# IMAGING NEL (NEURO)LES

## e nuovi approcci terapeutici


university of ferrara
600 YEARS OF LOOKING FORWARD.

*UOC di Reumatologia*
*Dipartimento di Scienze Mediche*

***A.Bortoluzzi***

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

# Classification of central NPSLE syndromes

## ACR 1999

**12 CNS syndromes**

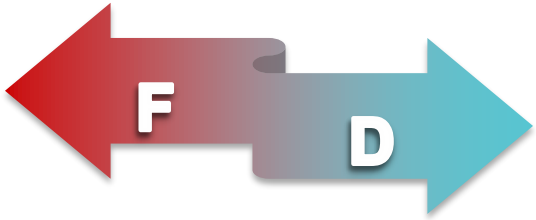
### NEUROLOGIC DISEASES

- *Cerebrovascular disease*
- *Seizures*
- *Movement disorder*
- *Myelopathy*

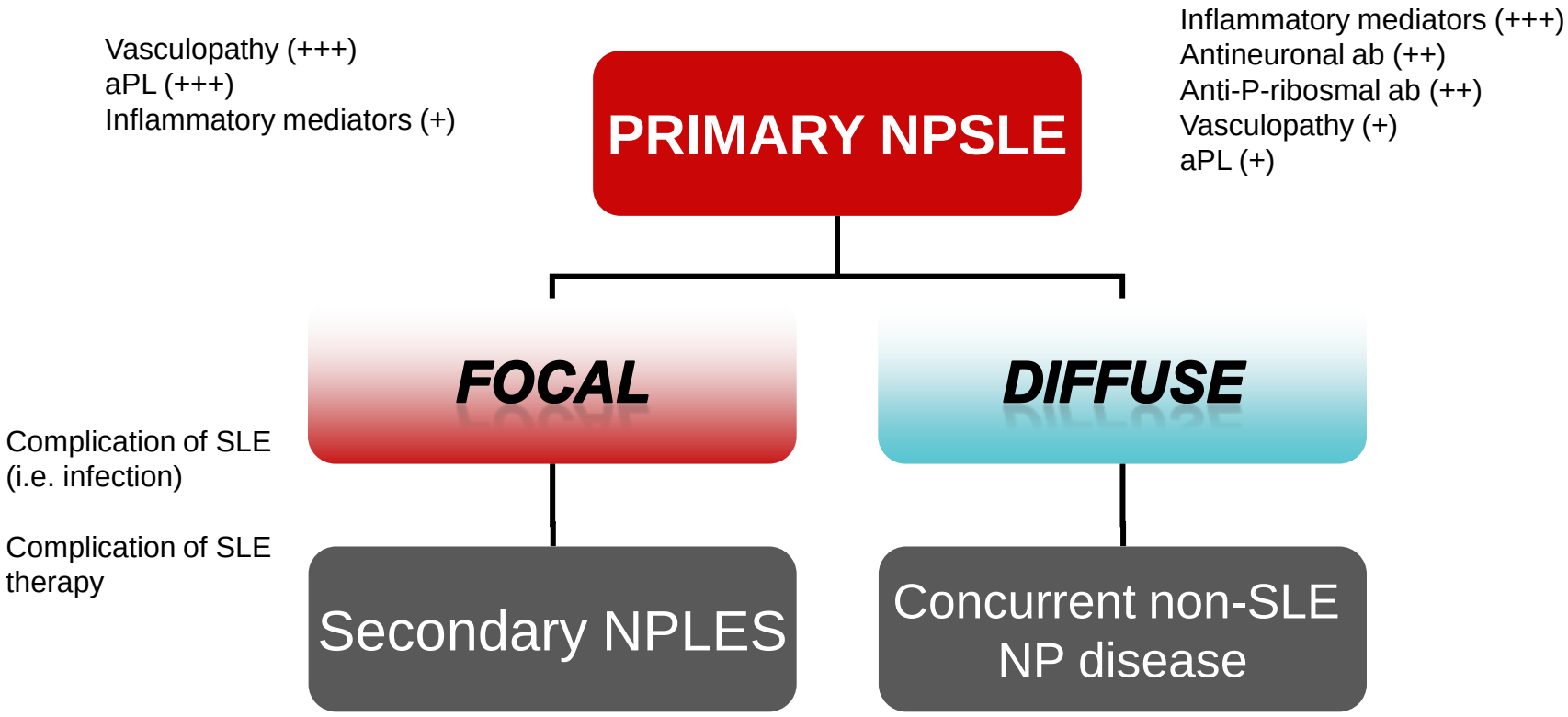
- *Headache*
- *Aseptic meningitis*
- *Demyelinating syndrome*
- *Headache*
- *Cognitive dysfunctions*

### PSYCHIATRIC DISEASES

- Acute confusional state
- Anxiety disorder
- Cognitive dysfunction
- Mood disorder
- Psychosis



# CNS involvement in SLE




Hanly, J. G. (2014) Diagnosis and management of neuropsychiatric SLE
*Nat. Rev. Rheumatol.* doi:10.1038/nrrheum.2014.15

nature REVIEWS RHEUMATOLOGY

# To date, there is no single neuroimaging technique able to check simultaneously all these pathogenetic pathways

## Morphological techniques

**Allow to detect anatomy and the consequences of different pathogenetic mechanisms:**

- Ischemia or Infarcts
- Hemorrhage
- Demyelination
- Edema
- Gliosis
- Atrophy

## Functional & Quantitative techniques

**Allow to detect more subtle pathologic processes such as :**

- Hypoperfusion
- Metabolic derangements
- Microarchitectural damage
- Functional impairment

# OUTLINE - cMRI

- ✓ **cMRI: menu of Head MRI Scans**
- ✓ cMRI in newly diagnosed NPSLE
- ✓ cMRI in early SLE
- ✓ cMRI in late SLE

# Diagnostic work-up in NP-SLE

## Focus on neuroimaging

**Recommendation**

EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs

*Bertsias et al, EULAR RECOMMENDATIONS. Ann Rheum Dis 2010*

**The imaging technique of choice**

**MRI (T1/T2-weighted)**

**MRI (T1 with gadolinium)**

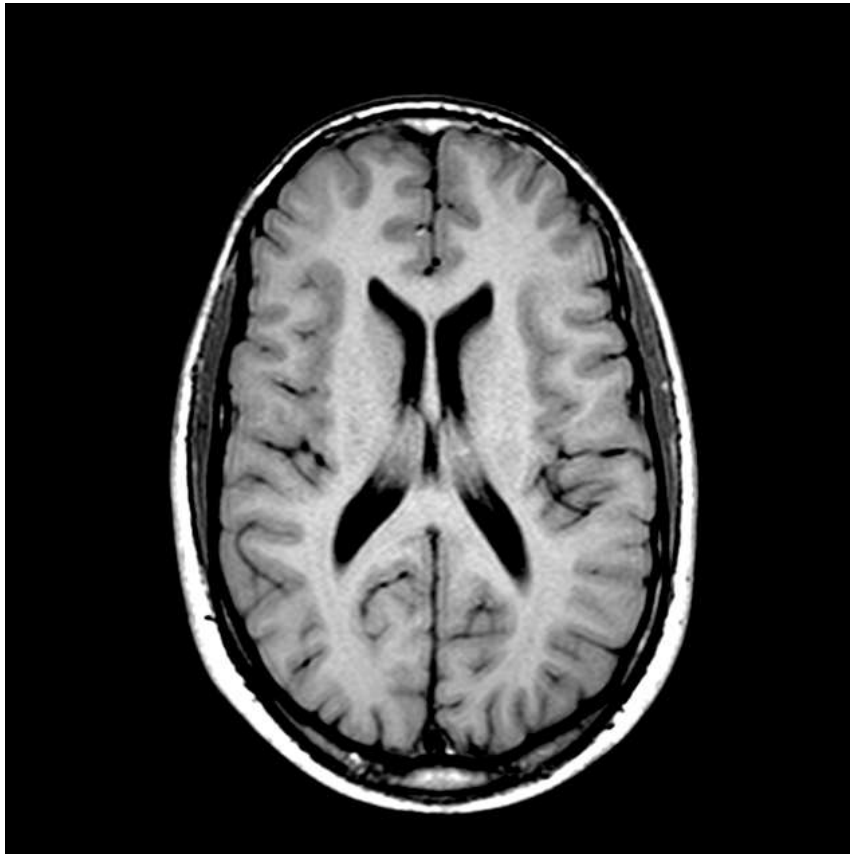
**MRI-FLAIR**

**DWI**

**Neuroimaging may detect NPSLE involvement and exclude other causes**

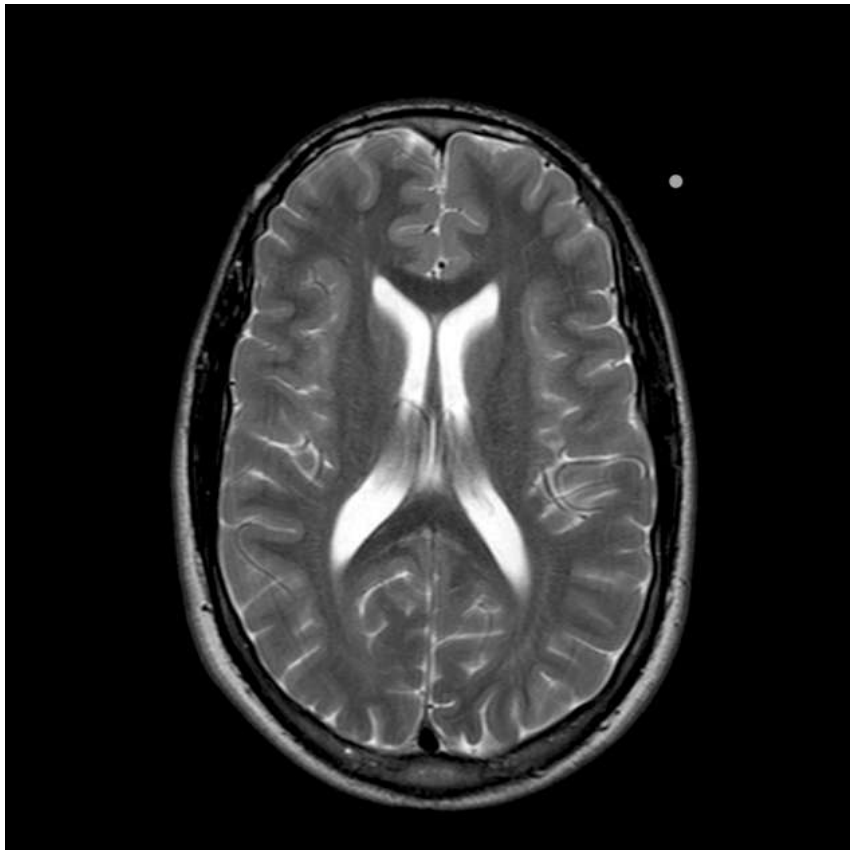
# cMRI - T1 characteristics

- **Cerebrospinal fluid** is dark
- useful for visualizing normal **anatomy**
- White matter brighter than gray
- W-W; G-G
- T1 CE



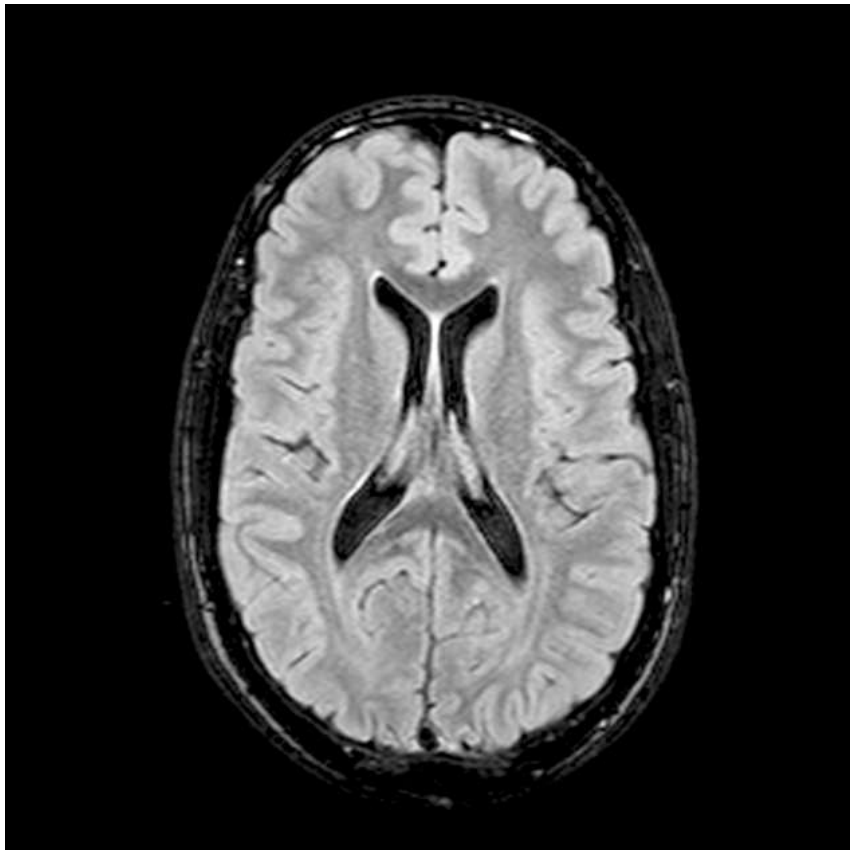
# cMRI - T2 characteristics

- CSF is light
- **Gray matter brighter than white**
- **T2** is useful for visualizing pathology
- to differentiate WML and perivascular spaces;
- to identify old infarcts



# cMRI - FLAIR

- **suppress CSF** signal
- Gray matter brighter than white
- ↑ WML (inflammation, edema)
- cortical or large subcortical infarcts;
- **to differentiate WML from perivascular spaces and lacunes**
- bring out the periventricular hyperintense lesions



The Journal of Rheumatology

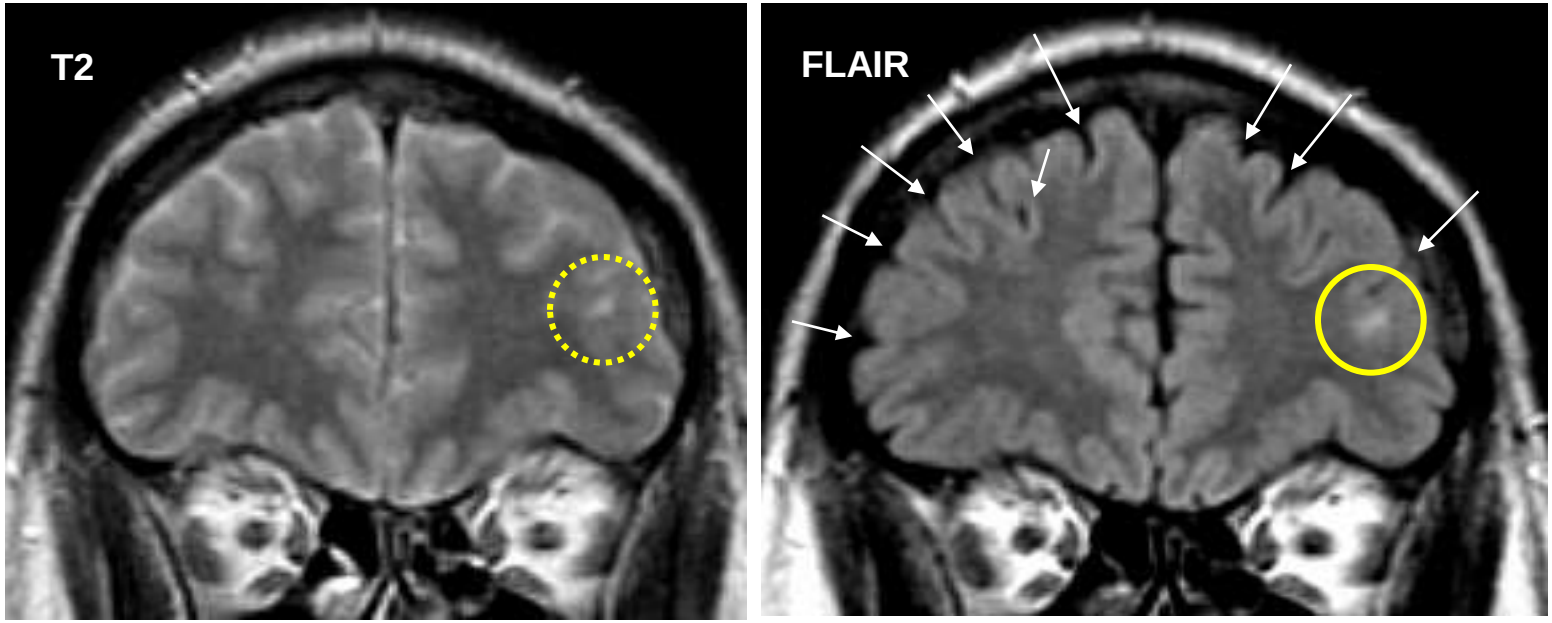
J Rheumatol 2003;30:1983–9

# Fluid Attenuated Inversion Recovery (FLAIR) Imaging in Neuropsychiatric Systemic Lupus Erythematosus

WILMER L. SIBBITT Jr, PAUL J. SCHMIDT, BLAINE L. HART, and WILLIAM M. BROOKS

**FLAIR produces a T2 weighted image …**

**… but with suppressed cerebrospinal fluid signal**




**FLAIR detected significantly more lesions than PD/T2 resulting in a 5 % greater diagnostic sensitivity**

# OUTLINE - cMRI

- ✓ cMRI: menu of Head MRI Scans
- ✓ **cMRI in newly diagnosed NPSLE**
- ✓ cMRI in early SLE
- ✓ cMRI in late SLE

# cMRI in newly NPSLE

Brain abnormalities in newly diagnosed neuropsychiatric lupus: Systematic MRI approach and correlation with clinical and laboratory data in a large multicenter cohort

Nicolae Sarbu [a], Farah Alobeidi [b], Pilar Toledano [c], Gerard Espinosa [c], Ian Giles [d], Anisur Rahman [d], Tarek Yousry [b], Sebastian Capurro [a], Rolf Jäger [b], Ricard Cervera [c], Nuria Bargalló [a,e,*]

**40.7 % NORMAL** | **108 pts, 40.6 yrs** | **59.3 % ABNORMAL**

## Inflammatory-like lesions

T2/FLAIR hyperintense lesions involving G or W-matter, mediumlarge, ill defined, **without vascular territory distribution**, with possible mass effect

## Large vessel disease

brain infarcts in a large-artery territory

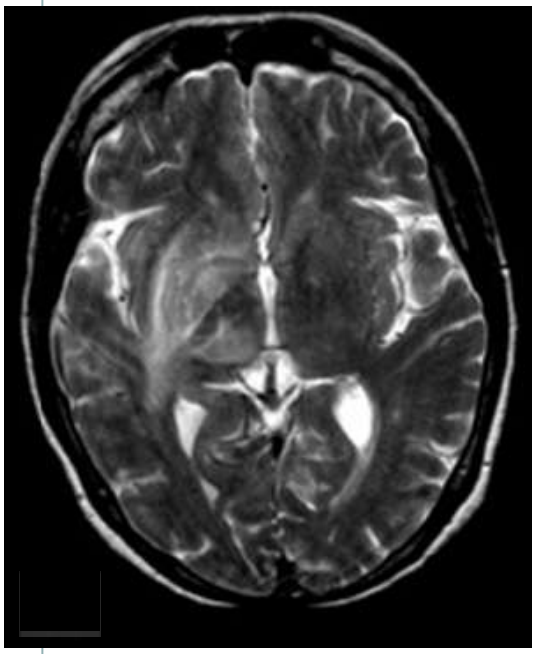
## Small vessel disease

WML (including also basal ganglia and infratentorial involvement), small subcortical infarcts,microbleeds, brain atrophy

Autoimmunity Reviews

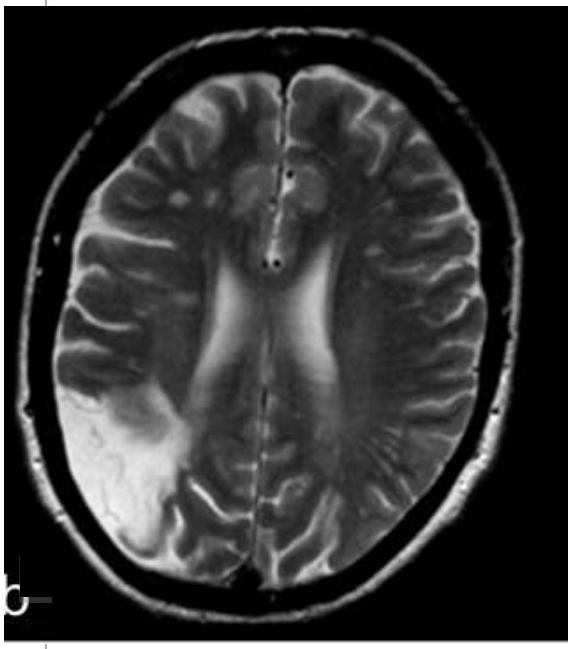
Sarbo et al. Aut. Rev. 2015 153-59

## *Inflammatory-like lesions* **7 %**



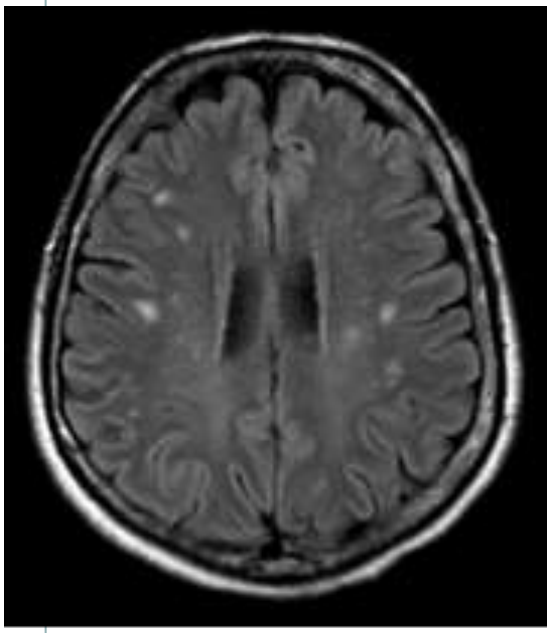
**Axial T2-weighted at the level of the basal ganglia in a patient with aseptic meningitis shows an ill-defined T2-hyperintensity involving the right basal ganglia, thalamus, and external and internal capsule**

## *Large vessel disease* **13 %**



**chronic infarct in the posterior superficial territory of the right middle cerebral artery together with focal white-matter hyperintensities**

## *Small vessel disease* **55.6 %**



**Headache 48.6 % CVD 78.9 % (microbleeds 41.7 %) cognitive disf. 78.6 %**

# Neuropsychiatric Systemic Lupus Erythematosus

## Lessons Learned From Magnetic Resonance Imaging

J. Luyendijk, S. C. A. Steens, W. J. N. Ouwendijk, G. M. Steup-Beekman, E. L. E. M. Bollen, J. van der Grond, T. W. J. Huizinga, B. J. Emmer, and M. A. van Buchem

**MR images of the first episode of active NPSLE in 74 patients were retrospectively reviewed**

The mean SD age of the patients at the time of imaging was 37.9 ± 13.7 years

**Focal WML (49 %) or both WM and GM (5%)**

**Diffuse cortical gray matter lesions (12%)**

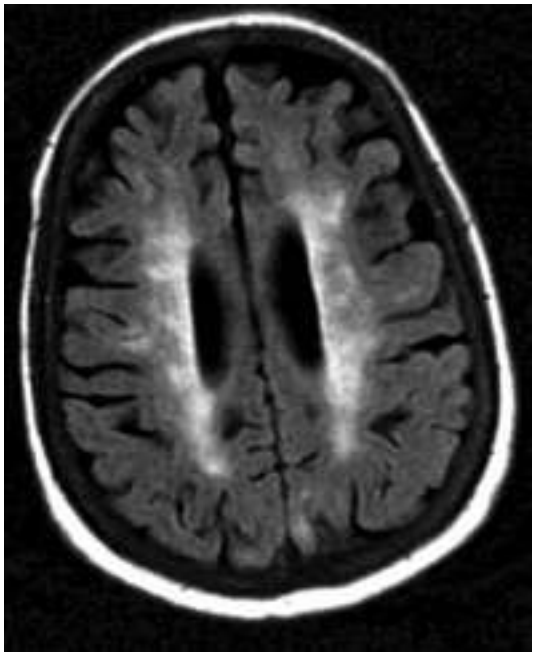
**Confluent WML (16 %)**

**Cortical atrophy (16 %)**

***Normal MRI 42 %***

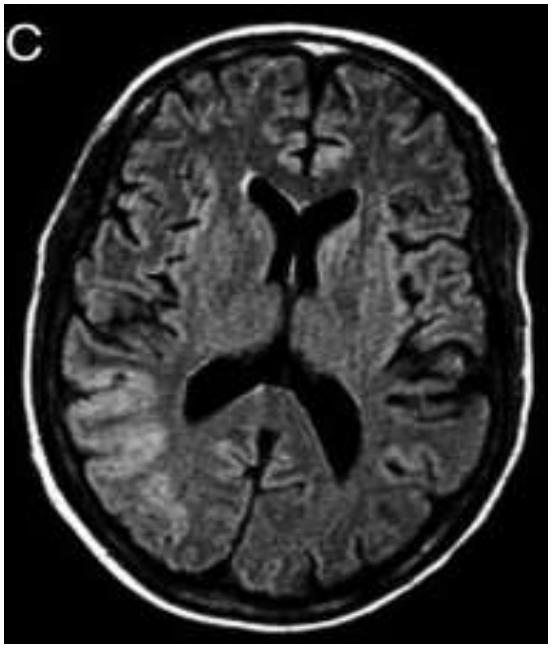
ARTHRITIS & RHEUMATISM
Vol. 63, No. 3, March 2011, pp 722–732

## Confluent WML



**FLAIR image**
extensive symmetric periventricular WMHIs in the **corona radiata, capsula interna, and centrum semiovale**

## Diffuse cortical gray matter lesions

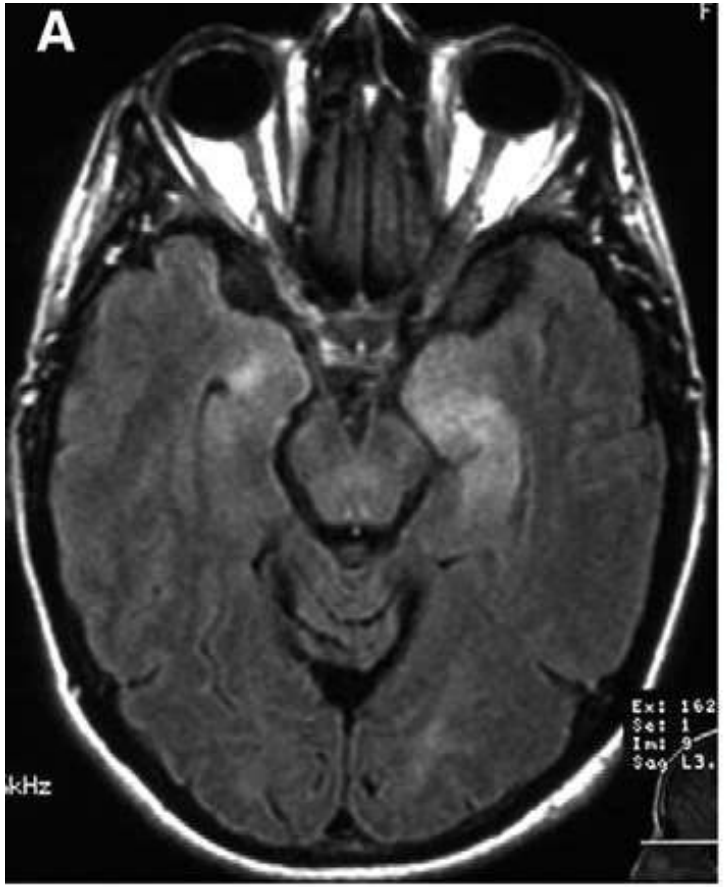



**FLAIR image**
diffuse hyperintense signal inthe cortical GMs

J. Luyendijk et al.

# GML: D.D.

- 12% larger diffuse
- Cortex ≥ 1 gyri and extending through the full width of the cortex
- PTG: inflammatory immune response by autoab against antigens or neurons
- D.D. paraneop encephalitis




Anti-NMDA receptor encephalitis: prominent psychiatric symptoms, memory loss, decreased consciousness (TERATOMA)

*Dalmau et al. Lancet Neurol* 2008; 7: 327–40

# Additional MRI characteristics of *acute episode*

T1- weighted GD sequence

↓

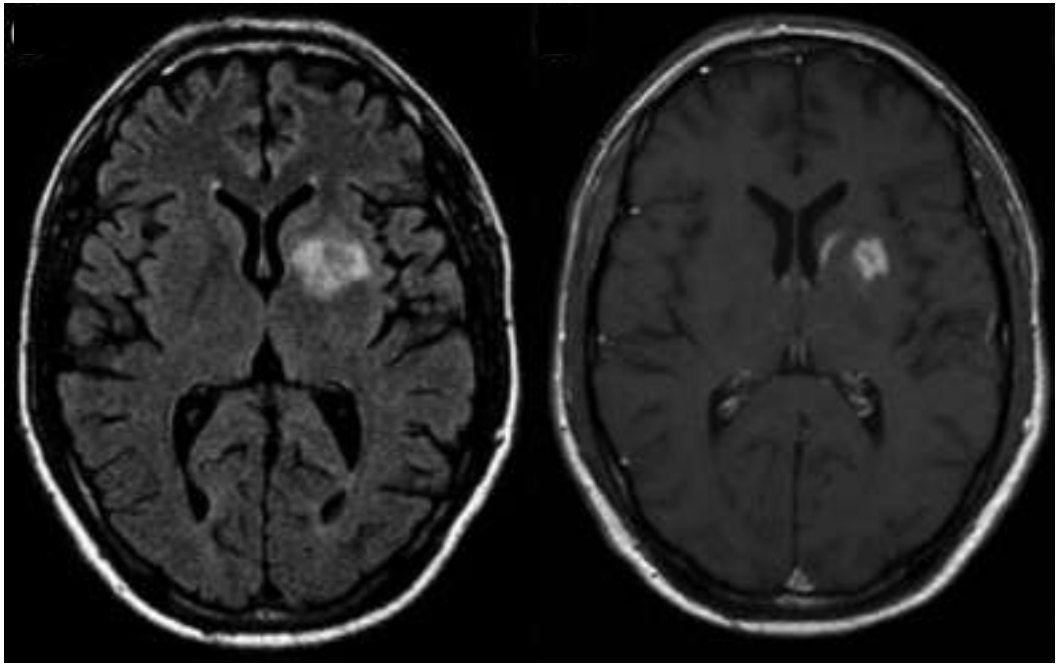
Blood-brain barrier distruption

**VASOGENIC EDEMA**

**ACTIVE ONGOING PATHOLOGIC PROCESS DURING ACTIVE NP SYMPTOM**

↑Signal in FLAIR

RING-SHAPED enhancement



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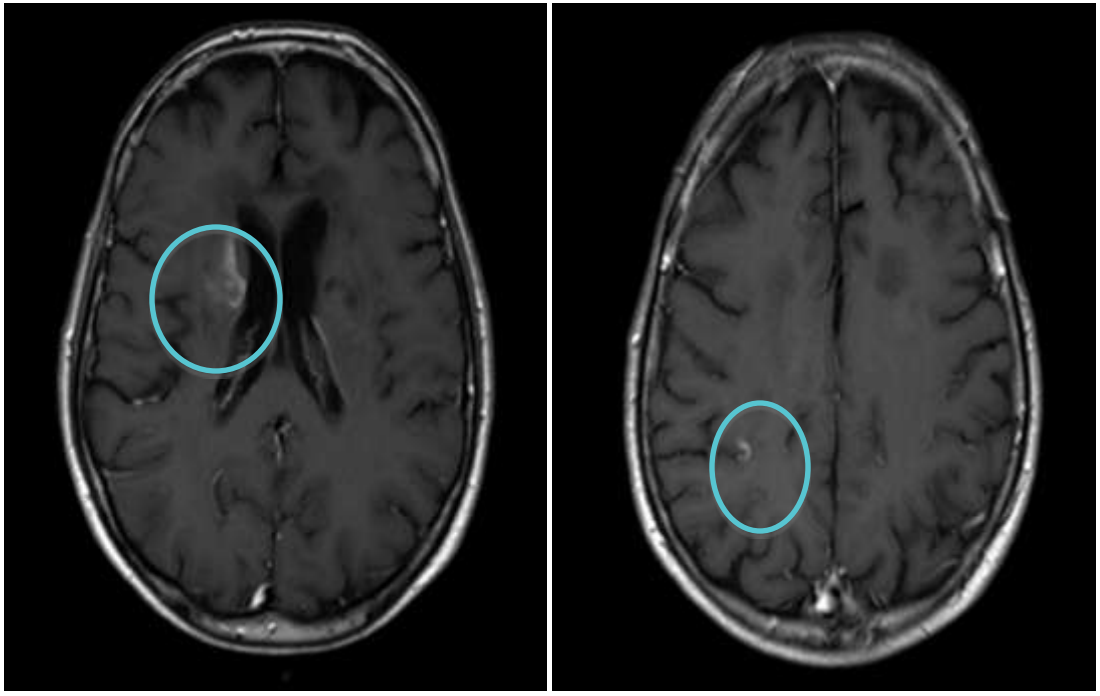
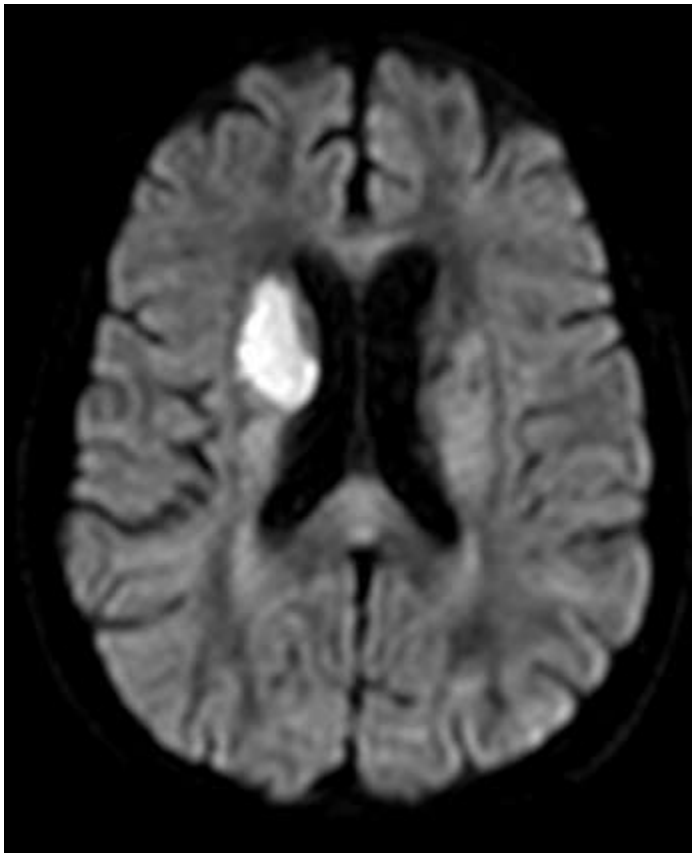


personal observation

# cMRI - DWI/ADC

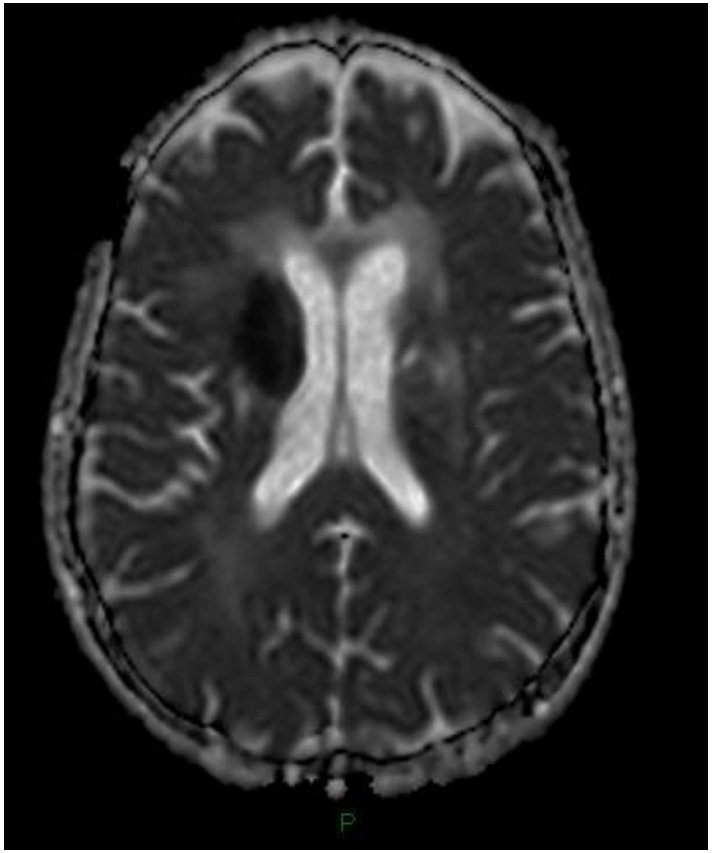
Brownian motion of H20 molecules and H20 diffusion in tissues

Pitfall: The DWI is a manipulated T2 image



Barriers (cell membranes) interfere with the free diffusion

"apparent diffusion coefficient" or **ADC**



# DWI in NPSLE

Brownian motion of H20 molecules and H20 diffusion in tissues

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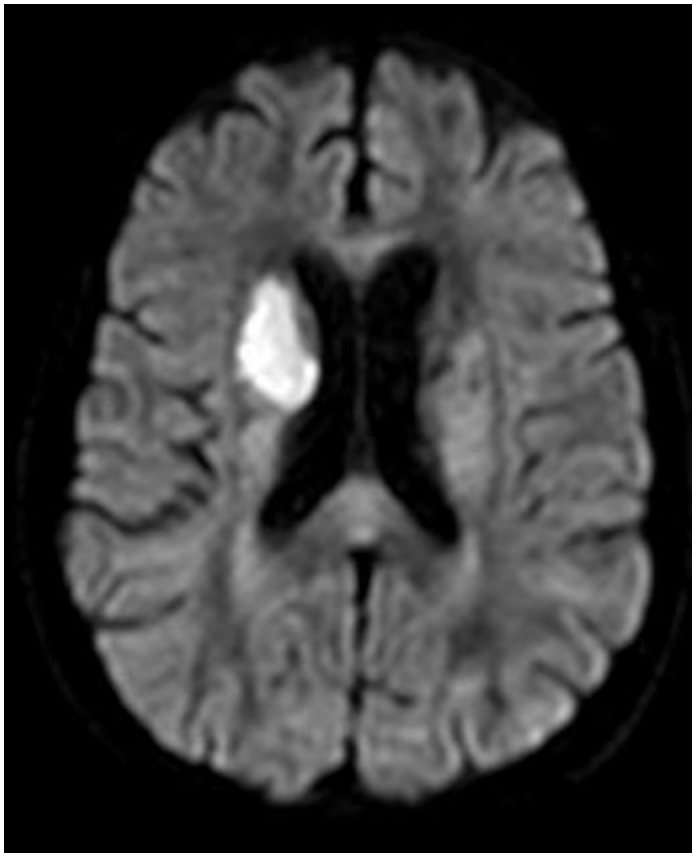


**ACTIVE ONGOING PATHOLOGIC PROCESS DURING ACTIVE NP SYMPTOM**

**early detection (within 1h) of acute ischemic insult**

**CYTOTOXIC EDEMA**

**differentiation between old and recent ischemic lesions**

# DWI in NPSLE

**Brain Diffusivity in Patients with Neuropsychiatric Systemic Lupus Erythematosus with New Acute Neurological Symptoms**

41–551 (2007)

Robert C. Welsh, PhD,[1*] Habib Rahbar, BS,[1] Bradley Foerster, MD,[1]
Majda Thurnher, MD,[2] and Pia C. Sundgren, MD, PhD[1]

**University Hospital of Michigan**

**NPSLE and SLE patients show increased general brain diffusivity compared with healthy controls, even when their routine MRI findings are normal**

Diffusion changes in patients with systemic lupus erythematosus

Lijuan Zhang[a], Melanie Harrison[b], Linda A. Heier[a], Robert D. Zimmerman[a], Lisa Ravdin[c], Michael Lockshin[b], Aziz M. Uluğ[a,*]

**Cornell University, New York**

Magnetic Resonance Imaging 25 (2007) 399–405

**Increased diffusivity suggests a loss of tissue integrity. Its measurement may be a sensitive tool sensitive in detecting early disease involvement**

# OUTLINE - cMRI

- ✓cMRI: menu of Head MRI Scans
- ✓cMRI in newly diagnosed NPSLE
- ✓**cMRI in early SLE**
- ✓cMRI in late SLE

The Journal of Rheumatology

J Rheumatol 2008;35:2348–54

# Brain Magnetic Resonance Imaging in Newly Diagnosed Systemic Lupus Erythematosus

MICHELLE PETRI, MOHAMMAD NAQIBUDDIN, KATHRYN A. CARSON, DANIEL J. WALLACE, MICHAEL H. WEISMAN, STEPHEN L. HOLLIDAY, MARGARET SAMPEDRO, SHALINI NARAYANA, PETER T. FOX, CRYSTAL FRANKLIN, PATRICIA A. PADILLA, and ROBIN L. BREY

**Objective** : to determine the prevalence of cerebral atrophy and focal lesions in a cohort of patients with newly diagnosed SLE (97 pts **< 9 months** from diagnosis underwent brain MRI)

| | |
|---|---|
| **Cerebral atrophy** | **18 %** |
| OLDER PTS | |
| ANXIETY DISORDER | |
| **Focal lesions** | **8 %** |

Mean age **38 yrs**

**These findings suggest that the brain may be affected extremely early in the course of SLE**

# Longitudinal analysis of gray and white matter loss in patients with systemic lupus erythematosus

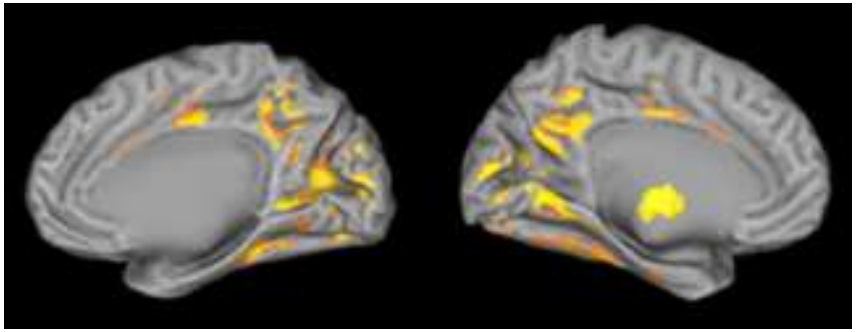
*NeuroImage 34 (2007) 694–701*

Simone Appenzeller,[a,b] Leonardo Bonilha,[c] Pablo A. Rio,[b] Li Min Li,[b,d] Lilan Tereza Lavras Costallat,[a] and Fernando Cendes[b,d,*]

## BRAIN ATROPHY

Voxel-based morphometry (VBM)

**Involves WM and GM especially in NPSLE**



**Patients with severe cognitive impairment had a more pronounced WM and GM reduction**

Reduced WM and GM volumes were independently associated with :

- **SLE duration and damage**
- **presence of APLA**

**Total corticosteroid dose was associated with GM reduction and not with WM loss in SLE patients**

**Atrophy is progressive in follow-up MRI**

# OUTLINE - cMRI

- ✓cMRI: menu of Head MRI Scans
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- ✓**cMRI in late SLE**

# cMRI in late SLE

**Small focal WML were more frequently seen in NP-SLE than in SLE without NP involvement**

| 107 patients examined | NPSLE 66 pts Pts N (%) | SLE without NP 41 pts Pts N (%) | p |
|---|---|---|---|
| Cortical atrophy | 6 (9) | 1 (2.4) | ns |
| Subarachnoid dilation | 12 (18.2) | 7 (17.1) | ns |
| Ventricular dilatation | 6 (9) | 0 | ns |
| Periventricular diff. WM changes | 4 (6) | 0 | ns |
| Hyperintense focal WM lesions | 39 (59)* | 14 (34) | 0.021 |

G. Castellino[1], M. Padovan[1], A. Bortoluzzi[1], M. Borrelli[2], L. Feggi[3], M. L. Caniatti[4], F. Trotta[1] and M. Govoni[1]

Rheumatology 2008;47:319–323
Advance Access publication 24 January 2008
doi:10.1093/rheumatology/kem354

# Single photon emission computed tomography and magnetic resonance imaging evaluation in SLE patients with and without neuropsychiatric involvement

G. Castellino[1], M. Padovan[1], A. Bortoluzzi[1], M. Borrelli[2], L. Feggi[3], M. L. Caniatti[4], F. Trotta[1] and M. Govoni[1]

**Baseline characteristics**

**41 SLE & 66 NPSLE**
-age **34 vs 41.7 yrs**
- disease duration at the moment of MRI evaluation **5.5 vs 4.6 yrs**

## *Topographic distribution*

| | NPSLE 39 patients[a] | | | | SLE 14 patients[a] | |
|---|---|---|---|---|---|---|
| | D | F | D+F | Percentage | | Percentage |
| Frontal | 17 | 4 | 21 | 53.8 | 10 | 71.4 |
| Parietal | 5 | 1 | 6 | 15.4 | 2 | 14.3 |
| Temporal | 5 | 0 | 5 | 12.8 | 0 | 0 |
| Occipital | 1 | 0 | 1 | 2.5 | 1 | 7.1 |
| Cerebellum | 3 | 1 | 4 | 10.2 | 0 | 0 |
| Monohemispheric | 7 | 2 | 9 | 23.1 | 7 | 50.0 |
| Bihemispheric | 18 | 9 | 27 | 69.2 | 7 | 50.0 |
| Single lesion | 5 | 1 | 6 | 15.4 | 6 | 42.8 |
| Multiple lesions (>5) | 5 | 6 | 11 | 28.2 | 2 | 14.3 |
| Large lesions (>10 mm) | 0 | 2 | 2 | 5.1 | 0 | 0 |

***Infra-tentorial lesions have been detected only in NPSLE; in NPSLE WMH are more frequently multiple, bi-emispheric, larger > 0.5 mm***

# WMHL: D.D.

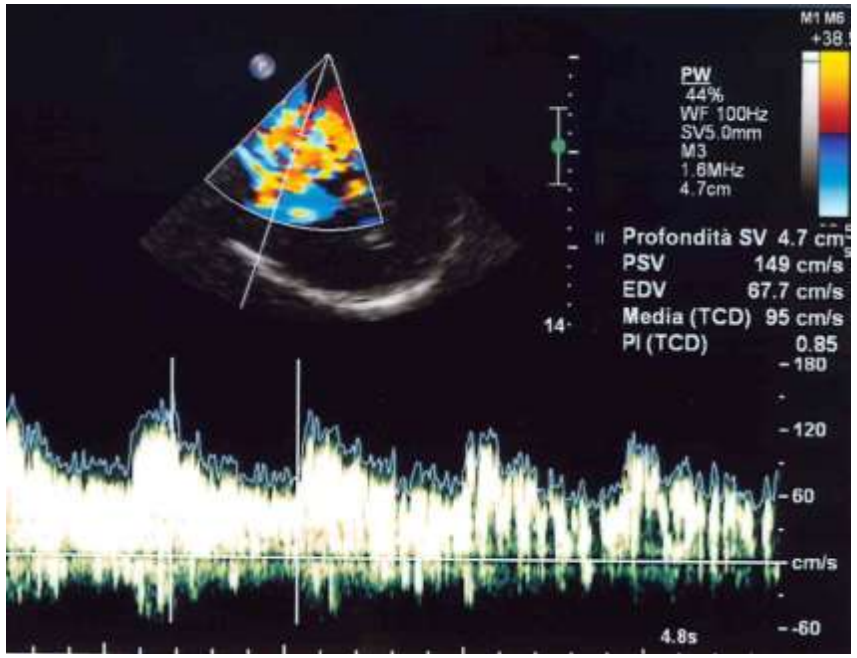
## *AGE*

- Focal hyperintens WML are indistinguishable from age related small vassel disease

## *Vascular Disease*

- hypertension
- heart valuvular disease
- other vasculophaties

**Transcranial doppler US**
Detection of **micro-embolic** signals in patients with history of CVD
PFO



# Advanced neuroimaging techniques

## WHEN MRI IS NORMAL OR DOES NOT PROVIDE AN EXPLANATION A MULTIMODALITY APPROACH IS REQUIRED

### MICROSTUCTURAL DAMAGE

- DIFFUSION-TENSOR IMAGING

### METABOLIC CHANGES

- MR SPECTOSCOPY

### HEMODYNAMIC DIFFERENCES

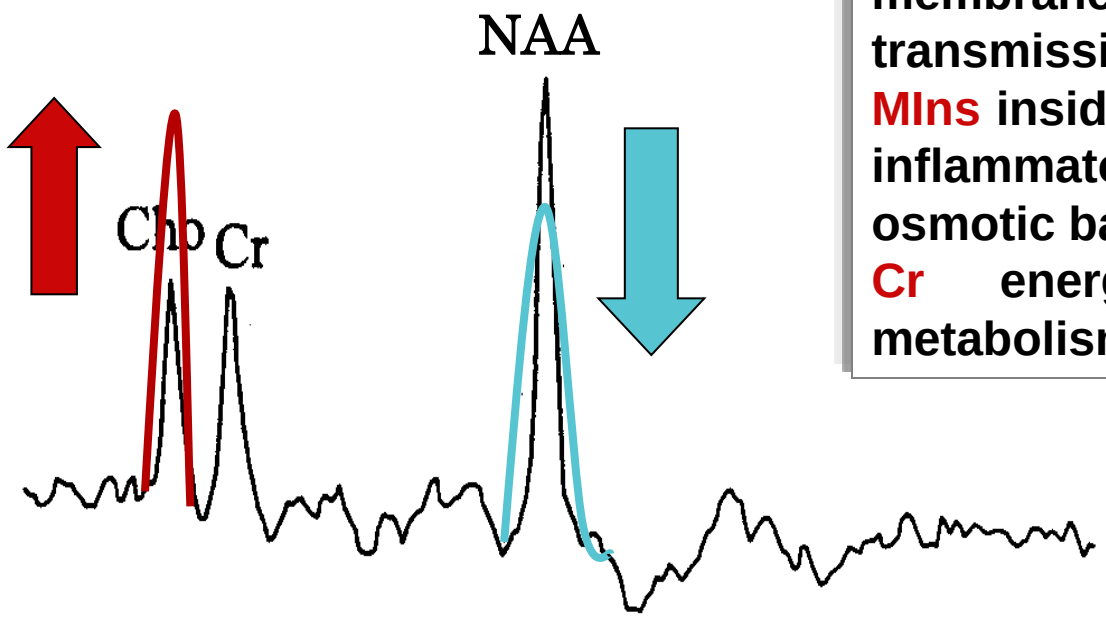
- PERFUSION MRI
- (SPECT)

# Brain tissue biochemistry

# 1H-Magnetic Resonance Spectroscopy

- **Explores the *in vivo* biochemical profile of brain tissue**

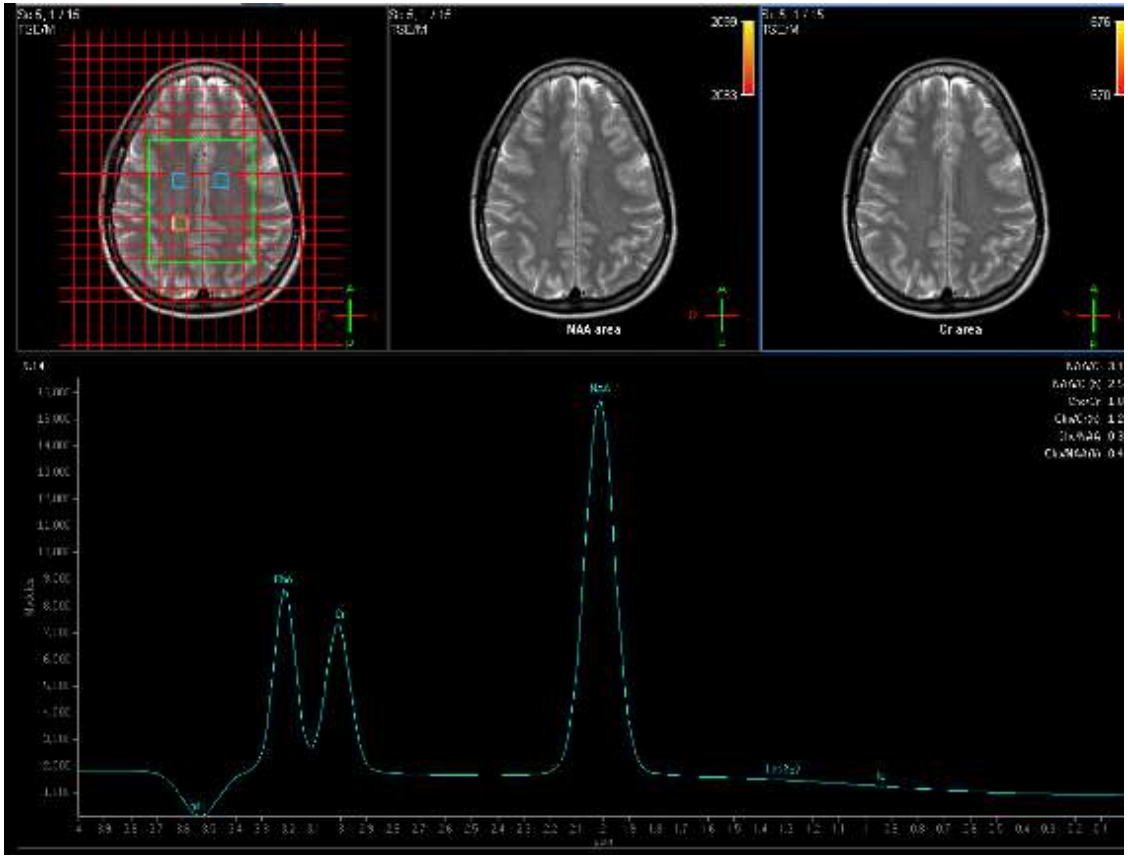
- **Provides quantitative and qualitative information about some brain metabolites dysplayed as spectra**




**NAA** neuronal and axonal density
**Cho** myelin content, neuronal membrane integrity and synaptic transmission
**MIns** inside glial cells, ↑correlates with inflammatory injury that changes ths osmotic balance (gliosis)
**Cr** energetic support for cell metabolism, reference metabolite

# MRS in NPSLE

**Spectra modifications (NAA decrease and Cho increase) have been demonstrated in NPSLE but are not specific for NPSLE**




reduction in NAA/Cr ratio and elevation of Cho/Cr ratio in normal appearing WM is associated with disease activity

*Sibbit et al 1997*
*Castellino et al 2005*

reduction in NAA/Cr in the cortex → neuronal damage in G&W matter

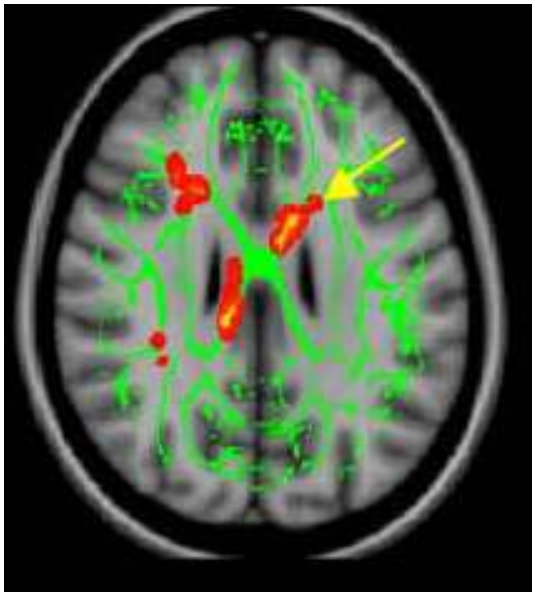
*Zimny et al. 2014*

# Brain microstructure
# Diffusion-Tensor Imaging

- **for *in vivo* mapping of brain microstructure, WM integrity**
- **Mobility of water within normal WM: anisotropic diffusion**
  ***fractional anisotropy* (FA) and *mean diffusivity*(MD)**

FA: marker of white matter fiber integrity
MD: measure of the average molecular motion, affected by cellular size and degradations in tissue integrity

**NPSLE - FA ABNORMALITIES**
**in CC and association tracts**
cingulum fibers
Inferior longitudinal fasciculus, inferior F-O fasciculus, superior longitudinal fasciculus
**Memory and learning processes**



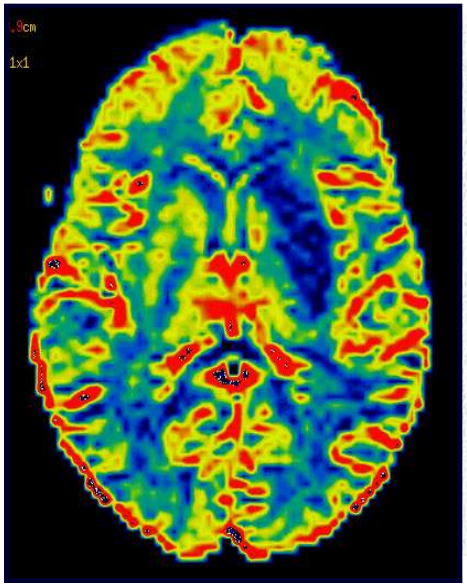
Body of corpus callosum

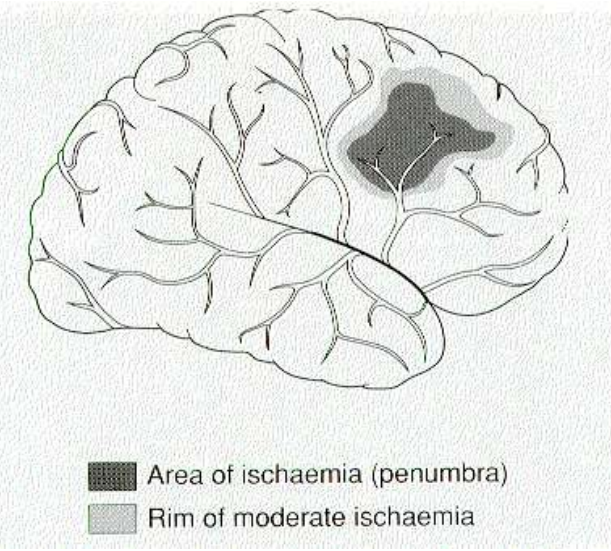
Jung et al. BMC Neurology 2010
Zimny et al. LUPUS 2014

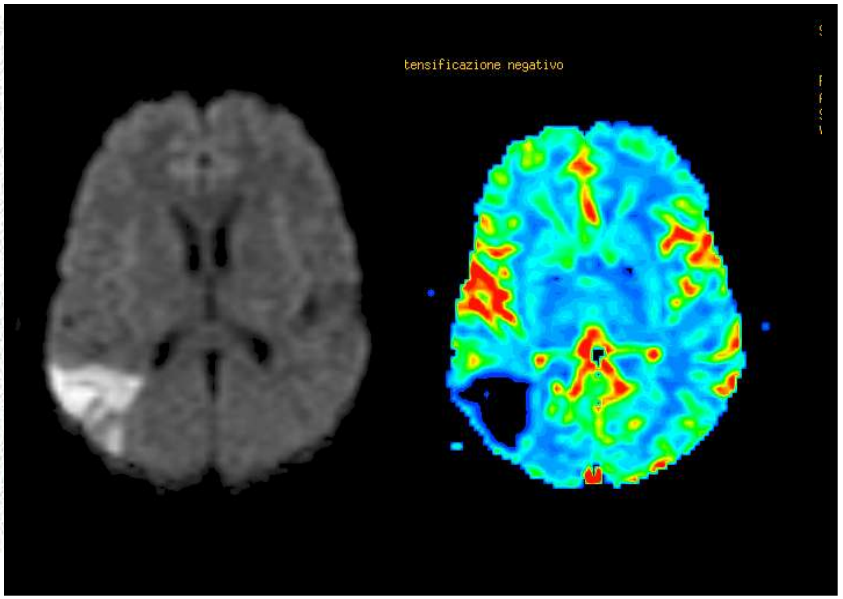
# Hemodynamics of cerebral microcirculation

## Perfusion Weighted Imaging

- **Measures regional CBF and identifies areas at risk of infarctual evolution after ischemic shot**



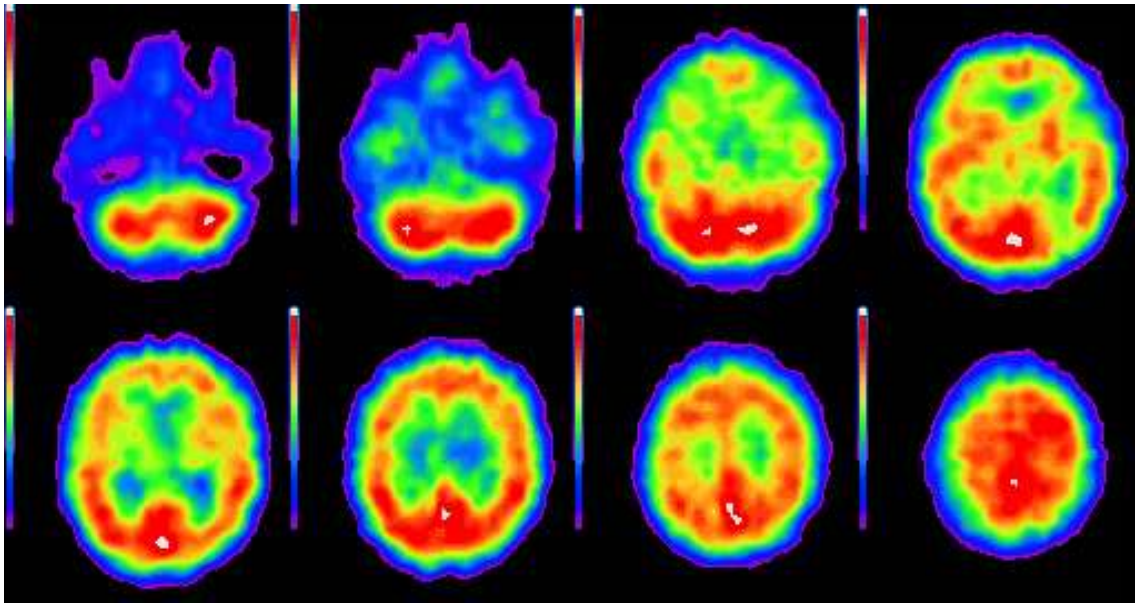



- **Uses paramagnetic contrast (gadolinium)**

# SPECT

**S**ingle
**P**hoton
**E**mission
**C**omputed
**T**omography



- *Explores brain perfusion (CBF + Neuronal viability)*
- *In NPSLE detects focal or multifocal areas of hypoperfusion*
- *Superior to MRI in diffuse (sensitivity 73% versus 54%) NPSLE*
- *Does not provide anatomical details; co-registration of MRI improves specificity (from 40–51% to 73–93%)*

# SPECT *versus* PWI in NPSLE

***Borrelli, Tamarozzi, Colamussi, Govoni, Trotta, Lappi : Radiol Med 2003***

- **SPECT (CBF + Neuronal viability) and PWI (CBF) explore <u>different aspects of brain perfusion</u>**

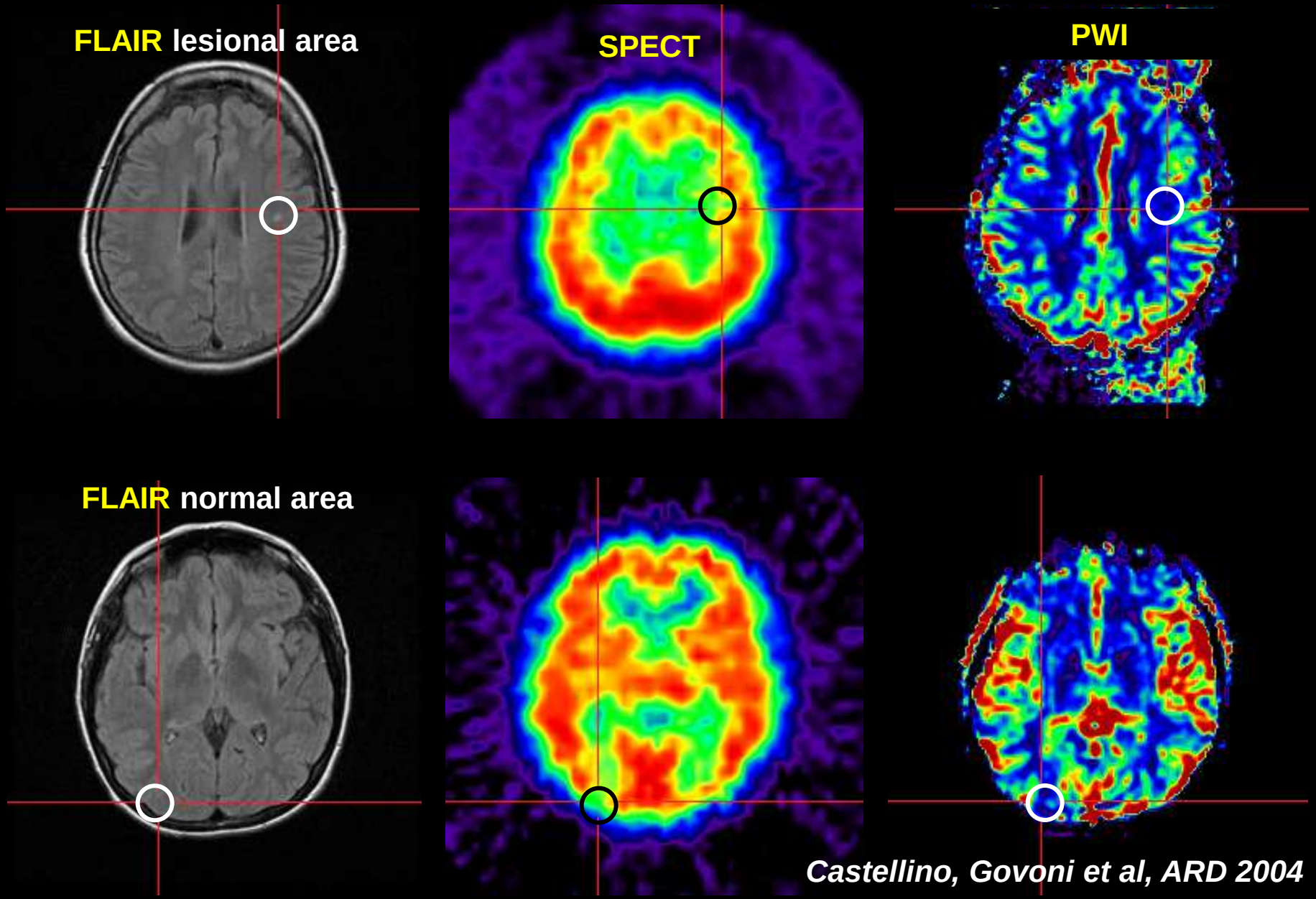
- **SPECT has proven to be <u>more sensitive than PWI</u> in detecting brain hypoperfused areas**

- **Combining SPECT with PWI might yield complementary information about the underlying pathogenetic mechanism of brain hypoperfusion**

Zardi et al. Aut. Rev 2014; 831-839

# MRI-FLAIR / SPECT / PWI co-registration in NP-SLE

## Berlin - EULAR 2004




*Castellino, Govoni et al, ARD 2004*

# What about management?

## Key points in the therapeutic approach to NPSLE

***Establish the diagnosis (primary or secondary SLE)***

***Search for secondary causes and treat aggravating and modifiable risk factors***

- i.e. make accurate work up

***Establish how much active/inactive the NP picture is***

- i.e. ***acute*** (ongoing) vs ***chronic*** and consider the ***activity*** of the underlying SLE too

***Identify the most probable pathophysiologic patway***

- i.e. consider ***focal*** versus ***diffuse***

# Therapy

## ✓ GC e immunosuppressive tp

| Category of Evidence | Strength of Statement | Agreement score |
|---|---|---|
| 1 | A | 9.1 |

- for NP manifestations felt to reflect an immune, inflammatory process
- azathioprine or cyclophosphamide
- In NPSLE refractory : plasma exchange, intravenous immunoglobulin, and rituximab

## ✓ Antiplatelet/anticoagulation therapy

| Category of Evidence | Strength of Statement | Agreement score |
|---|---|---|
| 2 | B | 9.6 |

- manifestations related to antiphospholipid antibodies, particularly in thrombotic CVD
- for primary prevention in SLE patients with persistently positive, moderate or high, antiphospholipid antibody titres

## ✓ Symptomatic therapies and treatment of aggravating factors

| Category of Evidence | Strength of Statement | Agreement score |
|---|---|---|
| 3 | D | 9.8 |

*Bertsias et al, EULAR RECOMMENDATIONS. Ann Rheum Dis 2010*

RHEUMATOLOGY 54

Original article doi:10.1093/rheumatology/keu482

**EULAR recommendations for neuropsychiatric systemic lupus erythematosus *vs* usual care: results from two European centres** Pamfil et al., Rheumatology 2015 epub

## GC e immunosuppressive tp

- 33/41 of inflammatory events received immunosuppressive therapy

**80.5 %**

## Antiplatelet/anticoagulation therapy

- 9/12 aPL (+) patients with such manifestations received anti-platelet/anticoagulation

**75 %**

- 7/31 aPL (+) patients were receiving anti-platelets prior to NPSLE

**22.6 %**

## Symptomatic therapies and treatment of aggravating factors

- Implemented in the vast majority

**80 - 100 %**

# About new TP

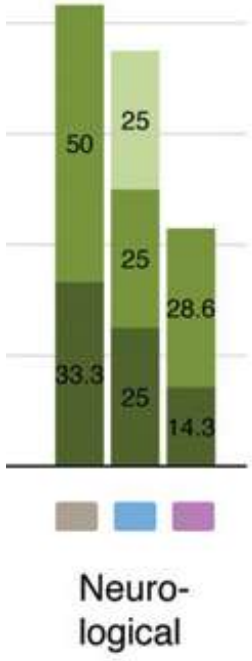


EXTENDED REPORT

## Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials

**Patients with active CNS manifestations were excluded from the studies**

Improvement in the small number of patients with baseline CNS involvement (n=45)
the most common abnormality: **LUPUS HEADACHE (N=24)**
**IMPROVEMENT RATES** for headache with placebo and belimumab 1 and 10 mg/kg were 20.0%, **100%** and **69.2%**, respectively.




Manzi et al. Ann Rheum Dis 2012;71:1833–1838

# Conclusive remarks

## *NEUROIMAGING SUPPORTS DIAGNOSIS*

**It should be advisable to obtain cMRI (also in asymptomatic patients) when SLE is diagnosed for the first time, to allow baseline staging in view of possible - "likely" - future neurological events**

## *HELPS THE ATTRIBUTION PROCESS*

## *ALLOW TO EXCLUDE OTHER CAUSES*

***… for diagnosis and treatment***

**"Physician expertise"**
**remains the GOLD STANDARD**