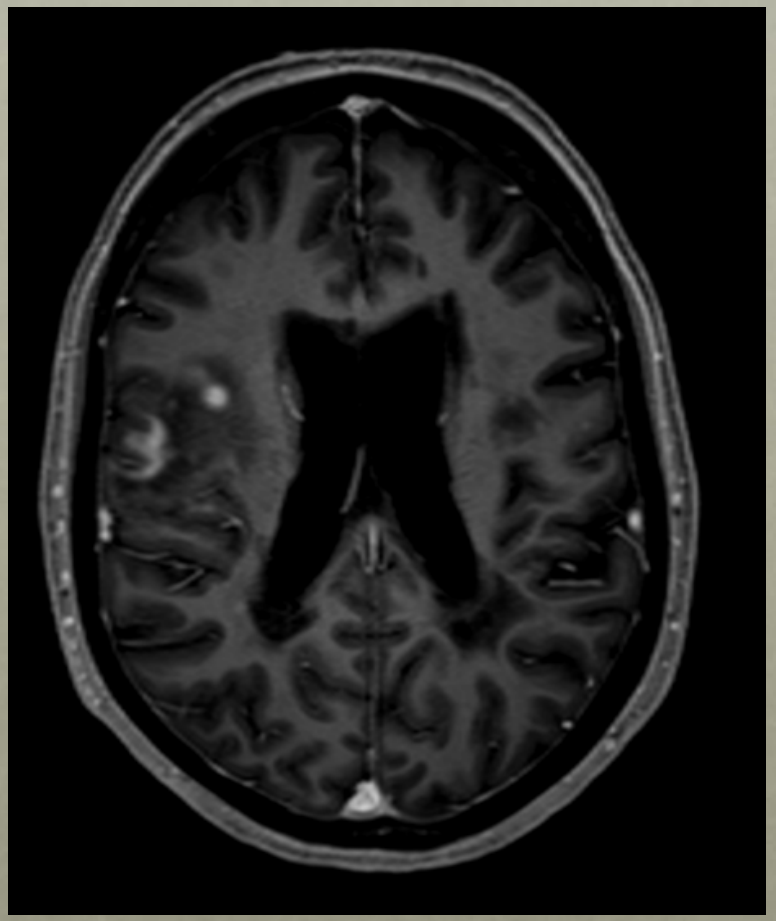

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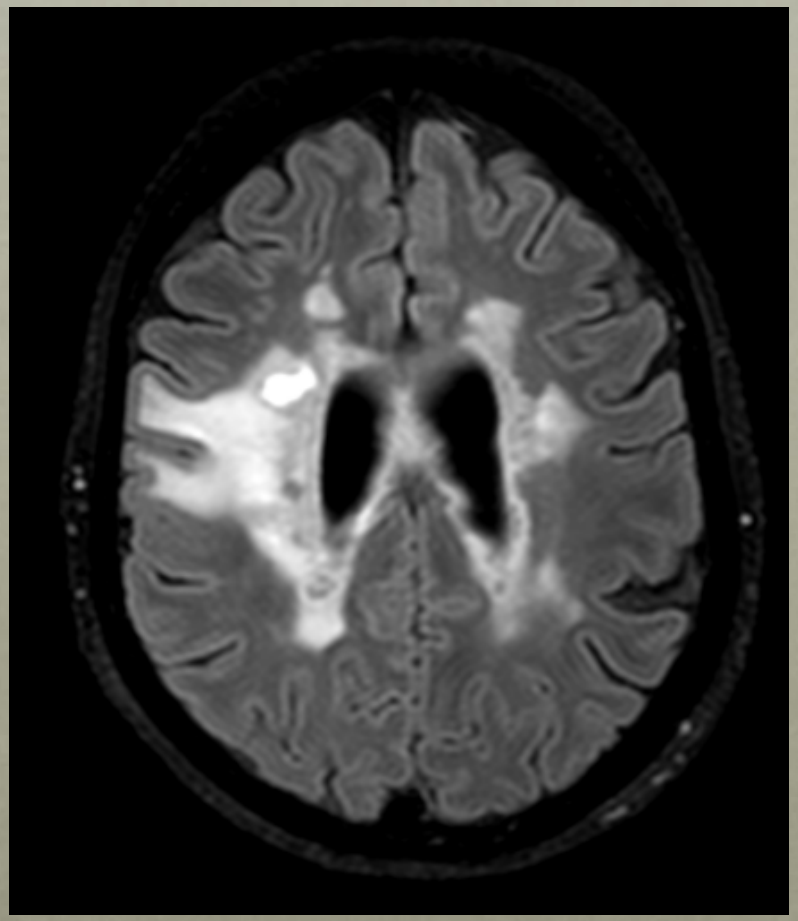

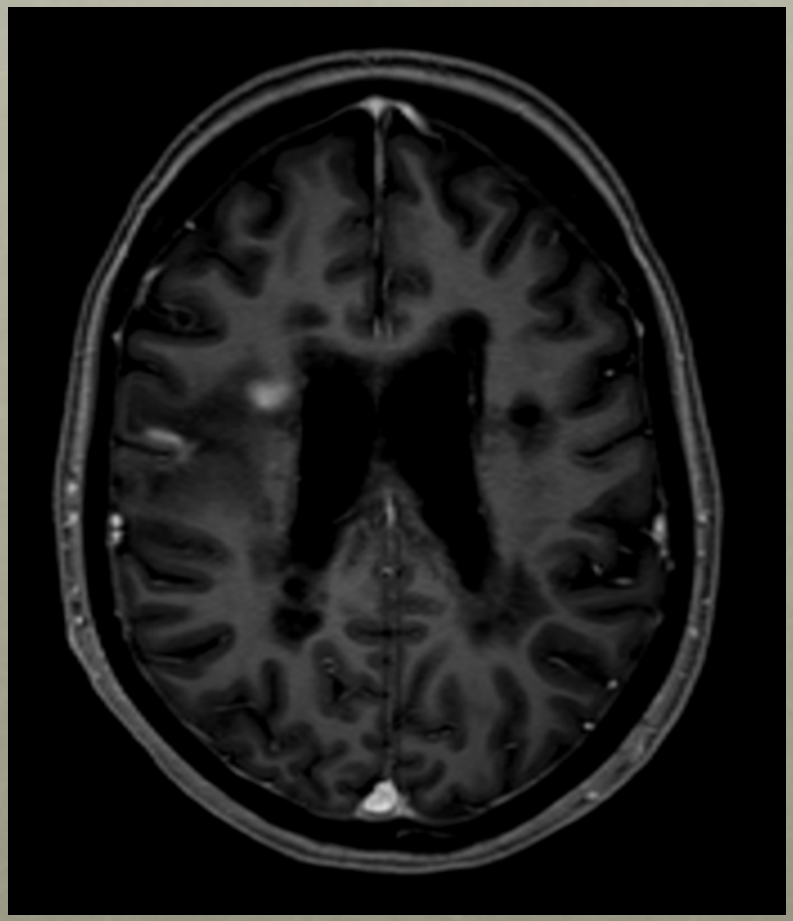

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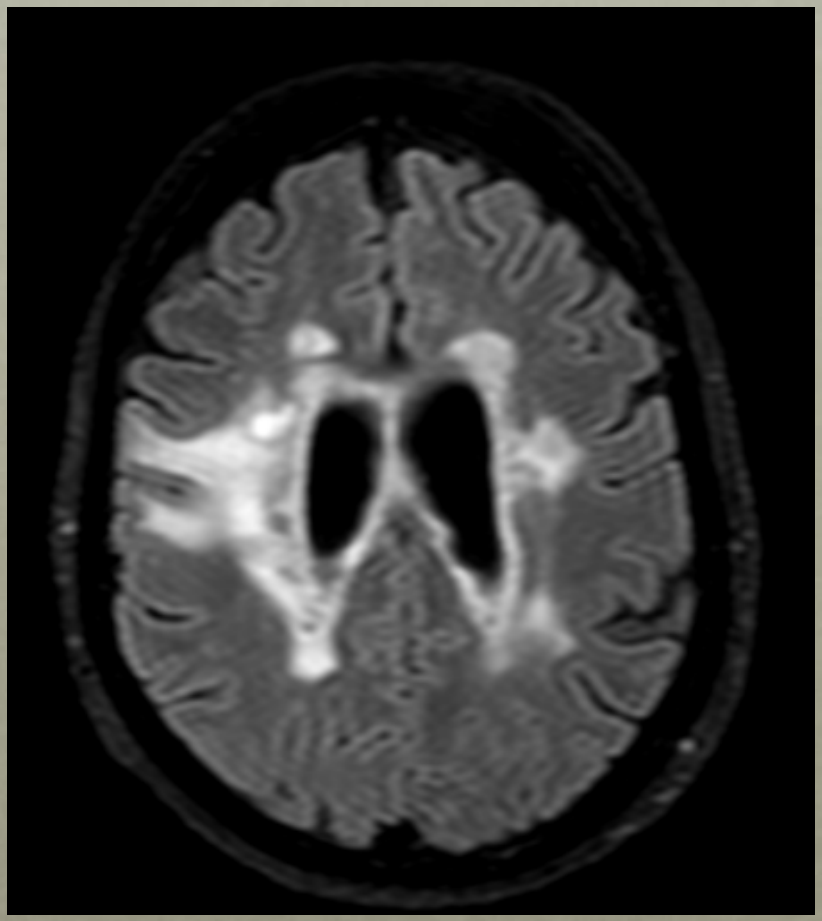

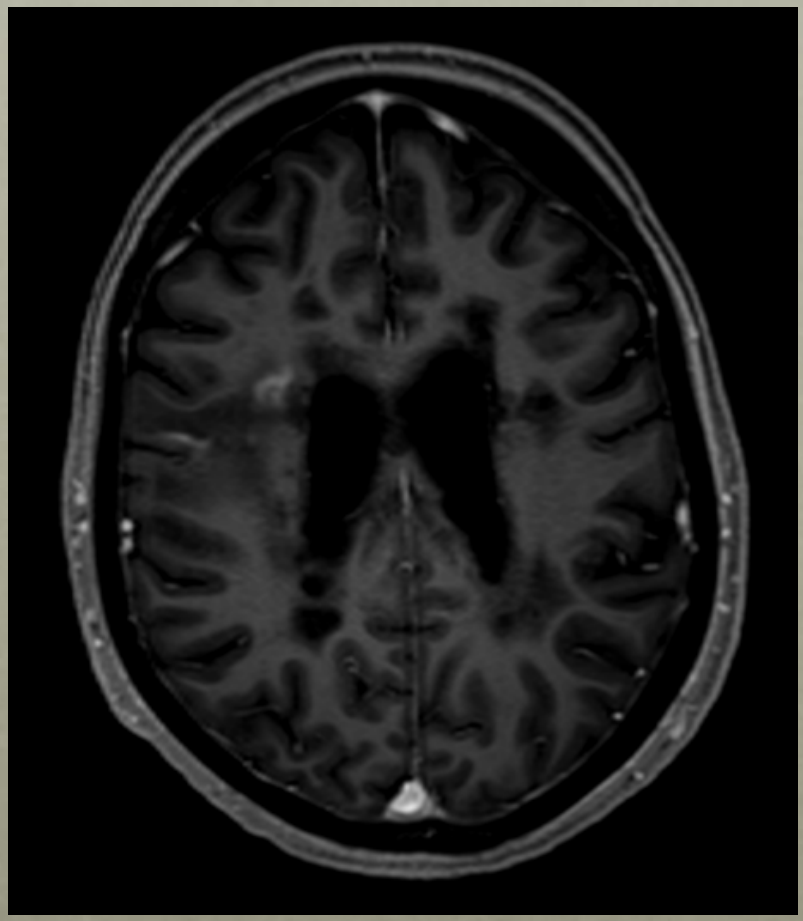

ONLINE FIRST

Rituximab-Associated Progressive Multifocal Leukoencephalopathy in Rheumatoid Arthritis

David B. Clifford, MD; Beau Ances, MD, PhD; Craig Costello, MBBS; Shari Rosen-Schmidt, MD; Magnus Andersson, MD; Deborah Parks, MD; Arie Perry, MD; Raju Yerra, FRACP; Robert Schmidt, MD, PhD; Enrique Alvarez, MD, PhD; Kenneth L. Tyler, MD

Objective: To describe the development of progressive multifocal leukoencephalopathy (PML) in patients with rheumatoid arthritis (RA) treated with rituximab.

Design: Case study.

Setting: Clinical care for patients with rheumatologic diseases. Most were referred to academic centers for care after diagnosis (Washington University, St Louis, Missouri; Karolinska Insitute, Stockholm, Sweden; and Royal Melbourne Hospital, Melbourne, Australia) while one was cared for in a neurology practice in Dallas, Texas, with consultation by an academic neurovirologist from the University of Colorado in Denver.

Patients: Four patients developing PML in the setting of rituximab therapy for RA.

Intervention: Rituximab therapy.

Main Outcome Measures: Clinical and pathological observations.

Results: Four patients from an estimated population of 129 000 exposed to rituximab therapy for RA are reported in whom PML developed after administration of this drug. All were women older than 50 years, commonly with Sjögren syndrome and a history of treatment for joint disease ranging from 3 to 14 years. One case had no prior biologic and minimal immunosuppressive therapy. Progressive multifocal leukoencephalopathy presented as a progressive neurological disorder, with diagnosis confirmed by detection of JC virus DNA in the cerebrospinal fluid or brain biopsy specimen. Two patients died in less than 1 year from PML diagnosis, while 2 remain alive after treatment withdrawal. Magnetic resonance scans and tissue evaluation confirmed the frequent development of inflammatory PML during the course of the disease.

Conclusion: These cases suggest an increased risk, about 1 case per 25 000 individuals, of PML in patients with RA being treated with rituximab. Inflammatory PML may occur in this setting even while CD20 counts remain low.

Arch Neurol. 2011;68(9):1156-1164. Published online May 9, 2011. doi:10.1001/archneurol.2011.103

PML vid Rituximab

PML reported with rituximab (15 April 2010)	
MS	0
RA	6
SLE + other autoimmune diseases	4 + 4
Other oncology[a] + CLL + other haematology	100 + 35 + 2
Unknown indications	2

Reported Rate of PML in RA patients treated with rituximab is very rare[b] (~1 / 20,000)

All cases associated with concomitant immunosuppression

[a] Över 1 miljon exponerade för Rtx inom onkologin

[b] Council for international Organization of Medical Sciences definition av "very rare" < 1/10 000

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Short communication

Rituximab treatment did not aggravate ongoing progressive multifocal leukoencephalopathy in a patient with multiple sclerosis

F. Asztely [a,*], E. Gilland [a], M.P. Wattjes [b], J. Lycke [a]

[a] Institute of Neuroscience and Physiology, Department of Clinical Neuroscience and Rehabilitation, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden
[b] Department of Radiology & Nuclear Medicine, VU University Medical Center, Amsterdam, The Netherlands

PML Diagnos

1. Kliniska symtom: Nylig personlighetsförändring, progredierande hemipares, språkstörningar, retrochiasmal synstörning

2. MRI: Fokal lesion som vanligen omfattar juxta/subcortical vitsubstans +/- cortex. Vid natalizumab-associerad PML, viss grad av av inflammation (Gd+ lesioner)

3. CSF:
   - Högsensitiv PCR för JCV
   - Negativ PCR i tidigt skede utesluter inte PML
   - Upprepade liquorprover kan krävas

4. Hjärnbiopsi
   - Huvudsakligen om det finns andra differntialdiagnoser, t ex malignitet

- Serologisk analys finns tillgänglig för MS-patienter

Uteslutande av PML kräver negativ CSF-PCR samt regress av MR-förändringar

Pathogenesis of progressive multifocal leukoencephalopathy and risks associated with treatments for multiple sclerosis: a decade of lessons learned

Eugene O Major, Tarek A Yousry, David B Clifford

Progressive multifocal leukoencephalopathy (PML) is a rare, devastating demyelinating disease of the CNS caused by *Lancet Neurol* 2018; 17: 467–80

	Pathology	Duration	Blood		CSF		MRI
			Antibody	DNA	Antibody	DNA	
Presymptomatic PML	Unknown, probably as in classic PML	Estimate of 3–6 months from viral entry into brain to onset of neurological symptoms*	Anti-JCV antibody increases; dynamic increase supports PML diagnosis	Transient, 50–500 copies per mL	Detectable, titre increasing	Generally low titre detectable, $10–10^7$ copies per mL	New lesion on surveillance MRI; generally small; DWI bright
Classic symptomatic PML without immune responses†	Demyelinating plaques, bizarre astrocytes, oligodendrocytes with nuclear inclusions, notably absent inflammatory response	3–6 months from onset of symptoms to death if no immune reconstitution	Marked increase typical of PML	Transient, 50–500 copies per mL	Detectable, titre increasing	$10–10^7$ copies per mL, rarely undetectable	Typical brain lesions‡, enlarging; rare if any contrast enhancement§; no mass effect
PML with IRIS§	Classic pattern plus inflammatory response with variable mix of CD8+ and CD4+ lymphocytes; might have declining levels of JCV	1–5 months after immune reconstitution¶, associated with potential for survival of PML; might be present at diagnosis in natalizumab-associated PML	Increases	Transient, 50–500 copies per mL	High titre	$10–10^7$ copies per mL; might increase then decrease during course of disease	Typical brain lesions;‡ contrast enhancement usual but not required for IRIS diagnosis§; punctate pattern and T1 bright cortical line indicate this stage of PML
Post-PML in survivors‖	Atrophy, fibrosis, rare JCV-infected cells	Years, depending on underlying disease; fixed lesion might support clinical improvement 6–12 months after diagnosis but is then clinically stable in most cases	Few data exist but probably relatively stable at high titres	Transient, 50–500 copies per mL	High titre	Often undetectable, but can remain detectable**	No contrast enhancement; brain atrophy in region of prior lesions

DWI=diffusion-weighted imaging. JCV=JC virus. IRIS=immune reconstitution inflammatory syndrome. PML=progressive multifocal leukoencephalopathy. *Duration of the presymptomatic stage depends on lesion location in the brain. †Typical of PML that develops in patients with untreated HIV or AIDS or in other highly immune-deficient settings in which virtually no immune response is seen. ‡Four key features suggest a PML lesion in asymptomatic patients: subcortical location (involvement of U-fibres), T1 hypointensity, DWI hyperintensity, and the presence of punctate T2-hyperintense lesions. Evolution of the lesion on subsequent scans is important in substantiating a diagnosis. §PML with IRIS can also occur at the presymptomatic and symptomatic phase when partial immune deficiency occurs (common at onset in patients with multiple sclerosis and natalizumab-associated PML). Punctate lesions and T1 cortical bands probably indicate inflammation with or without contrast enhancement. Previous use of corticosteroids reduces the chance of contrast enhancement without eliminating the inflammatory response. ¶PML with IRIS persists for up to 5 months or longer and might necessitate repeated treatment for suppression. ‖Death from PML typically occurs within 6 months of diagnosis, whereas survivors die of other causes months to many years later, often hastened by underlying diseases. **JCV DNA copy number typically decreases and is often undetectable in survivors of PML. However, virological cure does not occur and low levels of detectable virus in the CSF can persist indefinitely. For full footnotes, see appendix.

Table 2: **Clinical stages of PML**

Behandling vid PML

- Det finns ingen vedertagen behandling mot PML förutom att korrigera ev. immundefekt (behandla AIDS, avsluta läkemedel som påverkar immunsystemet etc.)
- Det finns ett antal läkemedel som använts på försök men stödet för meningsfull effekt är svagt

Mirtazapin

- Stämningshöjande läkemedel som binder till serotoninreceptorn 5HT2a
- JC-virus har in vitro visats använda denna receptor för att ta sig in i astrocyter
- Det finns positiva case reports och en studie som visade en icke-signifikant trend till att mirtazapin skulle vara bättre än ingen behandling alls

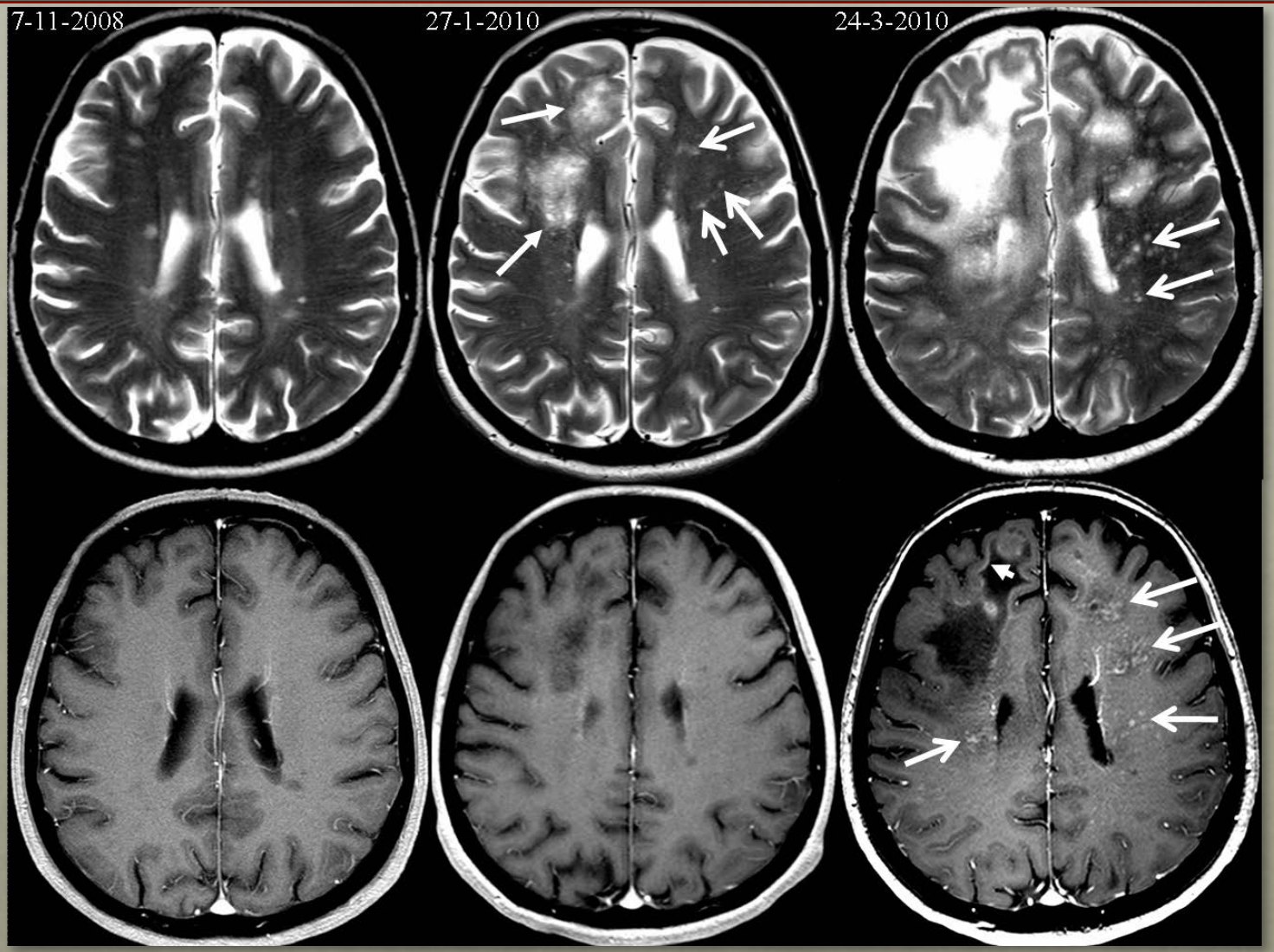
Cidofovir (Vistide)

- Antiviralt medel, inhiberar viralt DNA-polymerase och därigenom replikation
- Har använts för behandling av BK-virus (som tillhör samma familj som JC-virus)
- Det finns både negativa och positiva fallbeskrivningar för behandling av PML. Det finns även negativa retrospektiva observationsstudier för kombinationen av HAART och cidofovir. Nyttan är alltså inte säkerställd, men det finns en teoretisk bakgrund till att använda läkemedlet.
- Njurtoxiskt, därför ofta samtidig behandling med probenacid

IRIS vid korrigering av immundefekten

- Efter dagar till veckor uppstår vanligen IRIS (Immune Reconstitution Inflammatory Syndrome) när immunsystemet får möjlighet att bekämpa JCV i CNS
- Försämring av neurologiska symtom som kan bli livshotande
- Högdos Solu-Medrol 1 g x III – V förbättrar sannolikt prognosen och kan upprepas

PML-IRIS



Prognos

- Dålig
- Mortalitet hos patienter som drabbats av PML under natalizumab-behandling är kring 25%
- 1-årsöverlevnad hos HIV-PML visades i en grupp på 60 patienter i en amerikansk studie vara 52%
- I en litteraturstudie av 38 fall av PML hos personer med enbart diskret immundefekt samt immunokompetenta sågs mortalitet på 71% med medianöverlevnad på 8 månader

RISKSTRATIFIERING VID NTZ BEHANDLING

Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies

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Summary

Background Previous estimates of risk of progressive multifocal leukoencephalopathy (PML) in patients with multiple sclerosis receiving natalizumab were stratified by three risk factors: anti-John Cunningham virus (JCV) antibodies in serum, previous immunosuppressant use, and treatment duration, which were estimated using population-based assumptions. We aimed to calculate PML risk estimates from patient-level risk-factor data and to stratify risk by concentrations of anti-JCV antibody in serum (anti-JCV antibody index).

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Original Research Paper

PML risk stratification using anti-JCV antibody index and L-selectin

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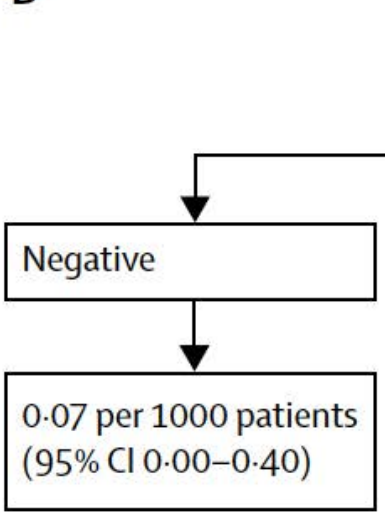


Natalizumab exposure (months)†	Patients without previous immunosuppressant use, per 1000 patients (95% CI)			Patients with previous immunosuppressant use, per 1000 patients (95% CI)
	Index ≤0·9	Index >0·9 to ≤1·5	Index >1·5	
1–12	0·01 (0·00–0·04)‡	0·1 (0·0–0·2)	0·2 (0·0–0·5)	0·4 (0·0–2·3)
13–24	0·06 (0·00–0·16)‡	0·3 (0·0–0·6)	1·0 (0·3–1·7)	0·5 (0·0–2·6)
25–36	0·2 (0·0–0·4)	0·8 (0·1–1·6)	2·8 (1·5–4·1)	3·9 (1·6–8·0)
37–48	0·4 (0·0–1·1)	2·1 (0·2–4·0)	7·1 (4·6–9·5)	8·8 (4·6–15·4)
49–60	0·5 (0·0–1·3)	2·4 (0·2–4·7)	8·2 (5·0–11·3)	8·8 (3·8–17·3)
61–72	0·6 (0·0–1·6)	3·0 (0·2–5·9)	10·2 (5·7–14·7)	5·6 (1·2–16·3)§

Figure 3: Updated PML risk estimate based on natalizumab exposure, previous immunosuppressant use, and anti-JCV antibody index

	Patients without previous immunosuppressant use, per 1000 patients			Patients with previous immunosuppressant use, per 1000 patients
	Index ≤0·9	Index >0·9 to ≤1·5	Index >1·5	
0	0·0 (0·0–0·0)	0·0 (0·0–0·0)	0·0 (0·0–0·0)	0·0 (0·0–0·0)
12	0·01 (0·00–0·03)	0·06 (0·00–0·15)	0·2 (0·0–0·5)	0·4 (0·0–1·0)
24	0·06 (0·00–0·17)	0·3 (0·0–0·7)	1·1 (0·4–1·8)	0·8 (0·0–1·8)
36	0·2 (0·0–0·6)	1·1 (0·3–2·0)	3·7 (2·3–5·2)	4·4 (1·5–7·2)
48	0·6 (0·0–1·6)	3·1 (1·2–5·0)	10·4 (7·7–13·2)	12·6 (7·2–18·1)
60	1·1 (0·0–2·8)	5·5 (2·7–8·3)	18·2 (14·1–22·4)	21·3 (14·1–22·3)
72	1·6 (0·0–4·3)	8·5 (4·8–12·2)	28·0 (22·0–34·0)	27·0 (18·4–39·5)

Data are cumulative risk estimates (95% CI) for the pooled cohort. Lengths of natalizumab exposure are given as number of infusions. PML=progressive multifocal leukoencephalopathy. JCV=John Cunningham virus.

Table 2: **Cumulative risk estimates of PML according to number of natalizumab infusions and anti-JCV antibody index scores in patients with and without previous immunosuppressant use**

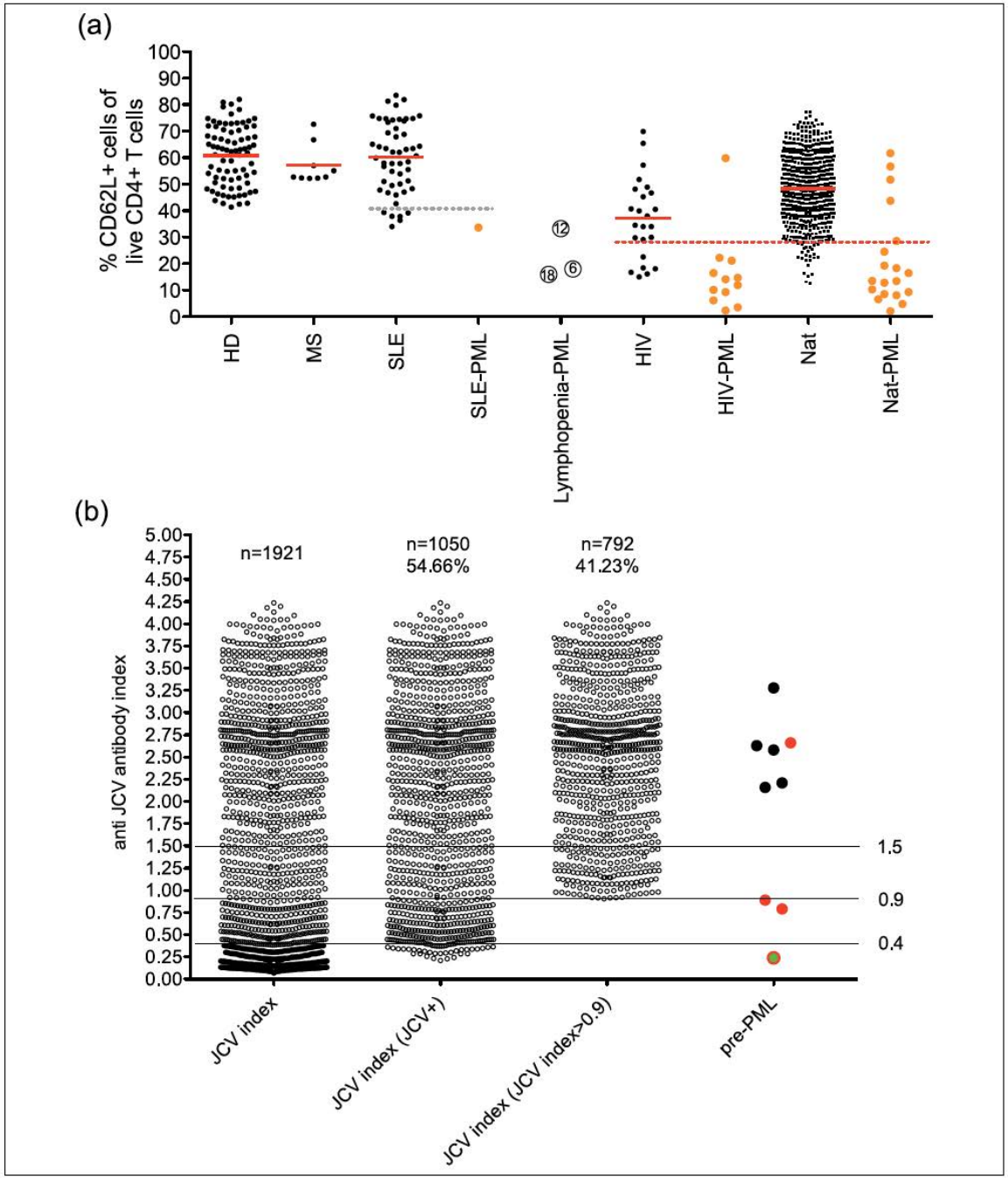
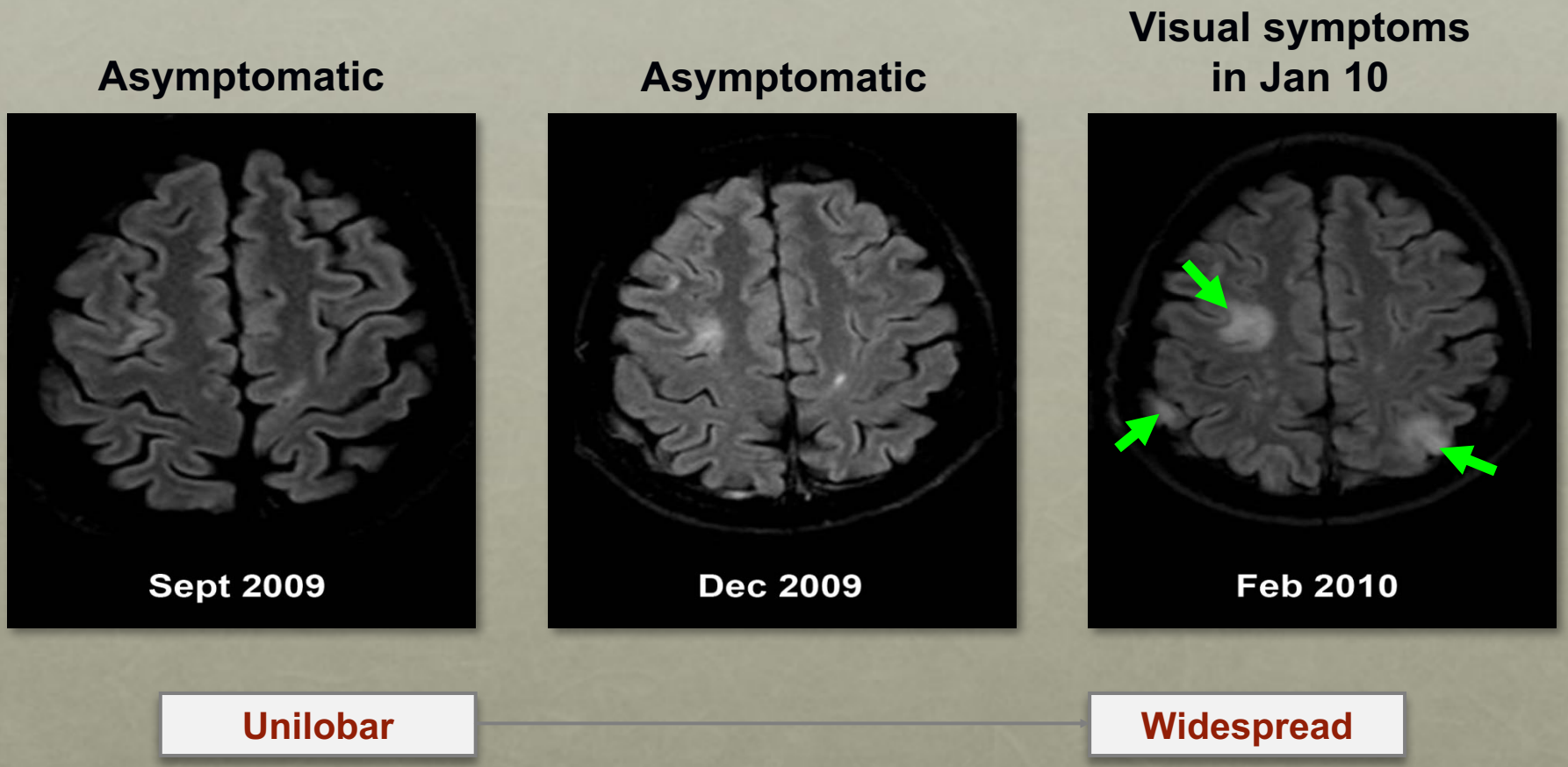


Figure 3. Assessment of CD62L in different associations of PML and of JCV index in a large cohort of German patients treated with natalizumab.

Prognosen förbättras av preklinisk detektion av PML



Dong-Si et al. Presented at AAN; March 16–23, 2013; San Diego, CA. P04.271.

Sammanfattning

- PML är ovanligt, även för neuroradiologen, bra att vara orienterad även som neurolog!
- Immundefekta individer av sjukdom eller behandling, ssk Tysabri!
- Kognitiva och fokalneurologiska symtom som progredierar över veckor. Drabbar ej ryggmärg eller synnerv
- MRI: FLAIR känsligast, fyller ut ett helt gyrus, punktformade T2 hyperintensiteter, DWI hyperintensiv
- Upprepade MR och LP, JCV-PCR kan vara negativ initialt vid Tysabri-associerad PML
- Om orsakad av Tysabri gör plasmaferes x V
- Vid IRIS högdos Solu-Medrol