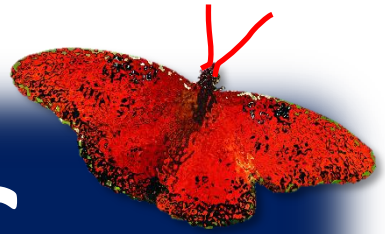


Neuro-psychiatric Lupus (NPSLE)

Pr. Laurent ARNAUD

Department of rheumatology. Strasbourg University Hospital (France)
National Reference Center for Rare Autoimmune Diseases

My disclosures

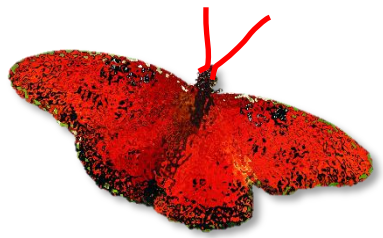
Laurent ARNAUD is a consultant for:

Alexion, Amgen, Astra-Zeneca, BMS, Boehringer-Ingelheim, GSK, Grifols, Janssen-Cilag, LFB, Lilly, Menarini France, Medac, Novartis, Pfizer, Roche-Chugaï, UCB

NPSLE is considered difficult-to-treat

Survey to colleagues on my twitter account @Lupusreference

- Neuropsychiatric lupus
- Refractory cytopenias
- Refractory lupus nephritis
- Fatigue (and other type 2 symptoms)
- Refractory cutaneous lupus
- Transverse myelitis
- Class V nephritis
- Lupus (nephritis) during pregnancy
- Renal thrombotic microangiopathy
- Macrophage activation syndrome
- Arthralgia without arthritis



Impact of NPSLE on mortality

x10

compared to the
general population

x2-3

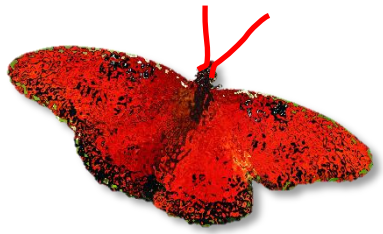
compared to
SLE patients
without NPSLE

10-YEAR MORTALITY
16% in NPSLE
8% in SLE without NP

Hanly et al. SLICC cohort ARD 2020

Today's NPSLE agenda

- ✓ What is NPSLE?
- ✓ How diverse are NPSLE manifestations
- ✓ How common is NPSLE among SLE patients?
- ✓ What are the typical manifestations of NPSLE?
- ✓ How do you attribute NP events to SLE (NPSLE)?
- ✓ Additional diagnostic considerations
- ✓ What is the treatment of NPSLE?



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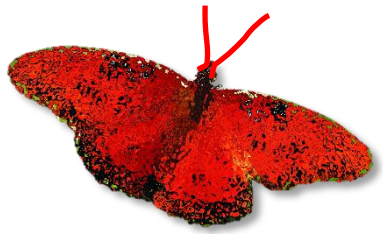
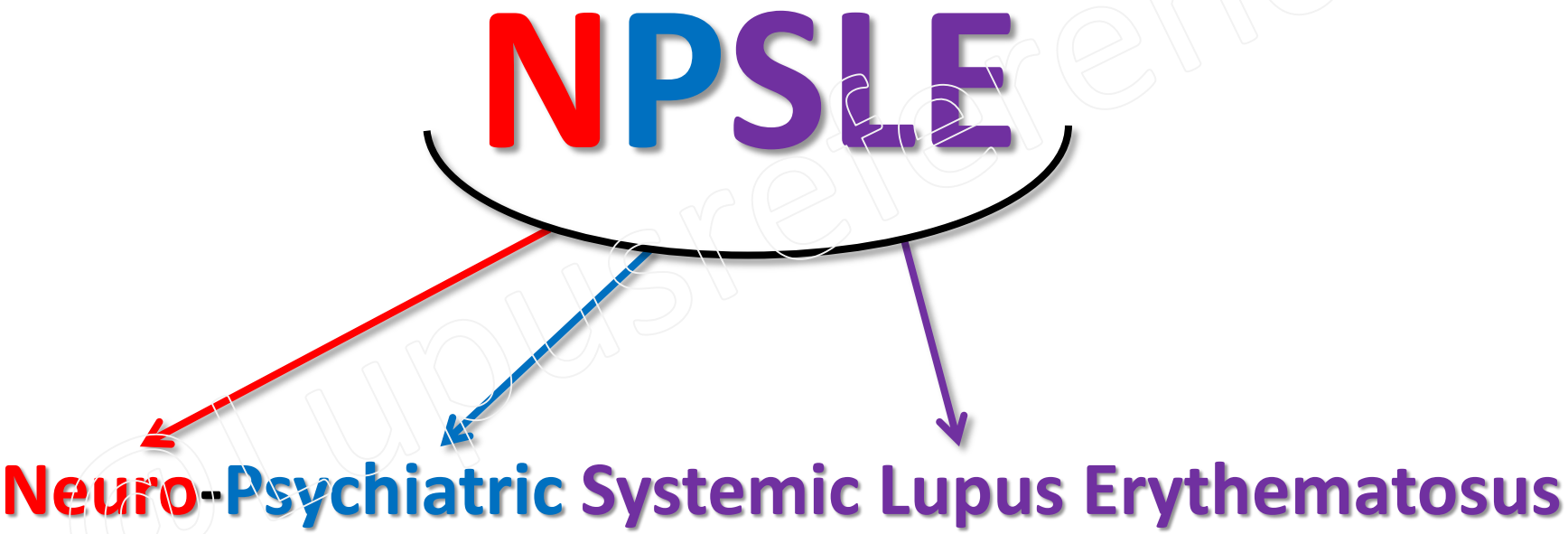
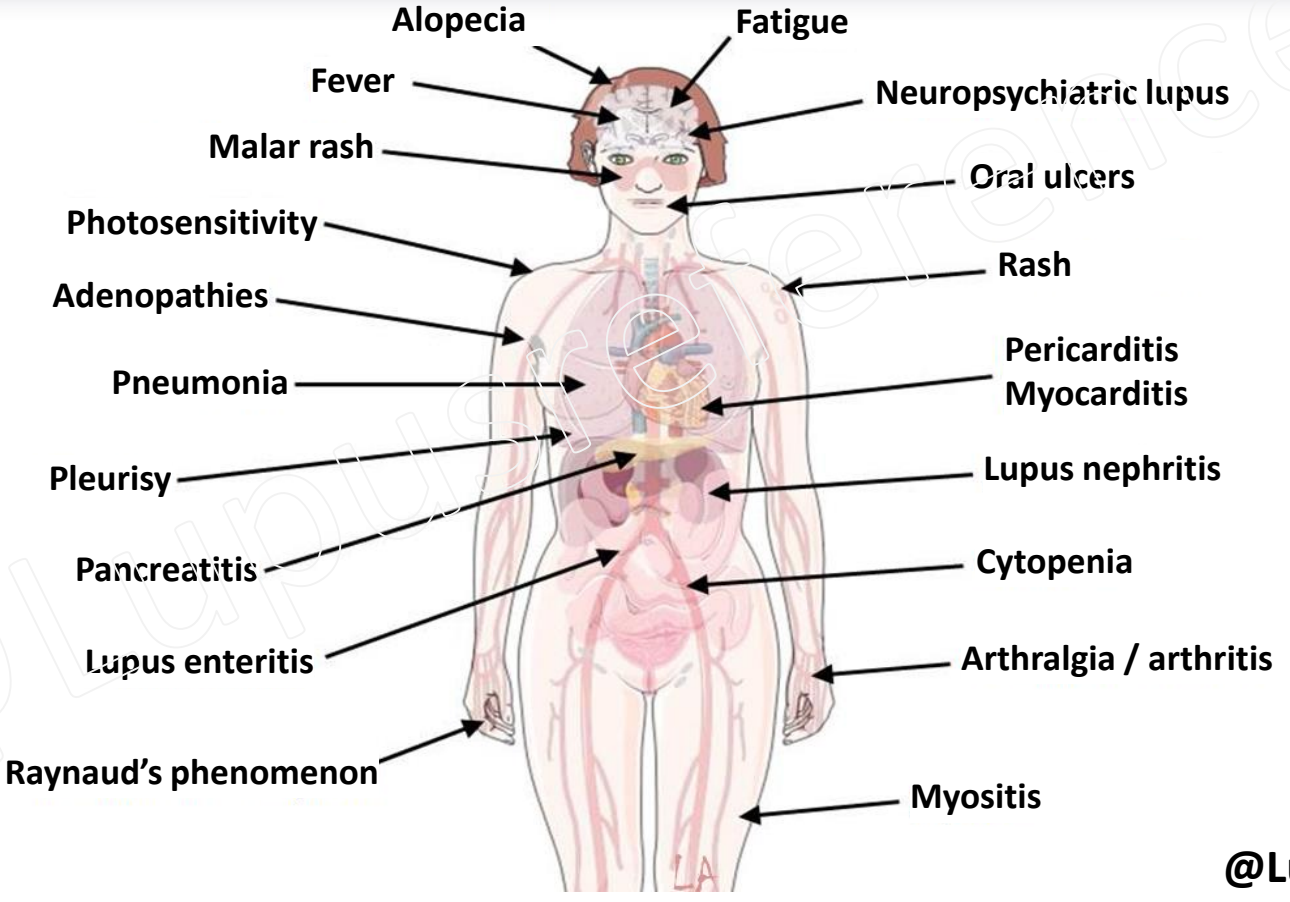


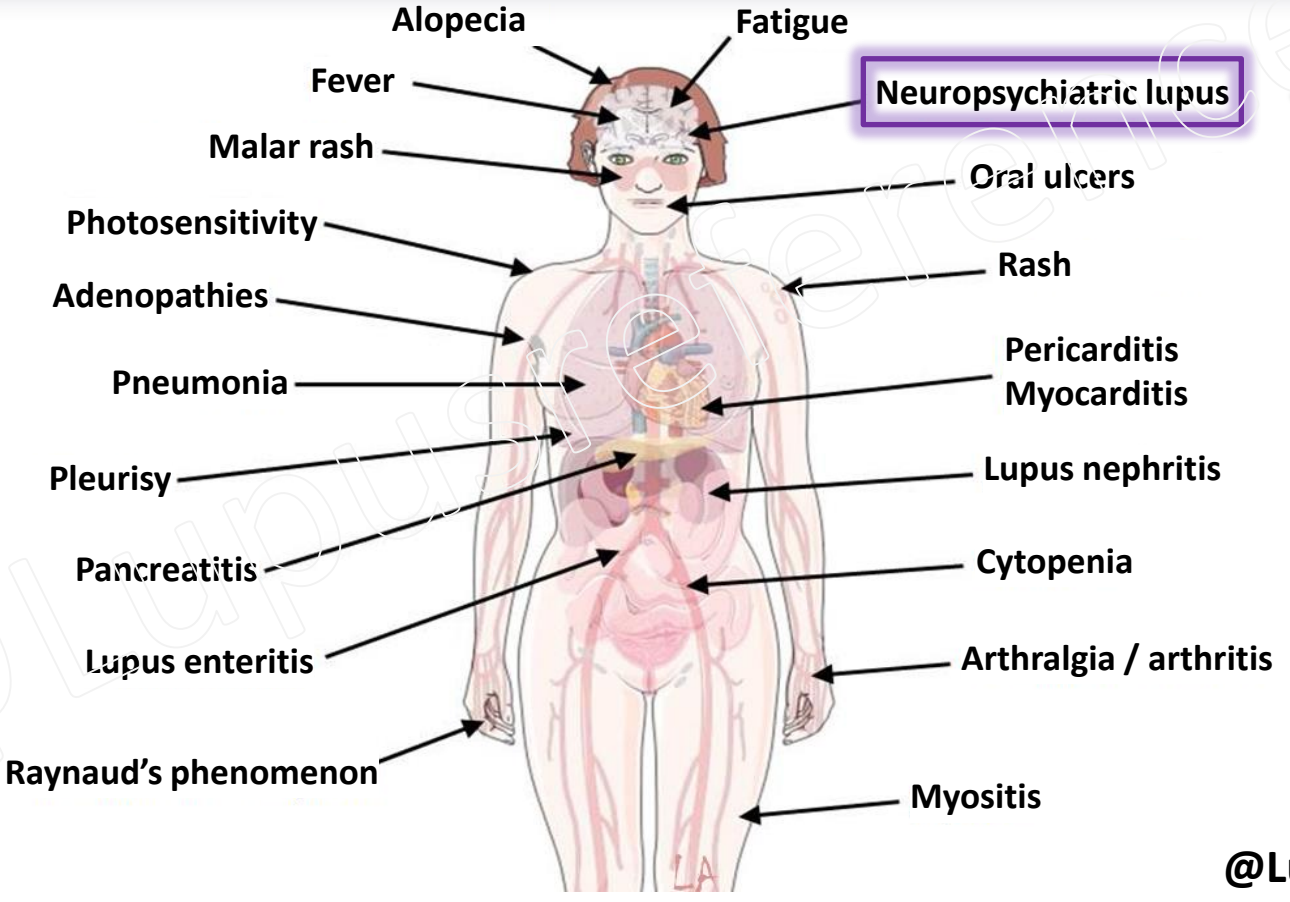
NPSLE & lupus



SLE is a (very) systemic disease



SLE is a (very) systemic disease



General management of symptoms in SLE

Symptom(s)

In SLE patients

« a neurological or psychiatric manifestation »

Attribution of NP symptoms to SLE

Symptom(s)

In SLE patients

Is this due to lupus ?

(versus infection, drugs, etc…)

General management of symptoms in SLE

Symptom(s)

In SLE patients

Is this due to lupus ?

(versus infection, drugs, etc…)

DECISION MADE BASED ON

Positive clinical findings

- **Objective findings? +++**
- Known manifestations of SLE?
- Any other symptoms of SLE?
- Recent changes in treatment?
- Recent lack of observance?

General management of symptoms in SLE

Symptom(s)

In SLE patients

Is this due to lupus ?

(versus infection, drugs, etc…)

DECISION MADE BASED ON

Positive clinical findings

- **Objective findings? +++**
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- Any other symptoms of SLE?
- Recent changes in treatment?
- Recent lack of observance?

Tests & imaging results

General management of symptoms in SLE

Symptom(s)

In SLE patients

Is this due to lupus ?

(versus infection, drugs, etc…)

DECISION MADE BASED ON

Positive clinical findings

- **Objective findings? +++**
- Known manifestations of SLE?
- Any other symptoms of SLE?
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- Recent lack of observance?

Tests & imaging results

Negative findings

- Exclusion of differential diagnosis

General management of symptoms in SLE

Symptom(s)

In SLE patients

Is this due to lupus ?

(versus infection, drugs, etc…)

DECISION MADE BASED ON

Positive clinical findings ✓

- **Objective findings? +++**
- Known manifestations of SLE?
- Any other symptoms of SLE?
- Recent changes in treatment?
- Recent lack of observance?

Tests & imaging results ✓

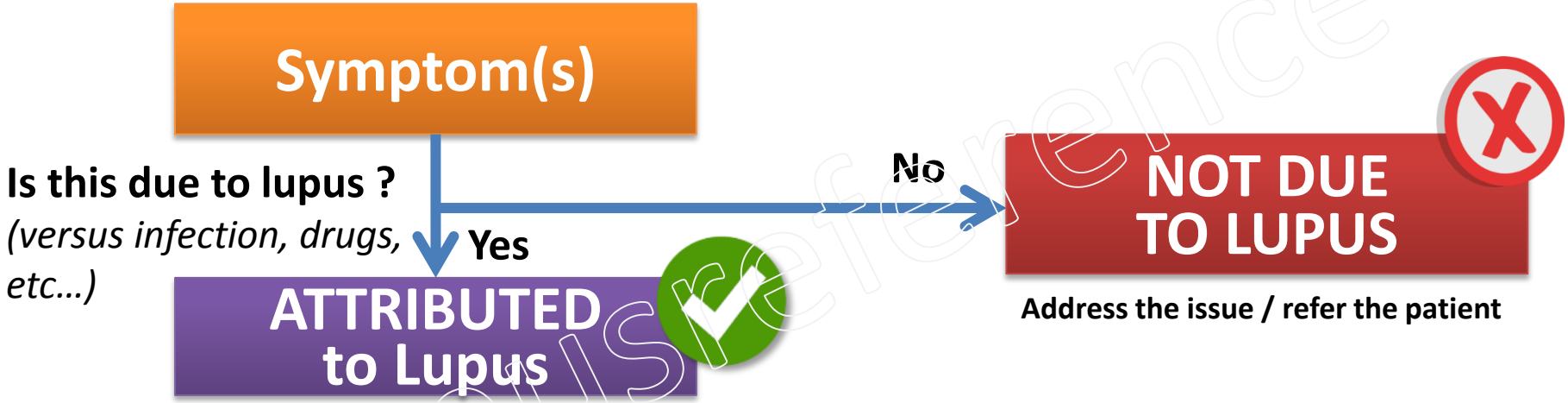
Negative findings ✗

- Exclusion of differential diagnosis

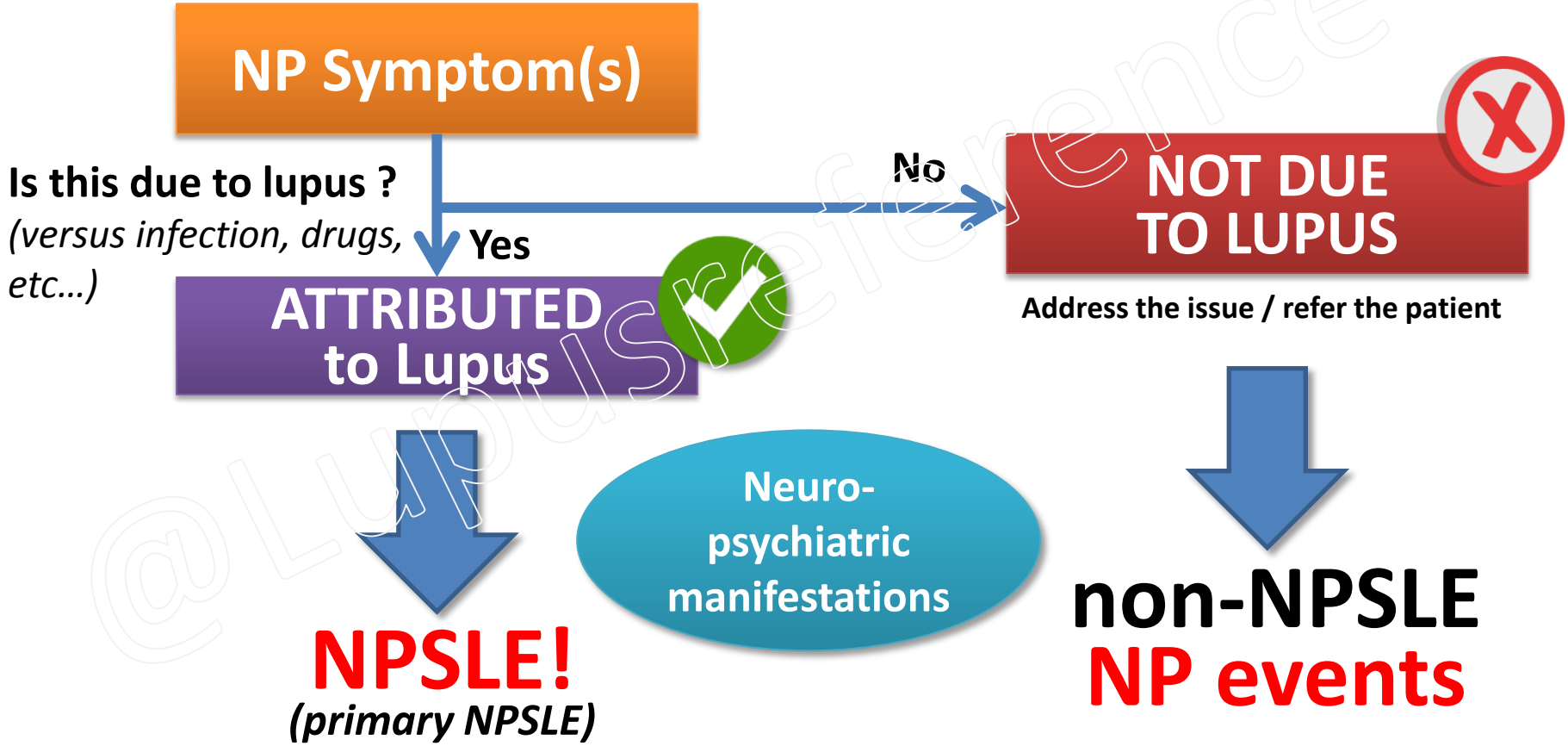
Probabilistic reasoning ±

- For instance: Inflammatory joint pain in a lupus patient more likely to be lupus than gout

General management of symptoms in SLE



General management of symptoms in SLE



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NPSLE manifestations are VERY diverse

ACR classification for Neuro-Psychiatric SLE (NPSLE)

NPSLE manifestations are VERY diverse

ACR classification for Neuro-Psychiatric SLE (NPSLE)

Central nervous system

Aseptic meningitis
Cerebrovascular disease
Demyelinating syndrome
Headache
Chorea
Myelopathy
Seizure disorders
Acute confusional state
Anxiety disorder
Cognitive dysfunction
Mood disorder
Psychosis

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Anxiety disorder
Cognitive dysfunction
Mood disorder
Psychosis

Peripheral nervous system

AIDP (Guillain–Barré)
Autonomic disorder
Mononeuropathy, single
Mononeuropathy, multiplex
Myasthenia gravis
Neuropathy, cranial
Plexopathy
Polyneuropathy

NPSLE manifestations are VERY diverse

ACR classification for Neuro-Psychiatric SLE (NPSLE)

None of these manifestations are SPECIFIC to SLE

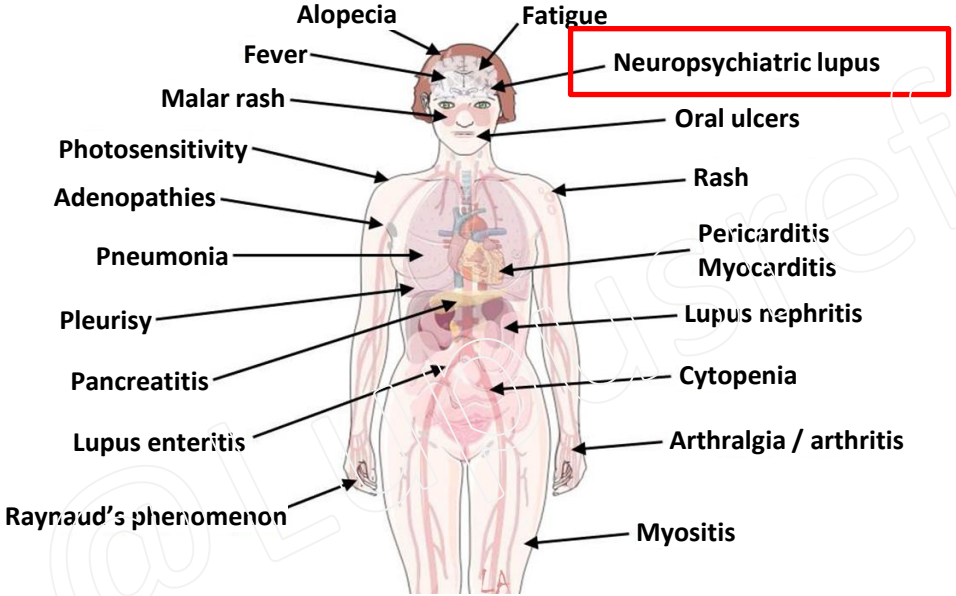
Central nervous system

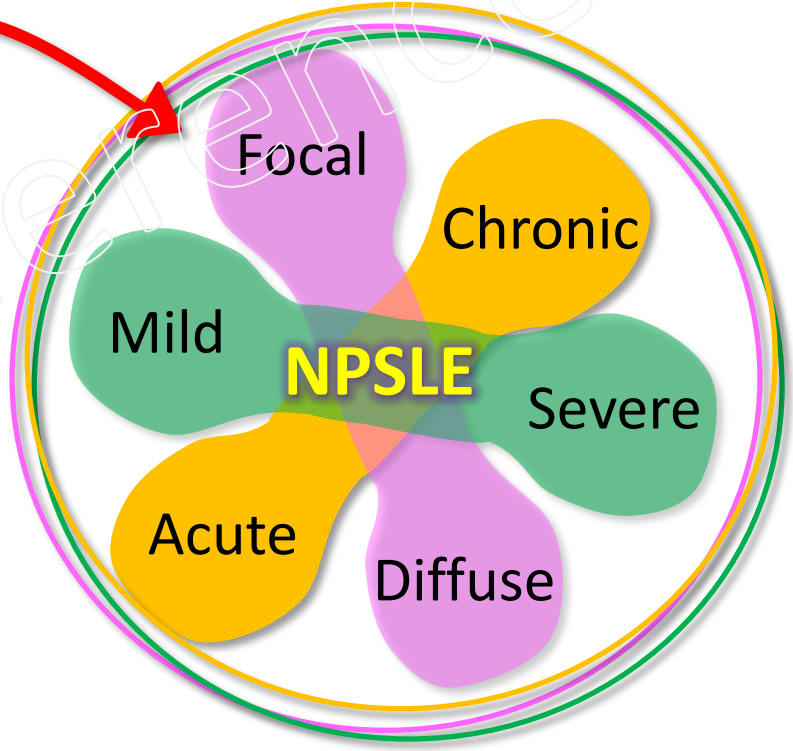
Aseptic meningitis
Cerebrovascular disease
Demyelinating syndrome
Headache
Chorea
Acu
Cognitive dysfunction
Mood disorder
Psychosis

Peripheral

disorder
Mononeuropathy, single
Mononeuropathy, multiplex
Myasthenia gravis
Neuropathy, cranial
Plexopathy
Polyneuropathy

NPSLE is very heterogeneous





Hanly et al. SLICC cohort ARD 2020

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Today's NPSLE agenda

- ✓ What is NPSLE?
- ✓ How diverse are NPSLE manifestations
- ✓ **How common is NPSLE among SLE patients?**
  - ✓ **How common are NP events in SLE patients**
  - ✓ **Which proportion of NP events are attributable to SLE**
- ✓ What are the typical manifestations of NPSLE?
- ✓ How do you attribute NP events to SLE (NPSLE)?
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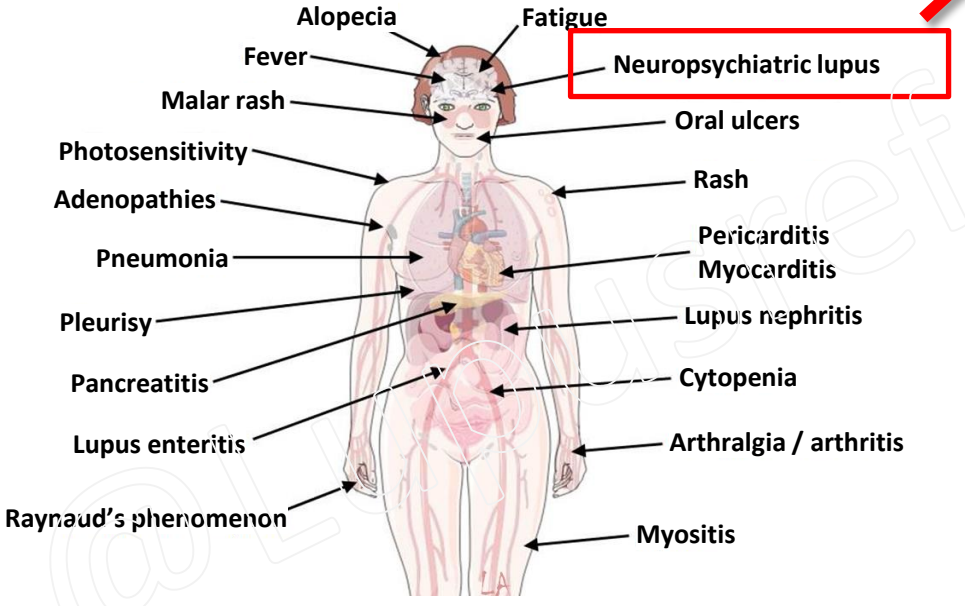
How common are NP events in SLE ?



52%

with NP events

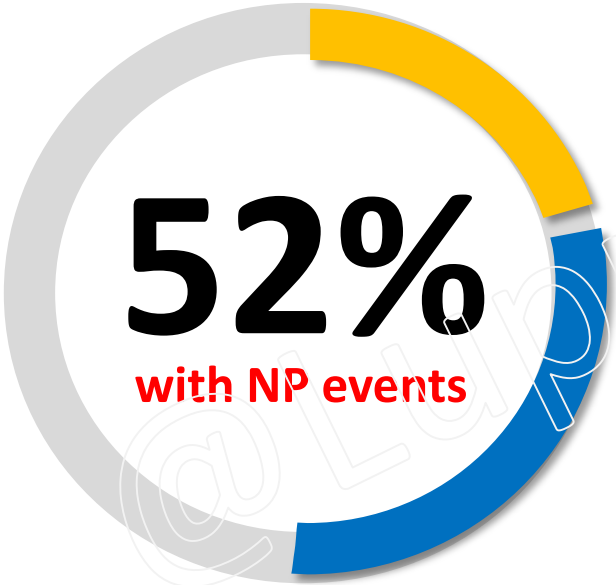
1827 patients

Mean follow-up: 7.6 ± 4.6 years

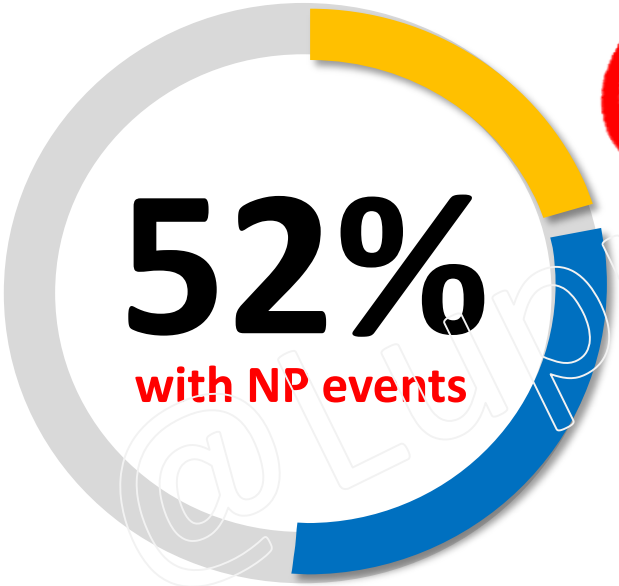
SLICC: 43 academic centres in 16 countries

Hanly et al. SLICC cohort ARD 2020

Which proportion are ATTRIBUTED to SLE?



Which proportion are ATTRIBUTED to SLE?



NP events
ATTRIBUTED to SLE
= NPSLE

18-30%

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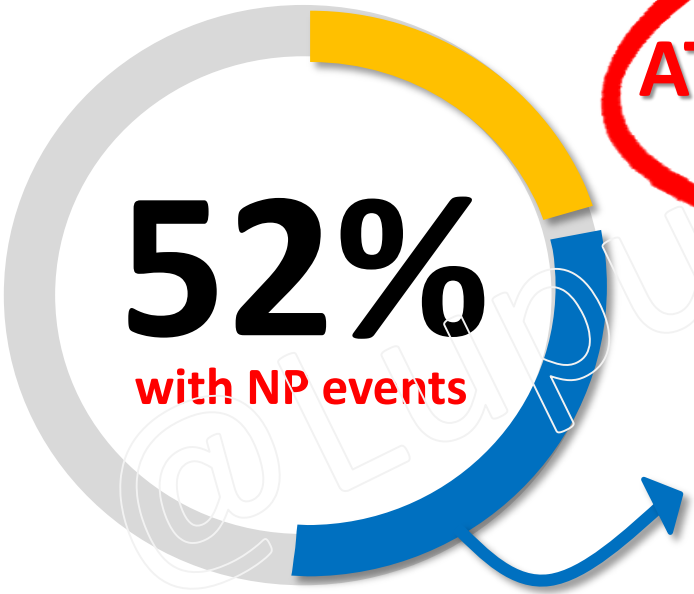
Which proportion are ATTRIBUTED to SLE?



NP events
ATTRIBUTED to SLE
= NPSLE

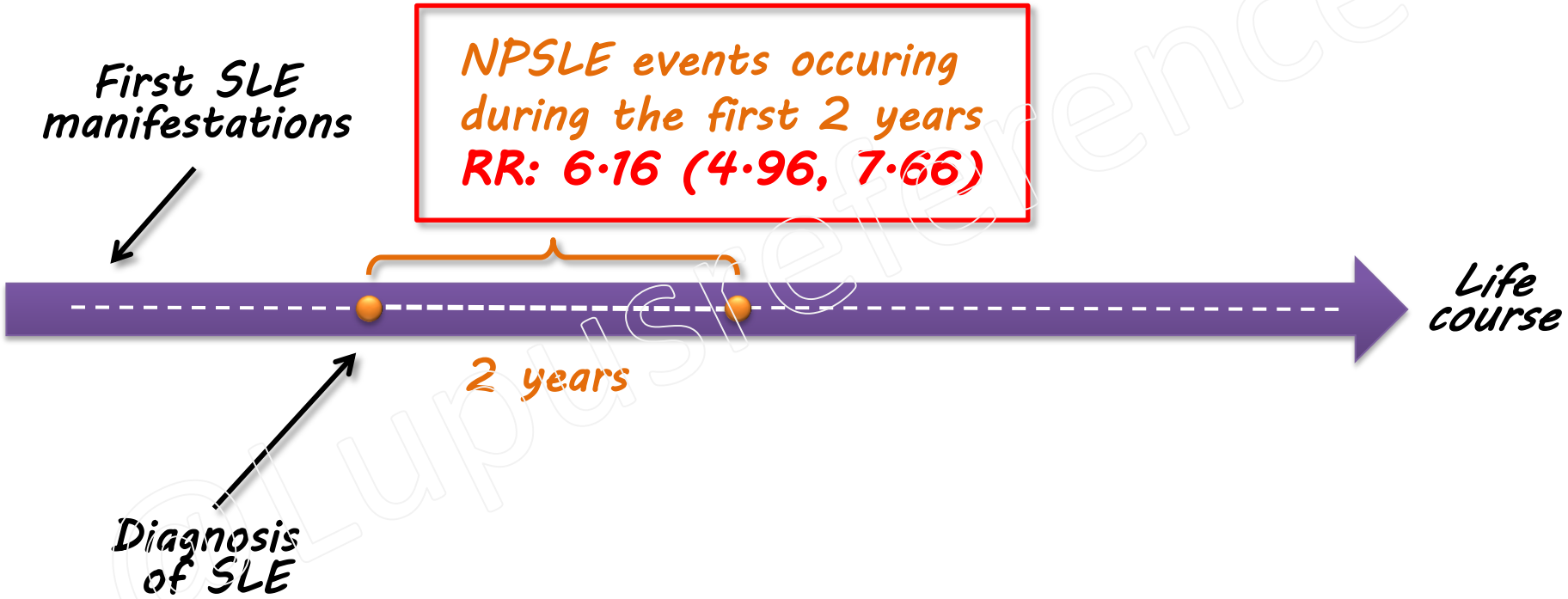
18-30%

NP events
NOT ATTRIBUTED
to SLE

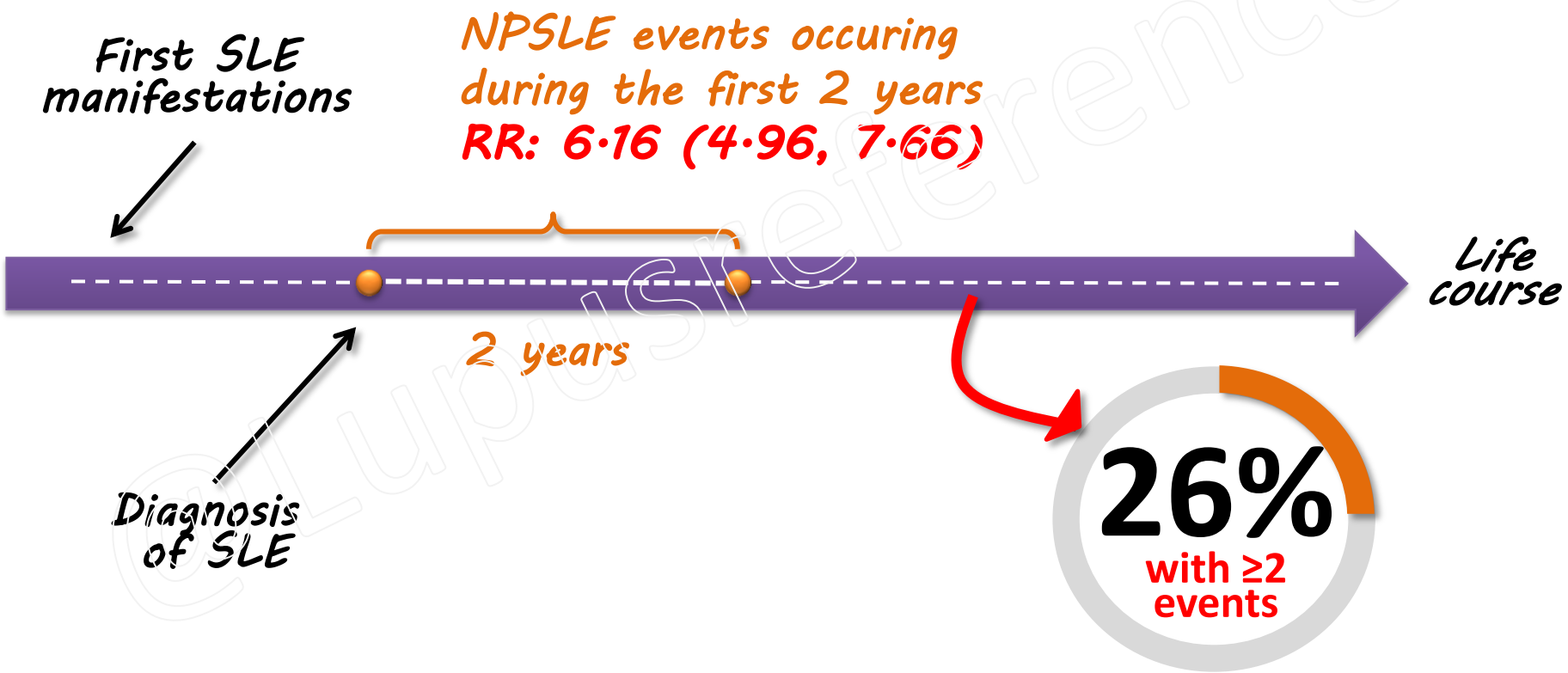
>70%

Hanly et al. SLICC cohort ARD 2020

When are NPSLE events occuring in SLE?



When are NPSLE events occuring in SLE?



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What are the typical manifestation of NPSLE?

ACR classification for Neuro-Psychiatric SLE (NPSLE)

Central nervous system

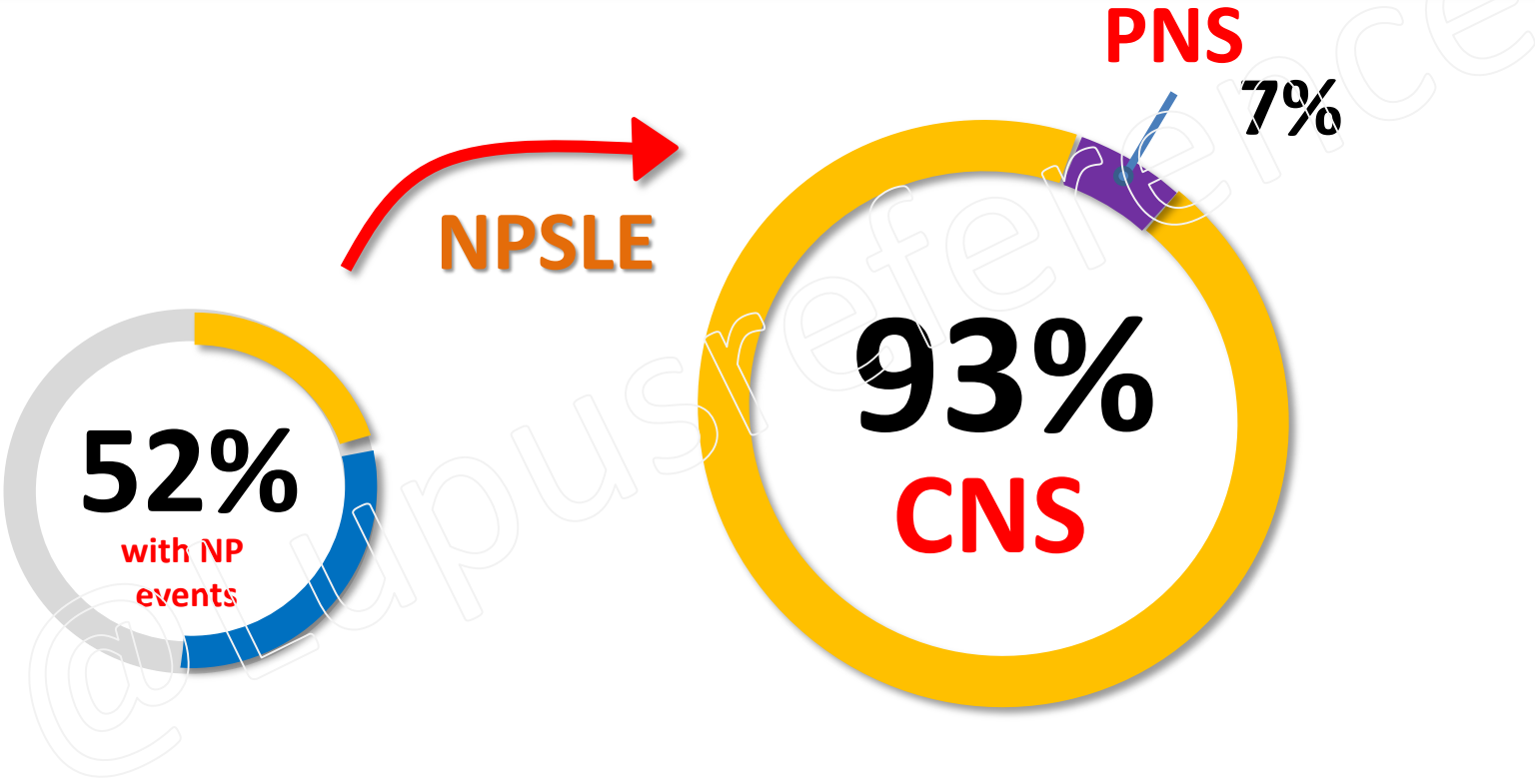
Aseptic meningitis
Cerebrovascular disease
Demyelinating syndrome
Headache
Chorea
Acu
Cognitive dysfunction
Mood disorder
Psychosis

Peripheral

Mononeuropathy, single
Mononeuropathy, multiplex
Myasthenia gravis
Neuropathy, cranial
Plexopathy
Polyneuropathy

None of these manifestations are SPECIFIC to SLE

What types of events are reported in NPSLE?



Hanly et al. SLICC cohort ARD 2020

What types of events are reported in NPSLE?

Studies	NPSLE (n)	Total SLE (n)	Aseptic meningitis	Cerebrovascular disease	Demyelinating syndrome	Headache	Movement disorder	Myelopathy	Seizure disorders	Acute confusional State	Anxiety disorder	Cognitive dysfunction	Mood disorder	Psychosis
Karimifar (2013)		100											60 (60.0%)	
Murray (2012)		694										107 (15.4%)	129 (18.6%)	
Cojocaru (2010)	47	78	3 (3.8%)	8 (10.3%)		5 (6.4%)			7 (9.0%)	15 (19.2%)				9 (11.5%)
Syuto (2009)	10	68		4 (5.9%)			1 (1.5%)			1 (1.5%)		1 (1.5%)	2 (2.9%)	
Abdel-Nasser (2008)	26	32		1 (3.1%)		15 (46.9%)			4 (12.5%)	2 (6.3%)	3 (9.4%)	12 (37.5%)	19 (59.4%)	1 (3.1%)
Avcin (2008)	23	137		7 (5.1%)		22 (16.1%)	2 (1.5%)	2 (1.5%)	4 (2.9%)			12 (8.8%)	4 (2.9%)	13 (9.5%)
Fragoso-Loyo 2008	47	96		8 (8.3%)		9 (9.4%)		1 (1.0%)	16 (16.7%)	8 (8.3%)				1 (1.0%)
Hanly (2008)	133	412		14 (3.4%)								14 (3.4%)	32 (7.8%)	7 (1.7%)
Magalhaes (2007)	59	138	1 (0.7%)	18 (13.0%)				2 (1.4%)	27 (19.6%)	5 (3.6%)	3 (2.2%)		16 (11.6%)	15 (10.9%)
Steup-Beekman (2007)	19	51		8 (15.7%)		5 (9.8%)		2 (3.9%)	2 (3.9%)	1 (2.0%)		9 (17.6%)	1 (2.0%)	
Hanly (2006)	15	65		3 (4.6%)				1 (1.5%)	4 (6.2%)	5 (7.7%)		15 (23.1%)	3 (4.6%)	1 (1.5%)
Harrison (2006)	42	93	2 (2.2%)	16 (17.2%)		37 (39.8%)		1 (1.1%)	7 (7.5%)		6 (6.5%)		15 (16.1%)	16 (17.2%)
Lapteva (2006)		60										28 (46.7%)	10 (16.7%)	
Yoshio (2005)	50	70	6 (8.6%)	10 (14.3%)		2 (14.3%)	31 (44.3%)	3 (4.3%)	10 (14.3%)	9 (12.9%)	8 (11.4%)		4 (5.7%)	8 (11.4%)
Conti (2004)	17	51									16 (31.4%)		15 (29.4%)	2 (3.9%)
Mikdashi (2004)	74	130		19 (14.6%)				5 (3.8%)	6 (4.6%)			20 (15.4%)		11 (8.5%)
Sanna (2003)	185	323		47 (14.5%)	3 (0.9%)	78 (24.0%)	4 (1.2%)	4 (1.2%)	27 (8.3%)	13 (3.7%)	24 (7.4%)	35 (10.8%)	54 (16.7%)	25 (7.7%)
Mok (2001)	96	518	1 (0.2%)	25 (4.8%)	2 (0.4%)	3 (0.6%)	3 (0.6%)	11 (2.1%)	37 (7.1%)	18 (3.5%)	2 (0.4%)		8 (1.5%)	15 (2.9%)
Karassa (2000)	32	128		9 (7.0%)					8 (6.3%)	6 (4.7%)		3 (2.3%)		3 (2.3%)
Georgescu (1997)	30	346											10 (2.9%)	8 (2.3%)
Arnett (1996)	30	394											15 (3.8%)	17 (4.3%)
Silva (1996)	42	93	9 (9.5%)	21 (23.8%)				4 (4.8%)	28 (30.9%)					28 (30.9%)
Toubi (1995)	96	196		56 (28.6%)			1 (0.5%)		24 (12.2%)					
West (1995)	52	66		25 (37.9%)		1 (1.5%)	1 (1.5%)	3 (4.5%)	9 (13.6%)	3 (4.5%)			5 (7.6%)	3 (4.5%)
Nojima (1992)	32	91							7 (7.7%)				7 (7.7%)	18 (19.8%)
Teh (1992)	39	116							6 (5.2%)				10 (8.6%)	13 (11.3%)
Schneebaum (1991)	82	269											8 (3.0%)	29 (10.8%)
Costallat 1990	16	66						1 (1.5%)	8 (12.1%)	2 (3.0%)				2 (3.0%)
Long (1990)	59	98	0 (0.0)									54 (55.1%)		
Alarcon-Segovia (1989)		500		49 (9.8%)		66 (13.2%)	1 (0.2%)	4 (0.8%)						
Bluestein 1981	27	45					4 (8.9%)	2 (4.4%)	8 (17.8%)					
Bresnihan (1979)	12	15				12 (80.0%)	3 (20.0%)			4 (26.7%)			4 (26.7%)	4 (26.7%)

CNS

Highly variable frequency

Ho et al. Autoimmun Rev 2016

What is the frequency of NPSLE manifestations

Neuropsychiatric manifestations of the peripheral nervous system in patients with SLE.

Studies	NPSLE (n)	Total SLE (n)	Acute inflammatory demyelinating polyradiculoneuropathy	Autonomic disorder	Mononeuropathy	Myasthenia gravis	Neuropathy, cranial	Plexoathy	Polyneuropathy
Syuto (2009)	10	68							1 (1.5%)
Fragoso-Loyo (2008)	47	96			3 (3.1%)				1 (1.0%)
Steup-Beekman (2007)	19	51						1 (2.0%)	1 (2.0%)
Hanly (2006)	15	65			3 (4.6%)		4 (6.2%)		
Harrison (2006)	42	93	2 (2.2%)		8 (8.6%)		2 (2.2%)		
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Karassa (2000)	32	128	3 (2.3%)				3 (2.3%)		
Silva (1996)	42	93					26 (28.6%)		
Bluestein (1981)	27	45					3 (6.7%)		
Bresnihan (1979)	12	15		2 (13.3%)			0 (0.0)		

Highly variable frequency

PNS

Ho et al. Autoimmun Rev 2016

What types of events are reported in NPSLE?

Frequent ********	**Cognitive dysfunction** **Mood disorder** **Anxiety** **Headache**	**6.6–80 (mild)	1–3% (severe)** **7.4–65** **6.4–40** **12.2–28.3**
Common *******	**Seizures** **Cerebrovascular disease**	**7.0–20** **8.0–15**
Infrequent *****	Psychosis Acute confusional status Mononeuropathy Polyneuropathy Myelopathy Demyelinating syndrome	0.6–11 0.9–7 0.9–6.9 1.5–5.4 0.9–3.9 0.9–2.7
Rare **-**	Aseptic meningitis Autonomic disorder AIDP (GBS) Cranial neuropathy Movement disorders (chorea) Myasthenia gravis Plexopathy	0.3–2.7 0.08–1.3 0.08–1.2 1.0 0.9 0.2 NR

Govoni et al. Rheumatology 2020 | Schwartz et al. Nat Rev Rheumatol 2019

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- ✓ **How do you attribute NP events to SLE (NPSLE)?**
- ✓ Additional diagnostic considerations
- ✓ What is the treatment of NPSLE?

MOST DIFFICULT QUESTION

Attribution of NP events to SLE (NPSLE)

Neuro-psychiatric manifestations in SLE patients

Attribution to SLE

What types of events are reported in NPSLE?

Frequent ****	**Cognitive dysfunction** **Mood disorder** **Anxiety** **Headache**	**6.6–80 (mild)	1–3% (severe)** **7.4–65** **6.4–40** **12.2–28.3**
Common ***	**Seizures** **Cerebrovascular disease**	**7.0–20** **8.0–15**
Infrequent *	Psychosis Acute confusional status Mononeuropathy Polyneuropathy Myelopathy Demyelinating syndrome	0.6–11 0.9–7 0.9–6.9 1.5–5.4 0.9–3.9 0.9–2.7
Rare -	Aseptic meningitis Autonomic disorder AIDP (GBS) Cranial neuropathy Movement disorders (chorea) Myasthenia gravis Plexopathy	0.3–2.7 0.08–1.3 0.08–1.2 1.0 0.9 0.2 NR

VERY COMMON
IN THE GENERAL POPULATION

Govoni et al. Rheumatology 2020 | Schwartz et al. Nat Rev Rheumatol 2019

Attribution of NP events to SLE (NPSLE)

Validity of the New American College of Rheumatology Criteria for Neuropsychiatric Lupus Syndromes: A Population-Based Evaluation

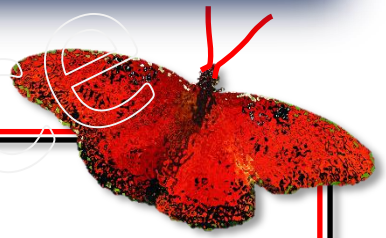
Table 3. Number of American College of Rheumatology (ACR) criteria and revised criteria for neuropsychiatric SLE among patient and control groups

	Patients	Controls	OR (95% CI)	Specificity
ACR criteria for NPSLE				
≥1	42 (91%)	25 (56%)	9.5 (2.2–40.8)	0.46
≥2	37	10	7.8 (2.7–22.0)	0.78
≥3	25	2	24.0 (3.3–1774)	0.96
≥4	10	—	∞	1.00
Revised criteria				
> 0	21	3	7.0 (2.1–23.5)	0.93
> 1	9	0	∞	1.00
> 2	6	0	∞	1.00
> 3	2	0	∞	1.00

MORE THAN 50% of controls (general population) had at least 1 criteria for NPSLE

Ainiala et al. Arthritis Care Res 2001

Attribution of NP events to SLE (NPSLE)



Some NP MANIFESTATIONS
<u>cannot be</u> attributed confidently to SLE

- Headaches
- Anxiety
- Mild depression
- Mild cognitive impairment (deficit in <3 of 8 domains)
- Polyneuropathy without electrophysiological confirmation

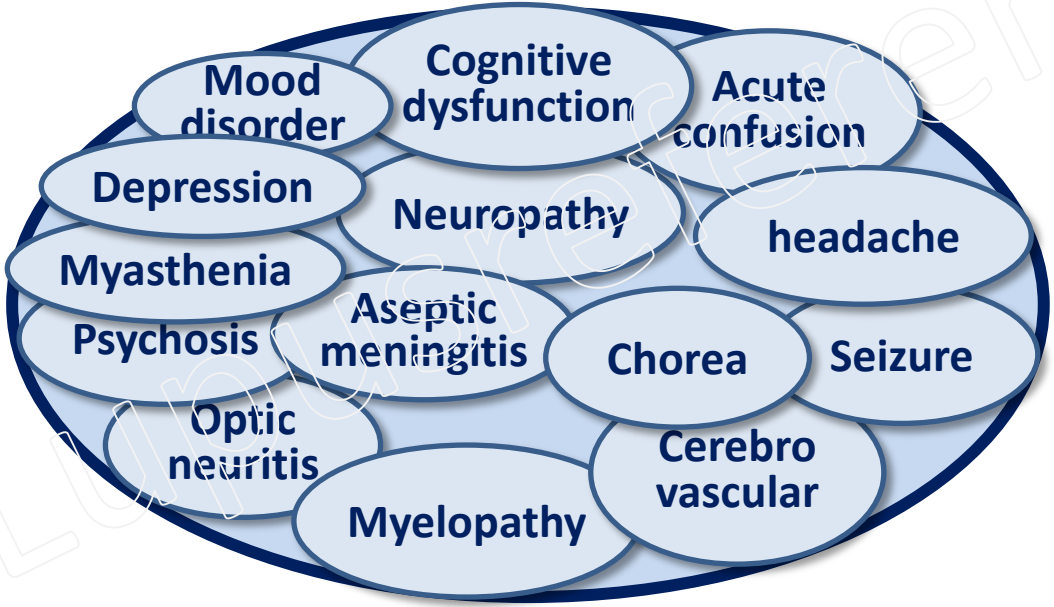
Lupus headache

Lupus headache is NOT just headache in a patient with lupus

Disease activity index	Definition
SLEDAI-2K	Severe, persistent headache; may be migrainous, but **must be nonresponsive to narcotic analgesia**.
SELENA-SLEDAI	Severe, persistent headache; may be migrainous, but **must be nonresponsive to narcotic analgesia**.
BILAG-2004	• Severe lupus headache (unremitting): disabling headache **unresponsive to narcotic analgesia & lasting ≥ 3 days** • Headache from intracranial hypertension
ECLAM	Recently developed, persistent or recurrent. Poorly responsive to the most currently used drugs but **partially or totally responsive to corticosteroids**

Attribution of NP events to SLE (NPSLE)

There are many « mimickers » of NPSLE



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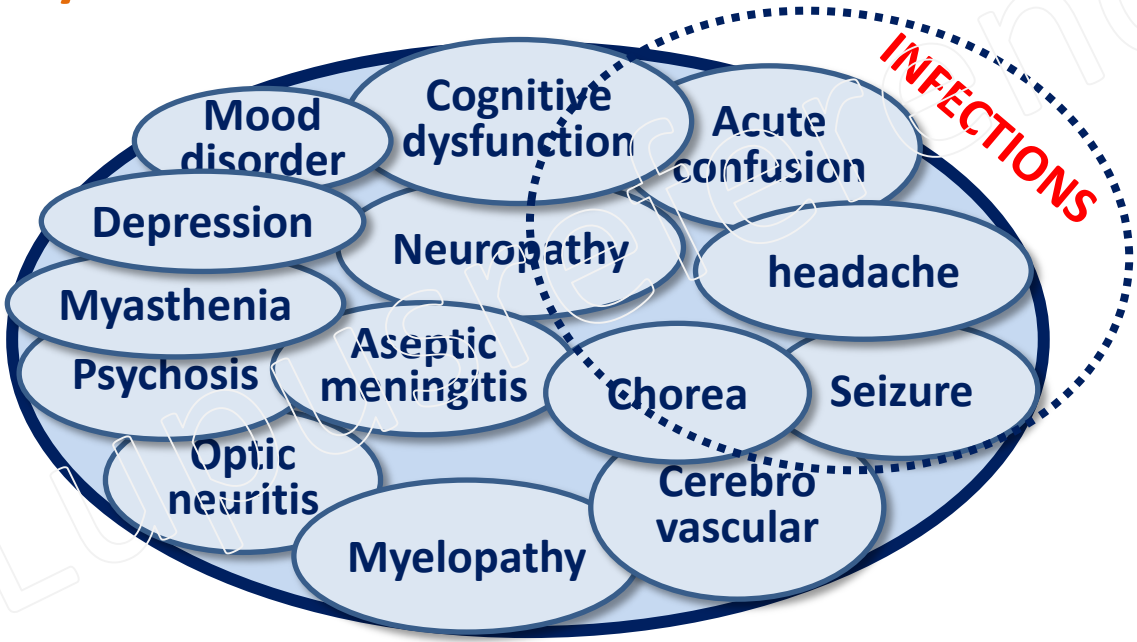

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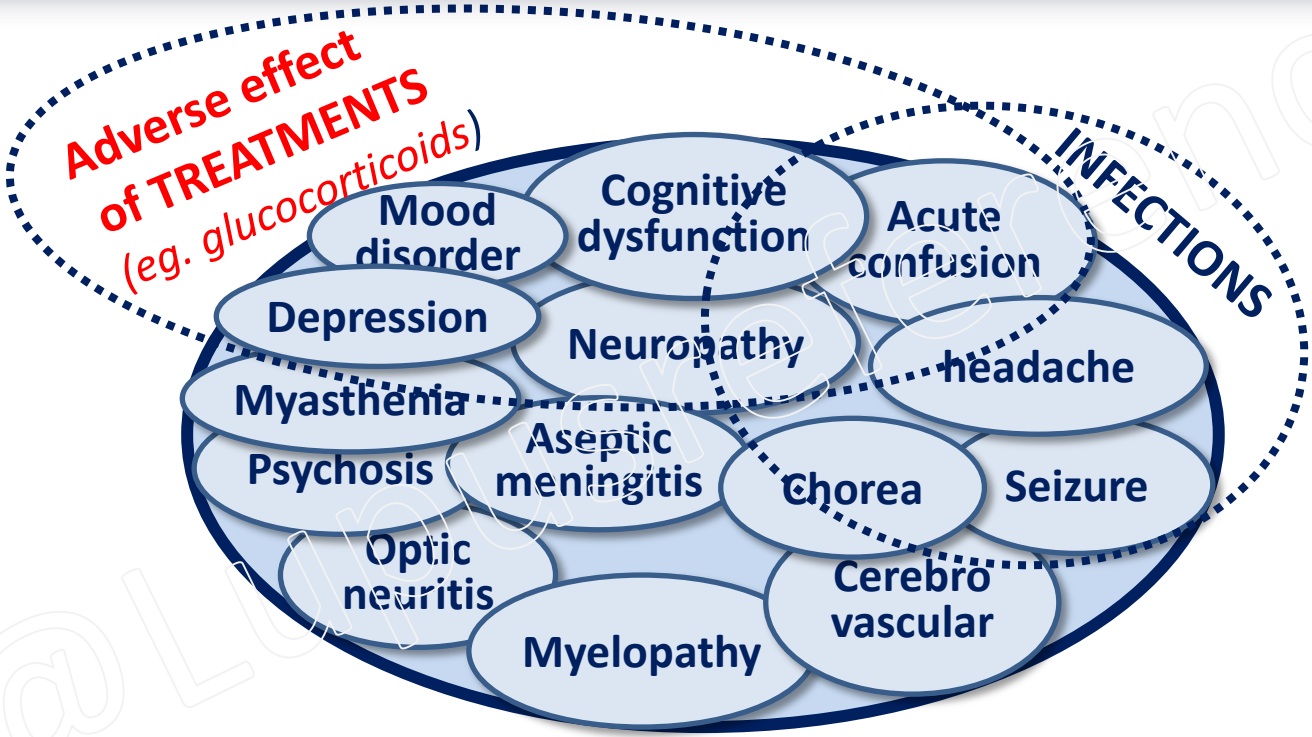
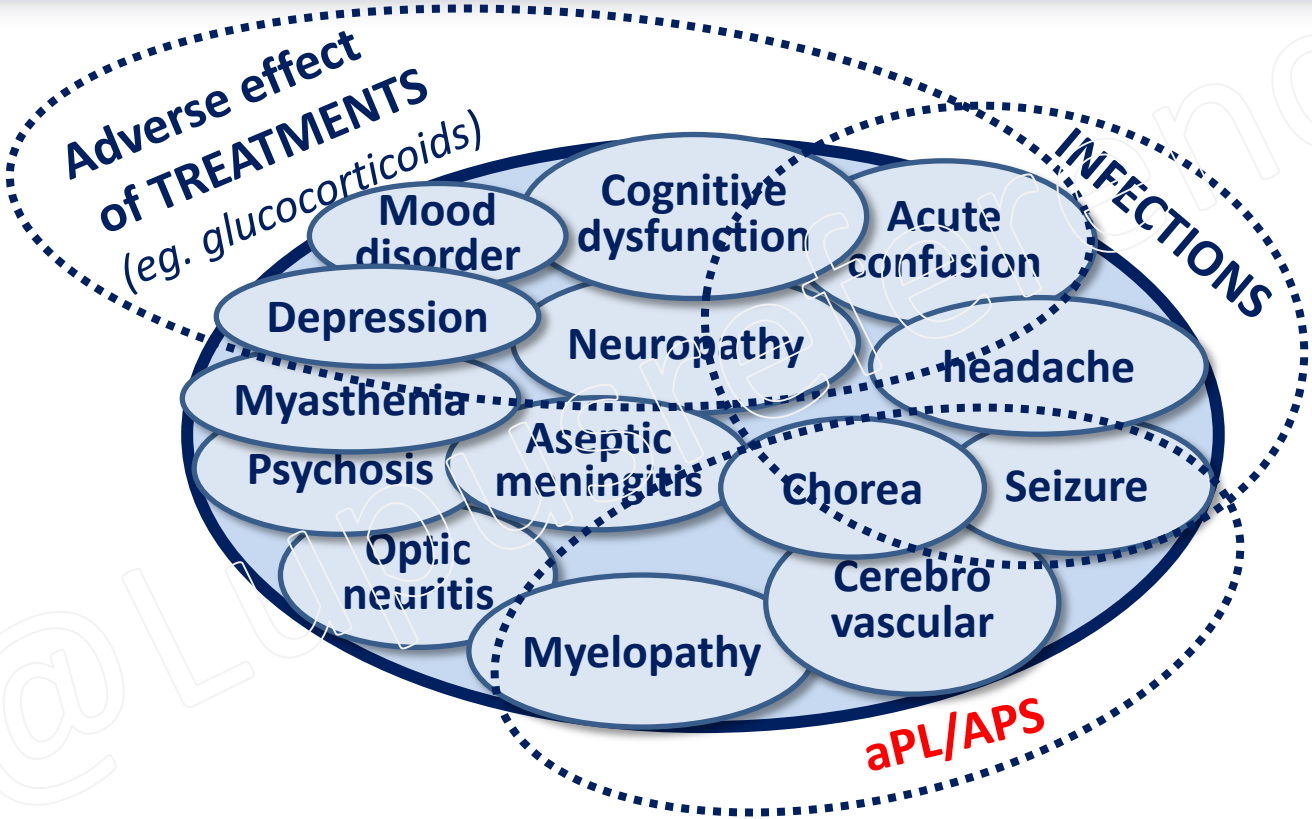


@Lupusreference

Case #2 | the « brain-fog »



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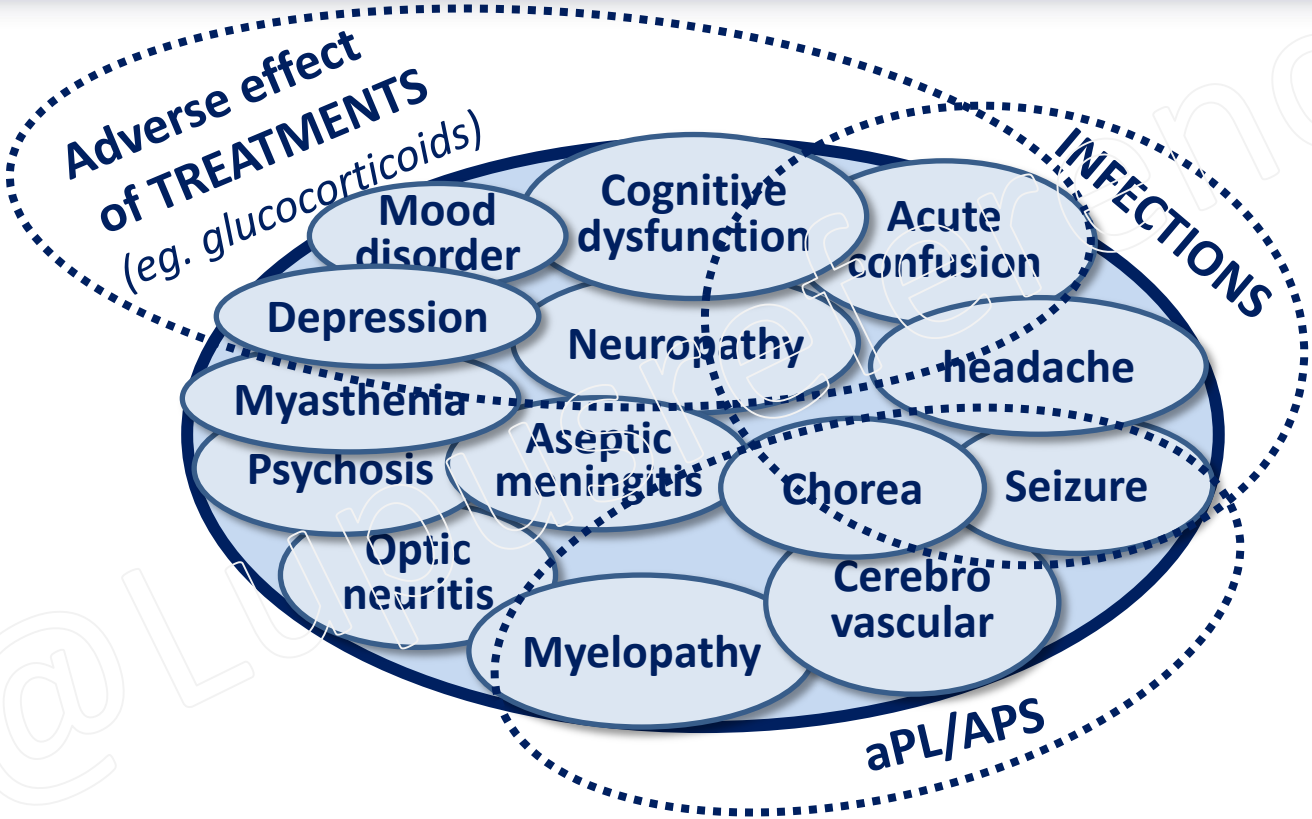
Attribution of NP events to SLE (NPSLE)



+ Metabolic

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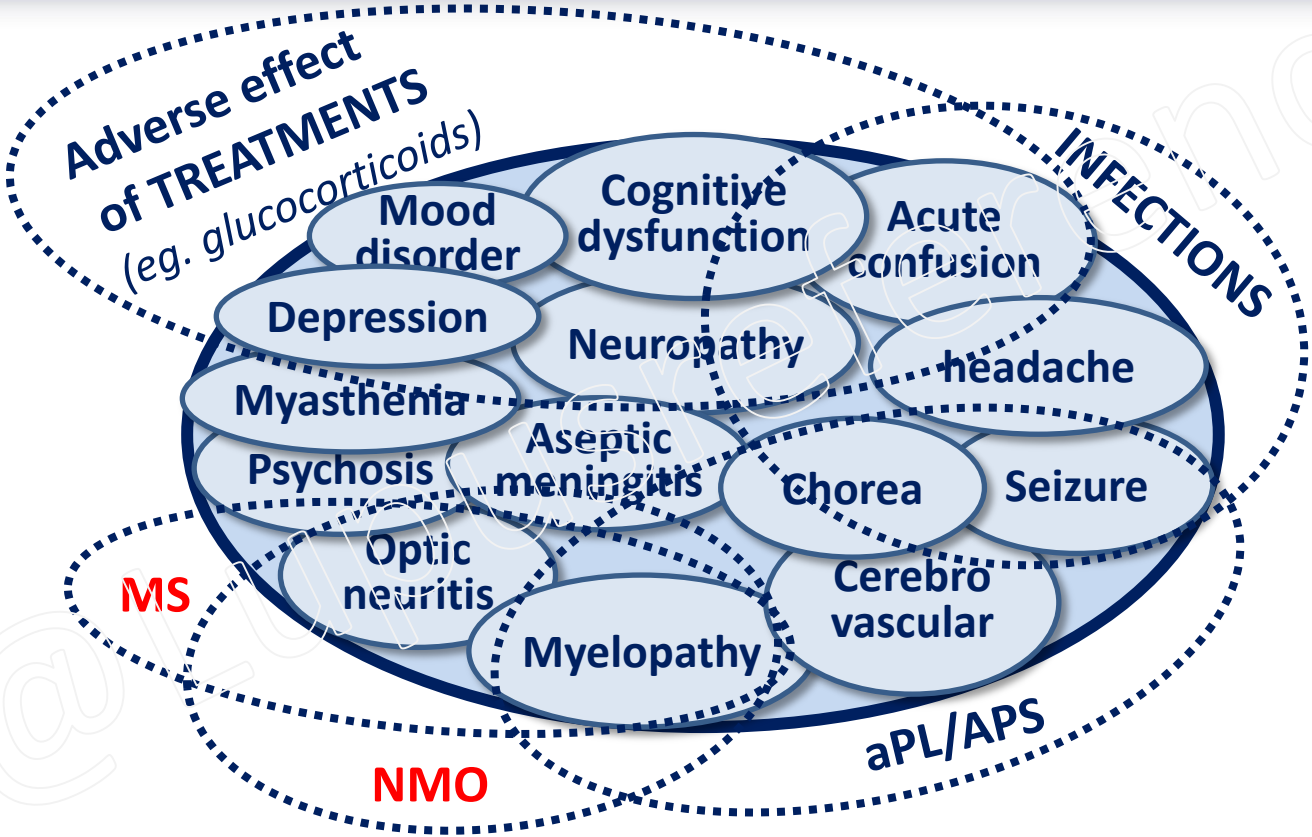
Attribution of NP events to SLE (NPSLE)



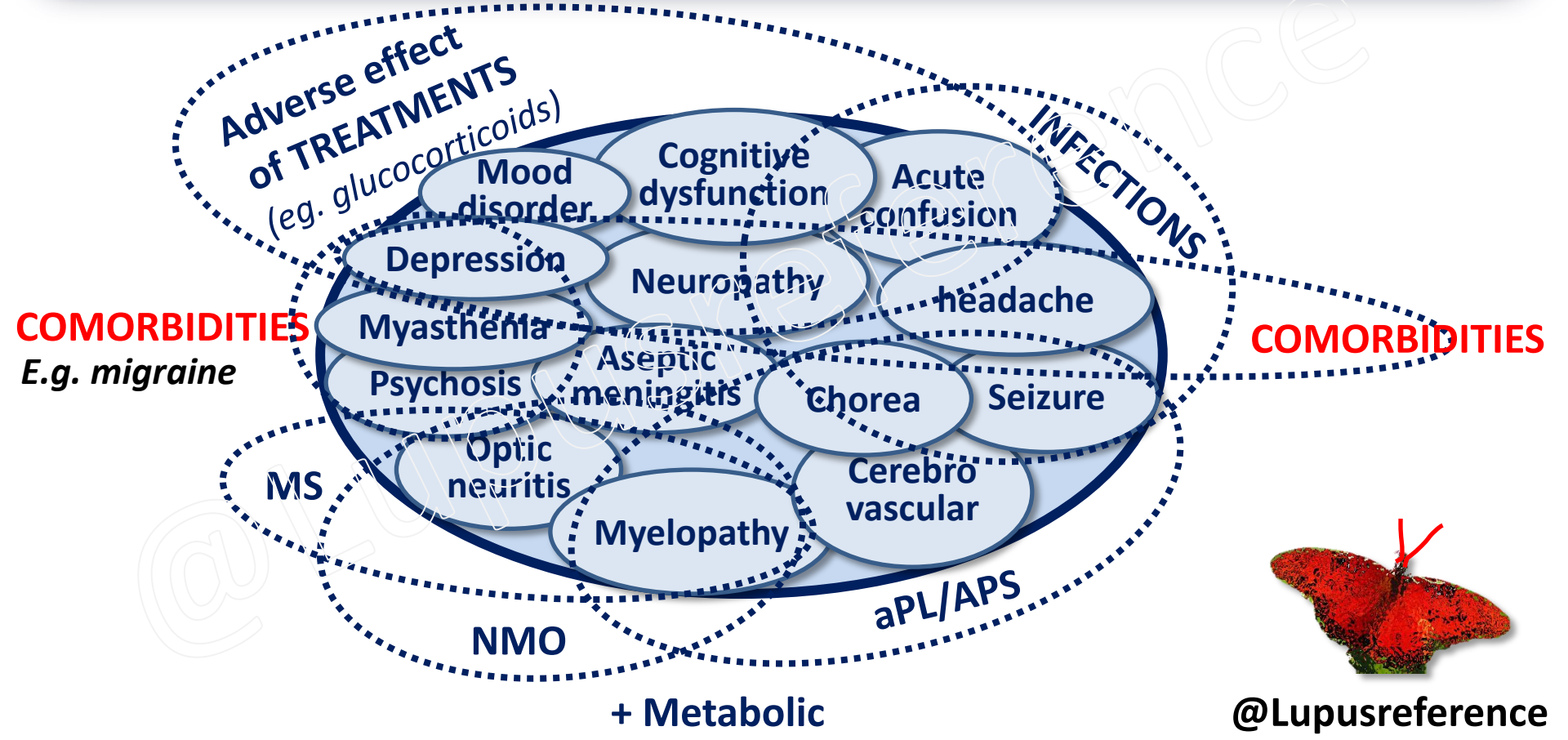
@Lupusreference

From NPSLE to Neuromyelitis optica (Devic's)

What is neuromyelitis optica ?

- **Optic neuritis or myelitis (simultaneous < 10% of cases)**
- **Isolated (or associated with SLE)**
- Proposed diagnostic criteria for NMO:
  - optic neuritis / acute myelitis + at least 2 of:
    - Contiguous spinal cord MRI on ≥3 levels
    - brain MRI ≠ multiple sclerosis;
    - **NMO-IgG (Anti-aquaporin-4 Ab) (+ aPL)**
- **Poor prognosis:**
  - High relapse rate with poor prognosis when relapsing
  - Monocular blindness or loss of ambulatory capacity in >50% within 5 years

Attribution of NP events to SLE (NPSLE)



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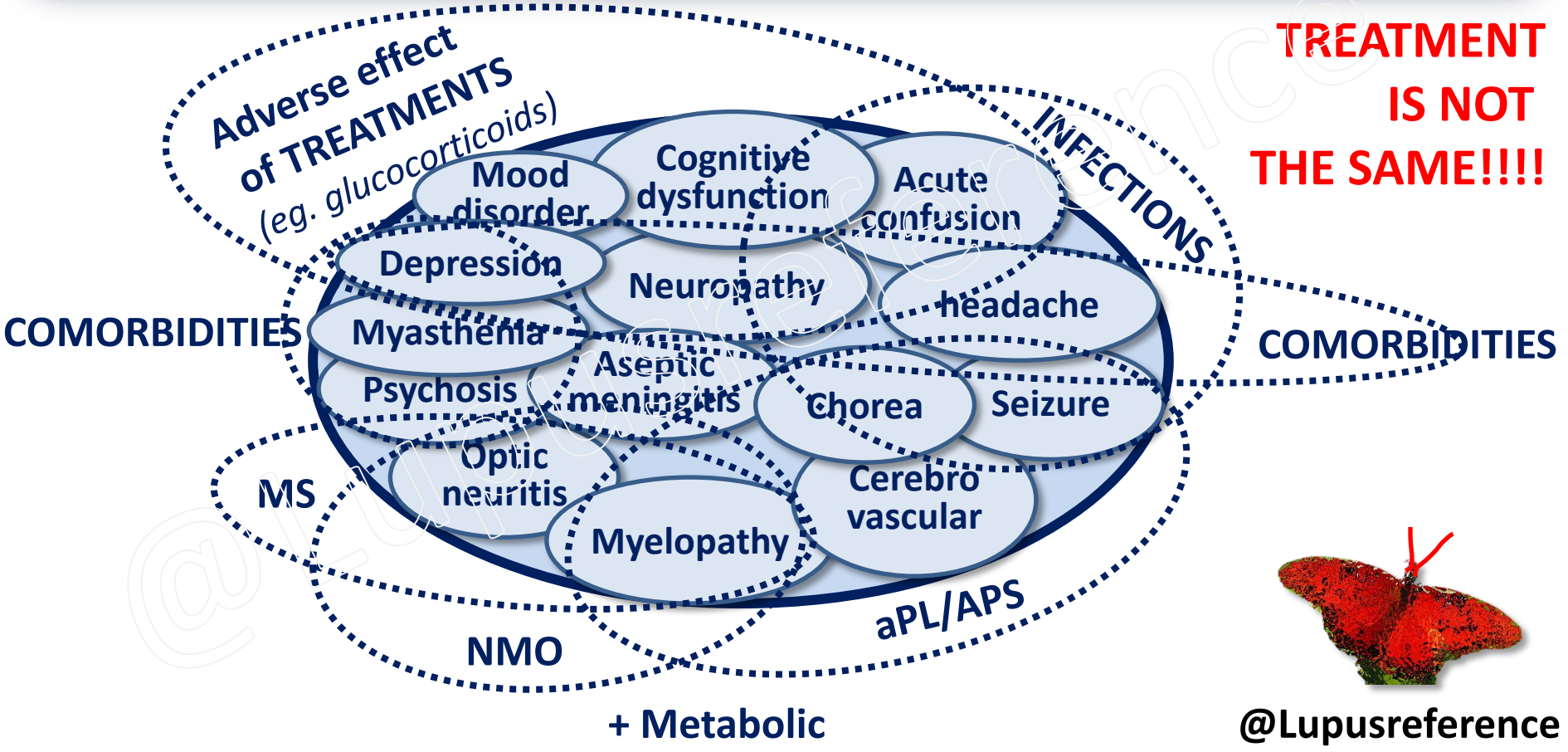
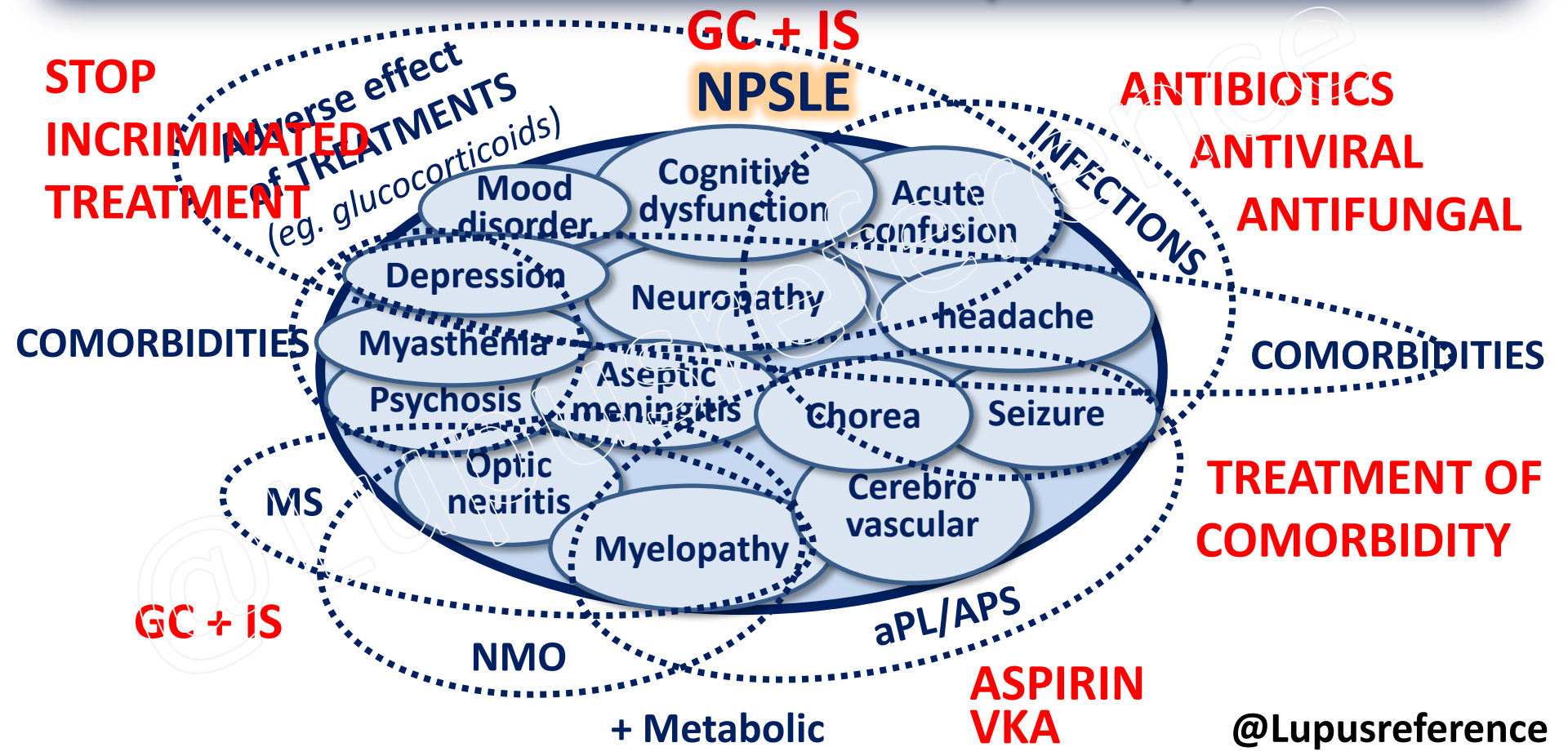


Attribution of NP events to SLE (NPSLE)



Attribution of NP events to SLE (NPSLE)

Neuro-psychiatric manifestations in SLE patients

@Lupusreference

When possible, try to confirm NP event using an objective method

Attribution to SLE

Document the involvement of CNS/PNS

CNS: Brain MRI + CSF

+/- brain-SPECT

+/- EEG

PNS: ENMG +/- CSF

(can be normal)

Search for confounding and favouring factors

Alternative diagnosis?

(e.g. infection, metabolic)

Change in medications?

Previous NPSLE involvement?

(can be present but play no role)

Ongoing SLE activity in other organs

Early in SLE history?

Flare in another organ ?

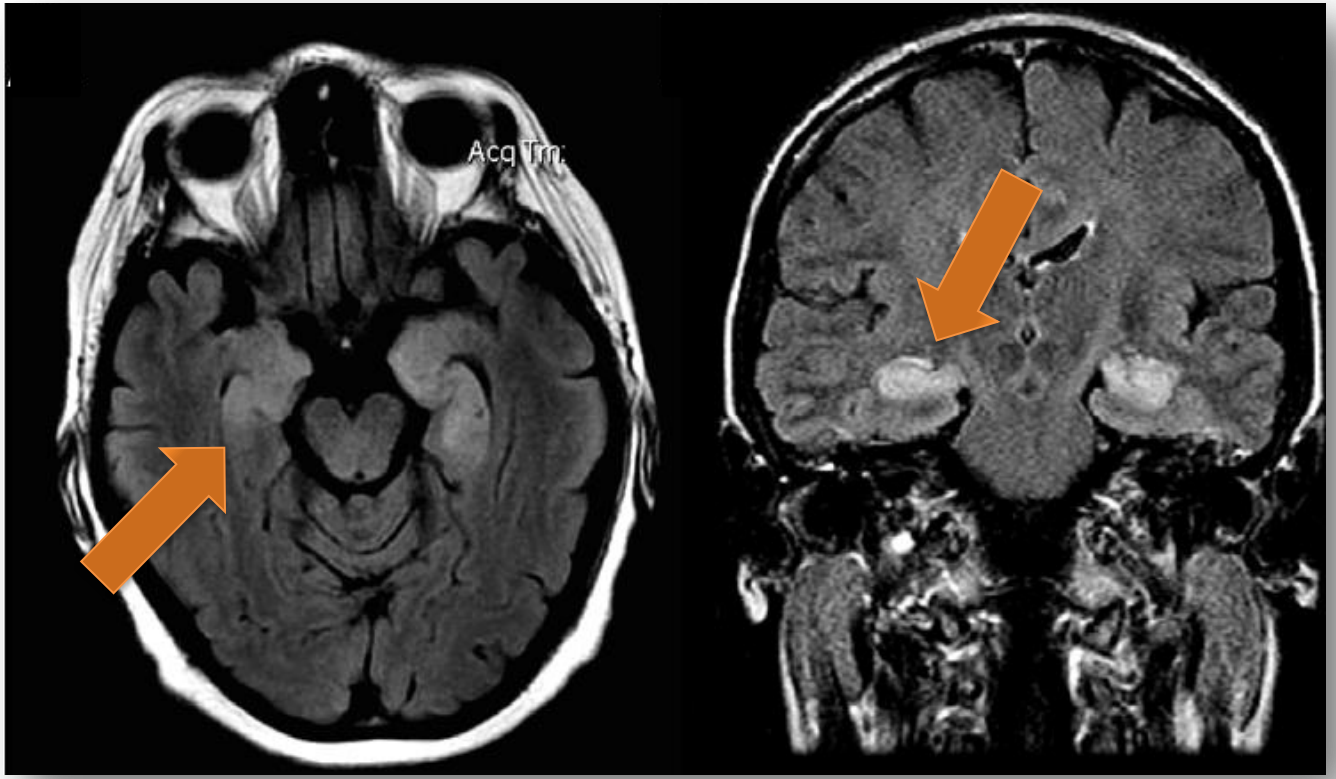
Serology (dsDNA, C3)

(isolated NPSLE flare are not uncommon)

+ Response to treatment | Reassessment/reattribution if needed

Attribution of NP events to SLE (NPSLE)

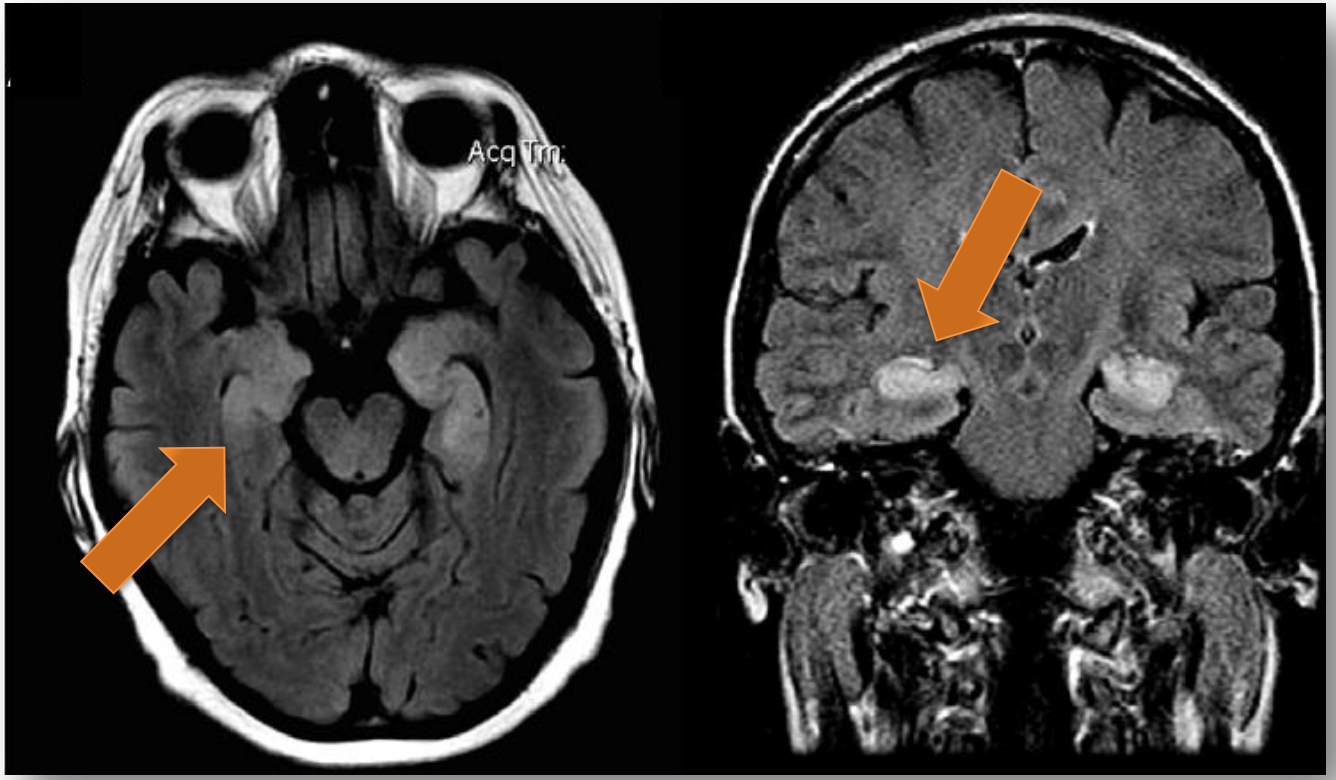
Typical limbic encephalitis



10.1016/j.nurt.2007.01.007.

The role of brain imagery

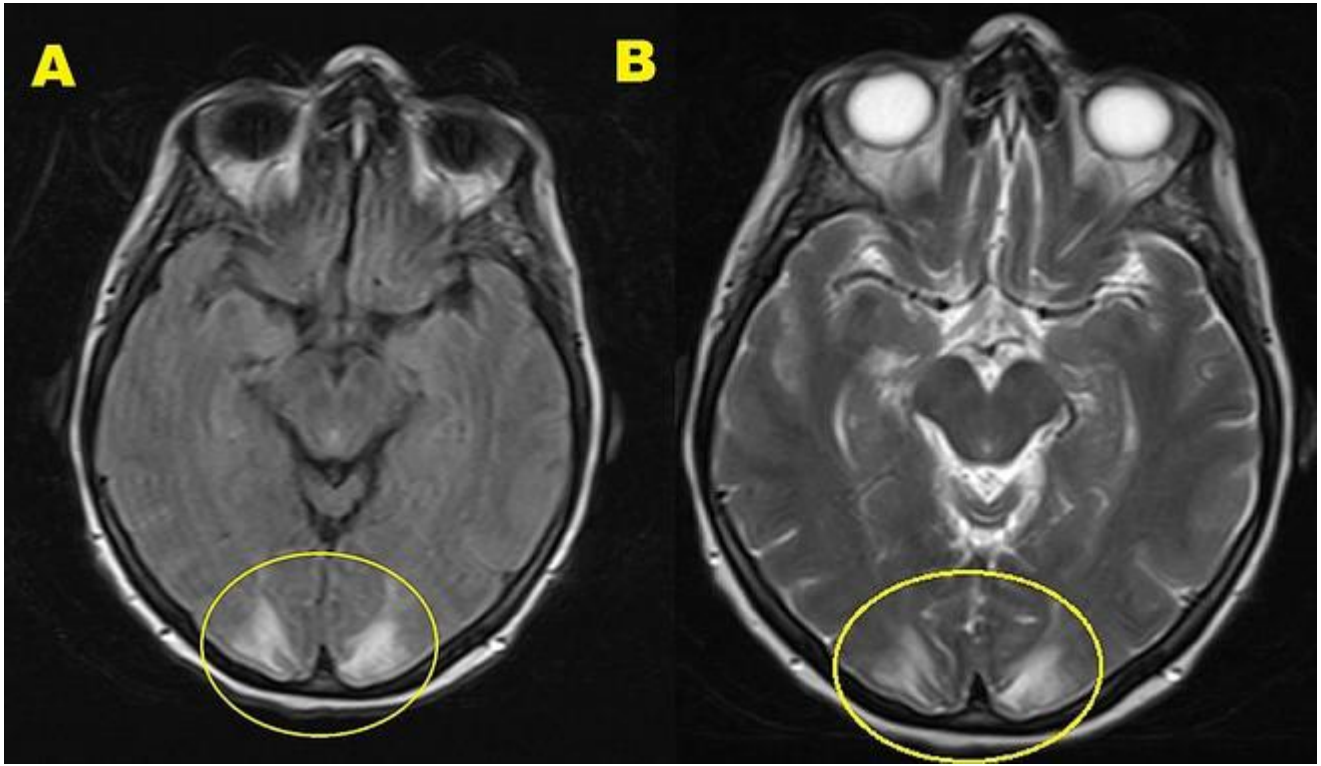
Typical limbic encephalitis



10.1016/j.nurt.2007.01.007.

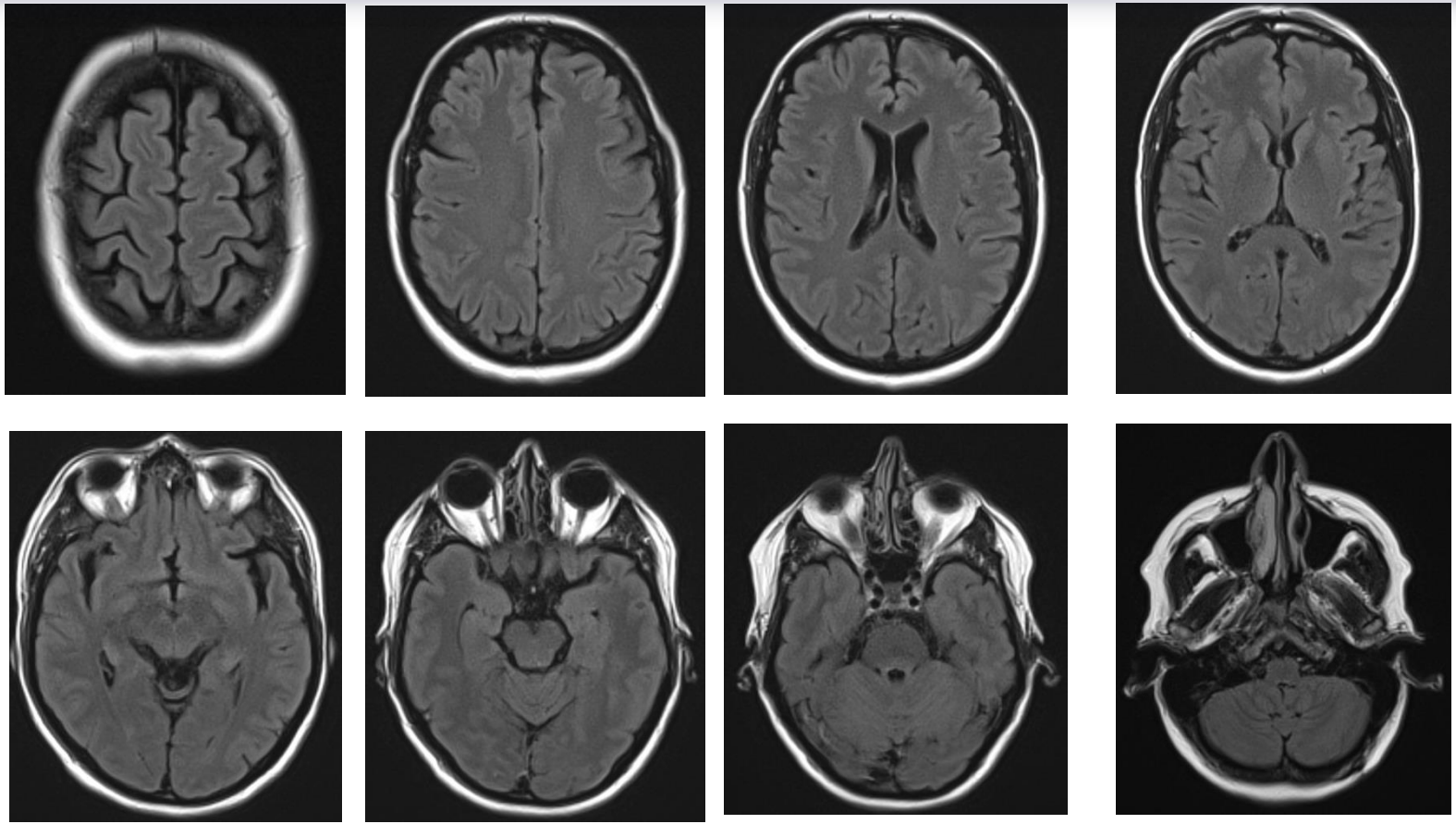
The role of brain imagery

Posterior reversible encephalopathy syndrome (PRES)



doi:10.7759/cureus.2686

The role of brain imagery



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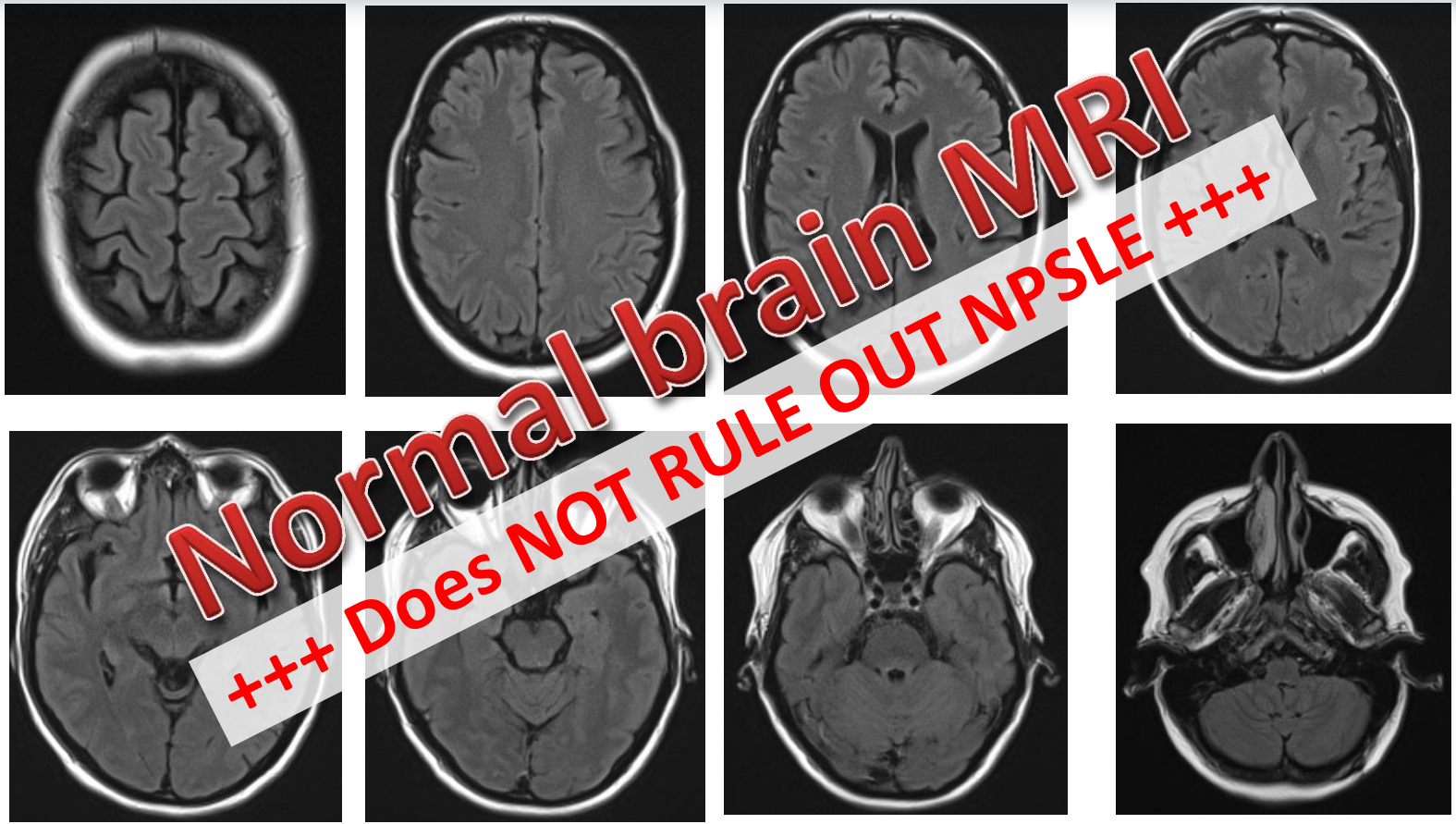

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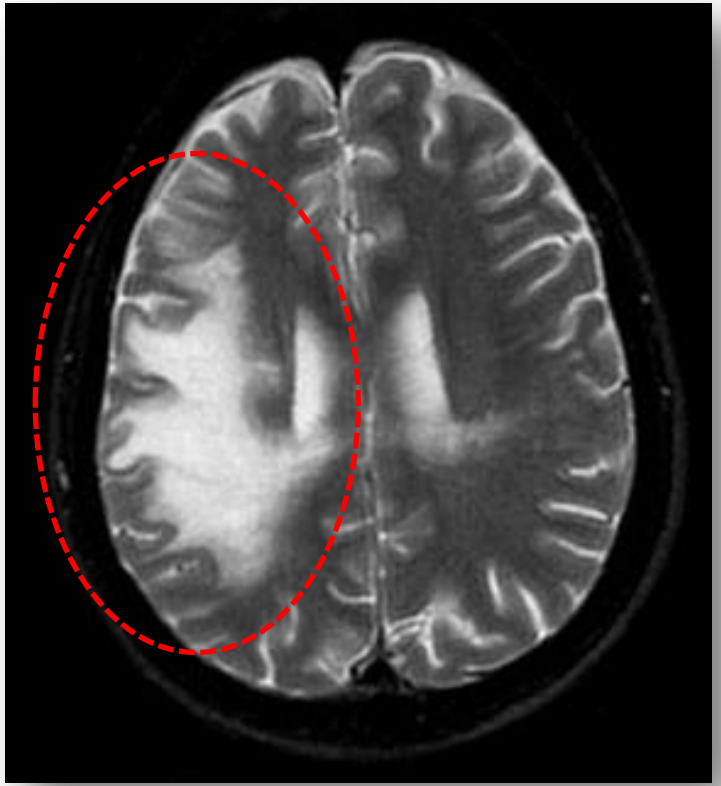
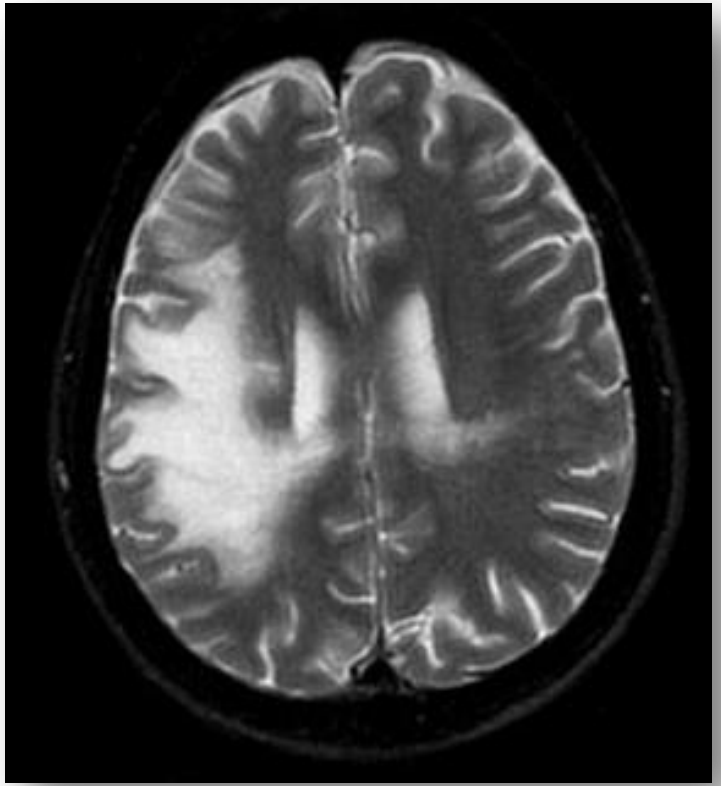


https://radiopaedia.org/images/3014589

The role of brain imagery



https://radiopaedia.org/images/3014589

Progressive Multifocal Leukoencephalopathy (PML)

≠

NPSLE

The role of brain imagery

https://radiopaedia.org/images/3014589

There is NO MRI image typical of NPSLE

Progressive Multifocal Leukoencephalopathy (PML)

≠

NPSLE

Cerebrospinal fluid analysis in SLE

CSF analysis is crucial to rule out an infection +++++

Reference	Number of patients with CNS involvement	Elevated CSF IgG index	% Oligoclonal bands
Tan et al. Clin Rheumatol 2018	76	84%	
Ernerudh et al. JNNP 1985	17		
Seibold. Semin Arthritis 1982	11 (of 17)	63%	81%
Hirohata. Arch Intern Med 1985	13		
Winfield et al. Am J Med 1983	19	-	42%

Poor quality of the literature / **intratechal synthesis is commonly seen**

The role of brain imagery

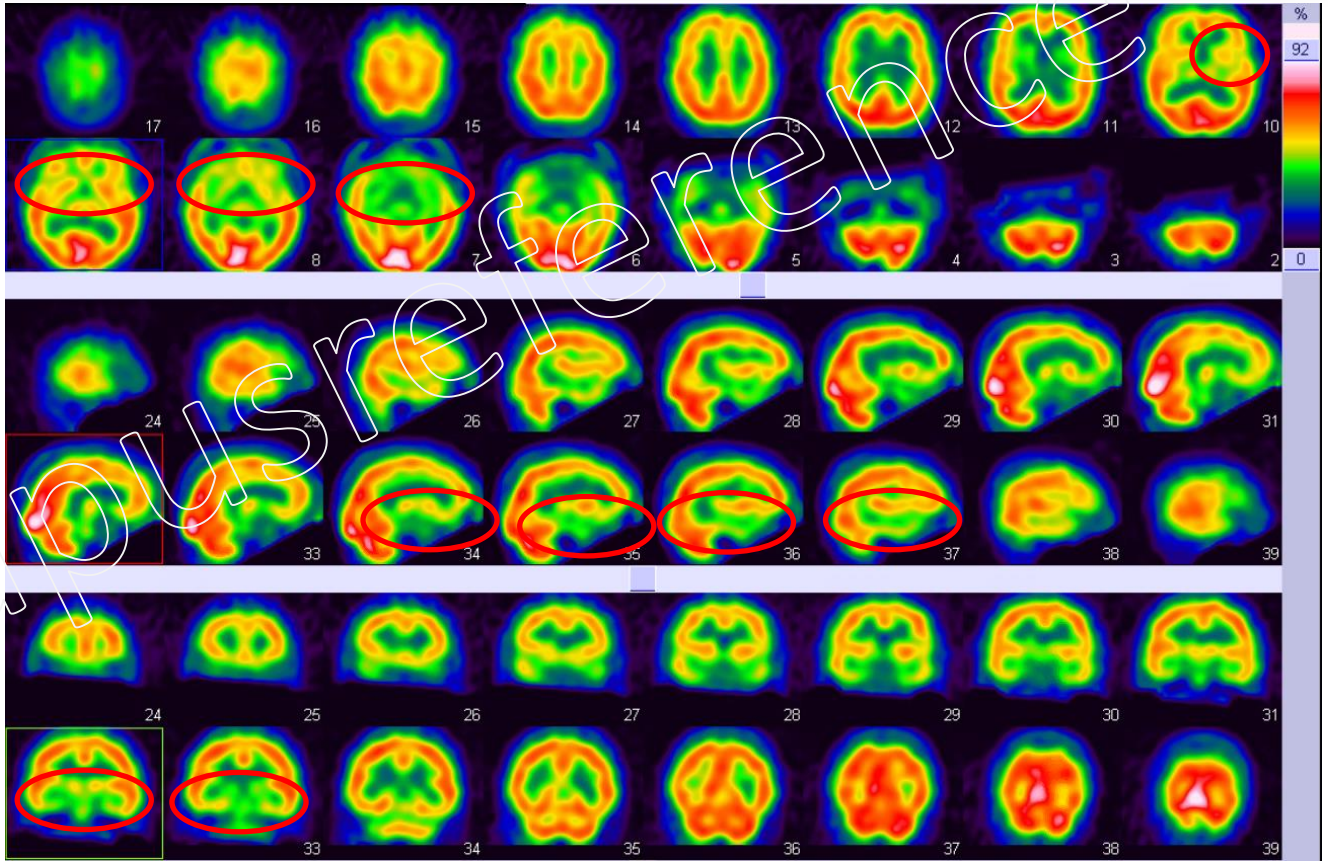
HMPAO-SPECT

SEVERE hypofixation of tracer in:

- Inner temporal regions (bilaterally)

LIMBIC ENCEPHALITIS

Anti-NMDAR and anti-neurons antibodies were negative



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Attribution of NP events to SLE (NPSLE)

Cognitive Disfunction

Substance abuse

Medication (steroids, sedatives)

History of learning disabilities

History of head injury

Other primary neurologic and psychiatric disorders

Metabolic disturbances, particularly uremia and diabetes

Antiphospholipid antibody syndrome

Coexisting emotional distress, fatigue, and pain.

Confounding factors

De … tribution of neuropsychiatric ev…

					Weight (points)
Tim…					
•					0
•					1.5
•					2.5
Mi…					
•					0
•					3
Confounding factors or not SLE-related associations (ACR glossary)					
Cognitive dysfunction	• SLE disease activity	(2)(25)(26)(27)(28)			SLEDAI ≥16
	• SLE damage	(29)(30)			SDI ≥1.0
	• Past or concurrent Major NPSLE[3]	(22)(31)(32)(33)(34)(35)			
	• aPL antibodies[1]	(22)(30)(36)(37)(38)			
	• Heart valve disease[2]	(11)(39)			Libman sacks endocarditis (aPL+)
	• Education level	(40)(37)(41)		(EP)	At least secondary school
	• Age	(40)(2)(42)(30)(41)(43)	• Age< 50 years	(EP)	
			• Response to IS or GC Rx	(EP)	
			• Abnormal neuroimaging	(EP)	MRI or SPECT

Favouring factors

Bortoluzzi et al. Rheumatology 2015

Attribution of NP events to SLE (NPSLE)

Cognitive Disfunction

Substance abuse

Medication (steroids, sedatives)

History of learning disabilities

History of head injury

Other primary neurologic and psychiatric disorders

Metabolic disturbances, particularly hypothyroidism and diabetes

Antiphospholipid antibody syndrome

Confounding factors

Limited applicability in clinical practice

Favorable factors

Cognitive dysfunction	• SLE disease activity • Past or concurrent Major NPSLE[3]	(2)(25)(26)(27)(28) (29)(30) (22)(31)(32)(33)(34)(35)			SLEDAI ≥16 SDI ≥1.0
	• aPL antibodies[1]	(22)(30)(36)(37)(38)			
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Bortoluzzi et al. Rheumatology 2015

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(isolated NPSLE flare are not uncommon)

Now I have done all this, what do I do ?

+ Response to treatment | Reassessment/reattribution if needed

Attribution of NP events to SLE (NPSLE)

Development and validation of a new algorithm for attribution of neuropsychiatric events in systemic lupus erythematosus

	Weight (points)
Time of the onset of NP event with respect to SLE clinical onset:	
• Before (>6 months before SLE onset)	0
• **Concomitant (within 6 months of SLE onset)**	1.5
• **After (>6 months after SLE onset)**	2.5
Minor or not specific NP events (as defined by Ainiala et al.)	
• Present	0
• **Absent**	3
Confounding factors or not SLE-related associations (ACR glossary)	
• **None or not applicable**	2.5
• Present (1 confounding factor)	1
• Present (>1 confounding factor)	0
Additional (or favouring) factors	
• None or not applicable	0
• **Present (1 additional or favouring factor)**	1
• **Present (>1 additional or favouring factor)**	2

How can we decide ???

NP event related (>7) or not related (<3) to SLE

Bortoluzzi et al. Rheumatology 2015

Attribution of NP events to SLE (NPSLE)

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Confounding factors or not SLE-related associations (ACR glossary)	
• **None or not applicable**	2.5
• Present (1 confounding factor)	1
• Present (>1 confounding factor)	0
Additional (or favouring) factors	
• None or not applicable	0
• **Present (1 additional or favouring factor)**	1
• **Present (>1 additional or favouring factor)**	2

Limited applicability in clinical practice

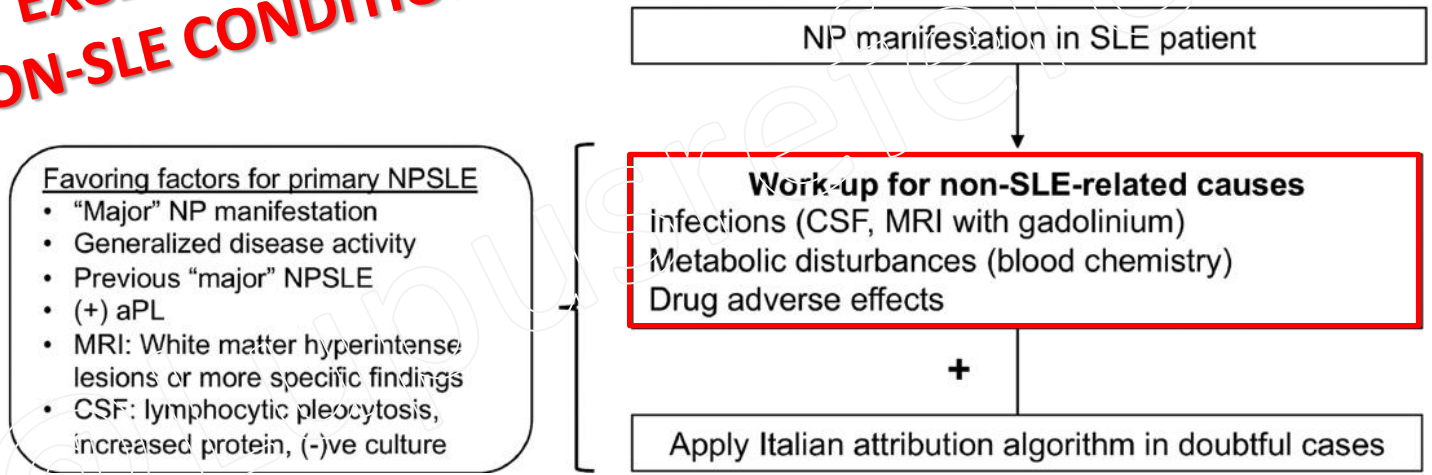
How can we decide ???

NP event related (>7) or not related (<3) to SLE

Bortoluzzi et al. Rheumatology 2015

Attribution of NP events to SLE (NPSLE)

Pragmatic strategy
EXCLUSION OF
NON-SLE CONDITIONS

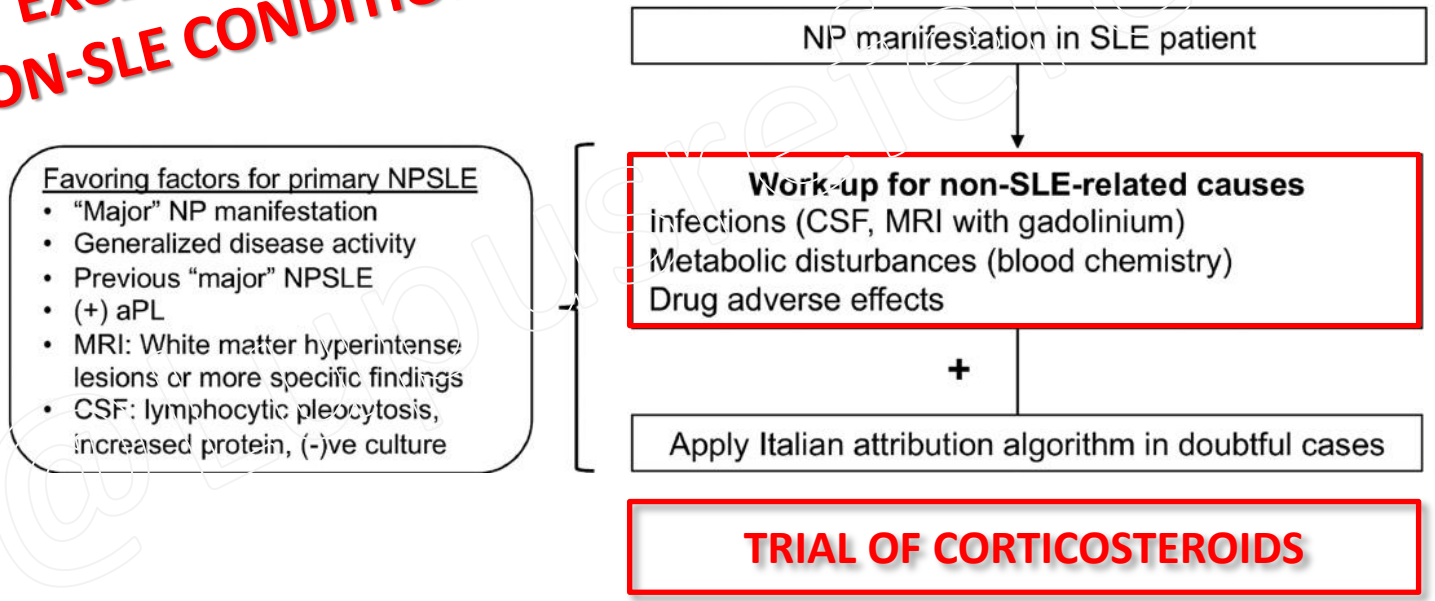


Infections
Metabolic
Etc…

Nikolopoulos…Bertsias. Exp Rev Clin Immunol 2021

Attribution of NP events to SLE (NPSLE)

Pragmatic strategy
EXCLUSION OF
NON-SLE CONDITIONS



Nikolopoulos…Bertsias. Exp Rev Clin Immunol 2021

Today's NPSLE agenda

- ✓ What is NPSLE?
- ✓ How diverse are NPSLE manifestations
- ✓ How common is NPSLE among SLE patients?
- ✓ What are the typical manifestations of NPSLE?
- ✓ How do you attribute NP events to SLE (NPSLE)?
- ✓ **Additional diagnostic considerations**
- ✓ What is the treatment of NPSLE?

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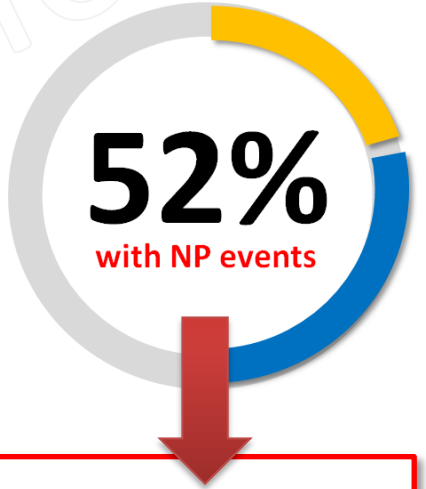

We can't perform an MRI and do CSF analysis in ALL SLE patients reporting NP manifestations

Today's NPSLE agenda

- ✓ What is NPSLE?
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- ✓ How common is NPSLE among SLE patients?
- ✓ What are the typical manifestations of NPSLE?
- ✓ How do you attribute NP events to SLE (NPSLE)?
- ✓ **Additional diagnostic considerations**
  - ✓ ***Minor* complaint vs *significant* NP involvement**
- ✓ What is the treatment of NPSLE?

Cognitive dysfunction in SLE

Lupus Fog and Memory Problems

By R. Morgan Griffin

FROM THE WEBMD ARCHIVES

Lupus fog -- the forgetfulness and fuzzy-headed feeling that can come with lupus (systemic lupus erythematosus, or SLE) – can be one of the most frustrating symptoms of the condition.

The term lupus fog means more than memory problems. It also refers to cognitive difficulties, such as trouble helping your child with homework, or writing a grocery list.

"It can really make your whole world fall apart," says Janet Foley Orosz, PhD, a public policy expert in Ohio who has struggled with lupus fog for almost 20 years. She's now collaborating on a web site and vocational program designed to help others with the condition.

There's no cure for lupus, so there's no cure for lupus fog either. But there are ways to work around your problems with concentration and memory. Here's what you need to know.

What Is Lupus Fog?

Lupus fog is a general name for the cognitive impairments that often appear with lupus, including concentration and memory problems, confusion, and difficulty expressing yourself. These cognitive problems are often worse during flares.

The good news: Lupus fog doesn't usually get progressively worse, like dementia or Alzheimer's disease, says Lisa Fitzgerald, MD, a rheumatologist at the Lupus Center of Excellence at the Beth Israel Deaconess Medical Center in Boston. Instead, memory issues will probably wax and wane, just like other lupus symptoms.

The exact cause of lupus fog is hard to pin down, experts say. In some cases, lupus can damage cells in the brain, leading directly to cognitive problems. However, in most cases other factors play a role, including fatigue, stress, and depression. Lupus fog is sometimes worse in people who also have fibromyalgia. Although it's possible that side effects from drugs such as NSAIDs or steroids could worsen lupus fog, experts say that switching medicines rarely resolves the problem.

https://www.webmd.com/lupus/features/lupus-fog-memory-problems#1 (Accessed 13th of Oct 2020)

Cognitive dysfunction in SLE

ACR criteria for Neuro-Psychiatric SLE (NPSLE)

Central nervous system

Aseptic meningitis
Cerebrovascular disease
Demyelinating syndrome
Headache
Chorea
Myelopathy
Seizure disorders
Acute confusional state
Anxiety disorder

Cognitive dysfunction

Mood disorder
Psychosis

Peripheral nervous system

AIDP (Guillain–Barré)
Autonomic disorder
Mononeuropathy, single
Mononeuropathy, multiplex
Myasthenia gravis
Neuropathy, cranial
Plexopathy
Polyneuropathy

Cognitive dysfunction in SLE

Frequency of CNS-involving NPSLE manifestations in various cohorts

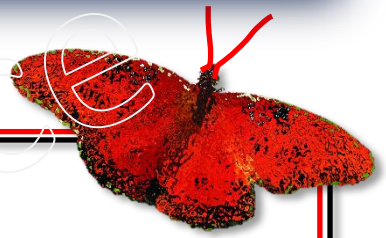
ACR Nomenclature	Ainiala, 2001[7] (*n*=46)	Sanna, 2003[8] (*n*=323)	Brey, 2002[9] (*n*=128)	Afeltra, 2003[10] (*n*=61)	Costallat, 2001[11] (*n*=527)	Hanly, 2010[12] (*n*=1206)		Mok, 2005[13] (*n*=282)	Ferrara University, 2014[15] (*n*=228)	Multiple italian Centers, 2014[15] (*n*=221)	Faria, 2014[16] (*n*=55)	Steup-Beekman, 2013[14] (*n*=102)
						Model A	Model B					
Aseptic Meningitis	1 (2)				2 (0.4)	4 (2.7)	4 (1.6)	1 (0.4)	3 (0.7)	0	6 (10.9)	3 (3)
Cerebrovascular Disease	7 (15)	47 (14.5)	2 (2)	15 (24)	13 (2.5)	18 (12.1)	40 (15.5)	21 (7.4)	68 (16.2)	61 (14.3)	16 (29)	44 (43)
Demyelinating Syndrome	1 (2)	3 (0.9)			1 (0.2)	1 (0.7)	3 (1.2)	0	3 (0.7)	4 (0.9)	1 (1.8)	
Headache	25 (54)	78 (24)	73 (57)	13 (21)	25 (62.5) (*n*=40)	0	0	8 (2.8)	116 (27.7)	95 (22.2)	4 (7.2)	23 (23)
Movement Disorder (Chorea)	1 (2)	4 (1.2)	1 (1)		4 (0.76)	4 (2.7)	5 (1.9)	2 (0.7)	7 (1.7)	3 (0.7)	1 (1.8)	5 (5)
Myelopathy		4 (1.2)		2 (3)	6 (1)	5 (3.4)	10 (3.9)	6 (2.1)	1 (0.2)	4 (0.9)	2 (3.6)	6 (6)
Seizure Disorders	4 (9)	27 (8.3)	21 (16)	7 (11)	39 (7)	39 (26.2)	54 (20.9)	17 (6)	19 (4.5)	61 (14.3)	10 (5.5)	28 (27)
Acute Confusional State	3 (7)	12 (3.7)			15 (3)	11 (7.4)	17 (6.6)	10 (3.5)	7 (1.7)	13 (3)		7 (7)
Anxiety Disorder	6 (13)	24 (7.4)	27 (21)	4 (6)	28 (70) (*n*=40)	0	0	3 (1.1)	15 (3.6)	28 (6.6)		1 (1)
Cognitive Dysfunction	37/46 (81)	35 (10.8)	53/67 (79)	32/61 (52)	32 (52)	8 (5.4)	22 (8.5)	10 (3.5)	61 (14.6)	56 (13.1)	6 (10.9)	27 (26)
– Minor	26/37 (70)		29/67 (43)									
– Moderate	7/37 (19)		20/67 (30)									
– Severe	4/37 (11)		4/67 (6)									
Mood Disorder	20 (43)	54 (16.7)	25 (20)	17 (27)	30 (75) (*n*=40)	18 (12.1)	47 (18.1)	10 (3.5)	67 (16)	49 (11.5)		8 (8)
Psychosis		25 (7.7)	6 (5)		28 (5)	8 (5.4)	13 (5)	15 (5.3)	13 (3.1)	17 (4)	5 (9.1)	6 (6)

from 5 to 80% of patients !!!

Cognitive dyfunction is the most common NPSLE event

Faria et al. Open Rheumatology 2017

Attribution of NP events to SLE (NPSLE)

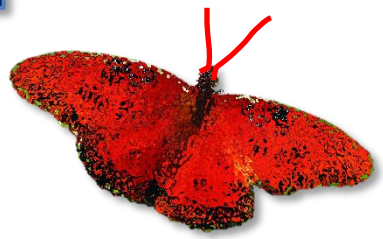


Some NP MANIFESTATIONS
cannot be attributed confidently to SLE

- Headaches
- Anxiety
- Mild depression
- **Mild cognitive impairment (deficit in <3 of 8 domains)**
- Polyneuropathy without electrophysiological confirmation

Cognitive dysfunction in SLE

Neuro-psychiatric manifestations in SLE patients

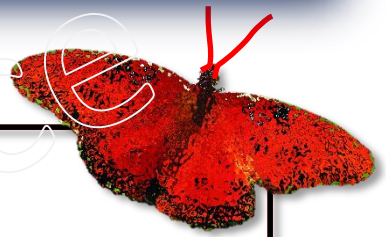


Is this pathologic and significant ?

=> *Usually* ***easy for neurological manifestations***

=> *Often* ***more difficult to psychiatric manifestations***
e.g. brain fog, mood disorders

Cognitive dysfunction in SLE

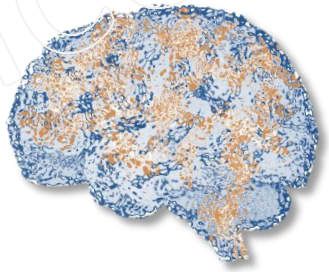


FOUR LITTLE « SECRETS »

- I always try to get some **feedback from family members or partner**
- I'm trying to see if **coping solutions are used**
  (e.g. post-it, alarms on telephone, etc…)
- Is this **fluctuating or permanent/worsening**
- is there any **confounder** (eg. Depression)?

Cognitive dysfunction in SLE

There is NO SPECIFIC PATTERN of cognitive dysfunction in SLE*



*Hanly et al. Arthritis Rheum 2019

Cognitive dysfunction in SLE

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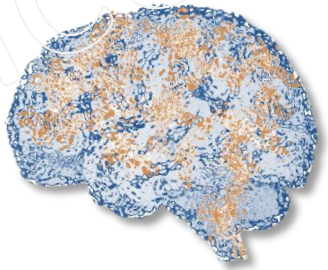

- **Abnormal tests may include:**
  - ***Cognitive slowing***
  - ***Decreased attention***
  - ***Impaired working memory***
  - ***Executive dysfunction*** *(e.g., difficulty with multitasking, organization, planning)*
- ***Formal attribution to SLE remains very difficult in case of mild cognitive impairement*** *(<3 impaired domains**)*

*Hanly et al. Arthritis Rheum 2019

**Ainiala et al. Arthritis Care Res 2001

Cognitive dysfunction in SLE

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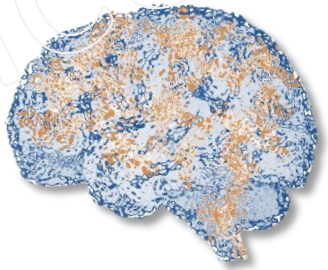

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Cognitive complaint → **Screening tests**

MoCA >> MMSE
Computerized testing

*Hanly et al. Arthritis Rheum 2019
**Ainiala et al. Arthritis Care Res 2001

Cognitive dysfunction in SLE

NAME OF TEST	TIME	DETAILS	REFERENCE
SELF-ASSESSMENT BY PATIENT			
Cognitive Symptom Inventory (CSI)	3-5 mins	**Not correlated with objective neuro-psychological testing**	Hanly et al. J Rheum 2012
Perceived Deficits Questionnaire 5-Item (PDQ-5)	3-5 mins	**Mean value similar with/without cognitive impairment** Only a low (negative) correlation with HVLT-R	Nantes & Touma. J Rheum 2017

Cognitive dysfunction in SLE

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Perceived Deficits Questionnaire 5-Item (PDQ-5)	3-5 mins	**Mean value similar with/without cognitive impairment** Only a low (negative) correlation with HVLT-R	Nantes & Touma. J Rheum 2017
EXTERNAL-ASSESSMENT BY PHYSICIAN			
Montreal Cognitive Assessment (MoCA)	10-15 mins	PPV and LR+ similar to MMSE but **NPV higher**	Nantes & Touma. J Rheum 2017
Mini Mental State Examination (MMSE)	10-15 mins	NPV lower than MoCA. **Tends to miss many patients with mild CI**	Nantes & Touma. J Rheum 2017
Hopkins Verbal Learning Test-Revised (HVLT-R)	25–30 min	Focuses on verbal learning and memory. Requires trained personnel (administration/Interpretation)	Julian et al. Arthritis Care Res 2012

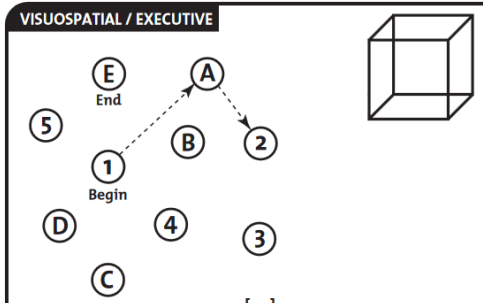
Cognitive dysfunction in SLE

Montreal Cognitive Assessment

MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

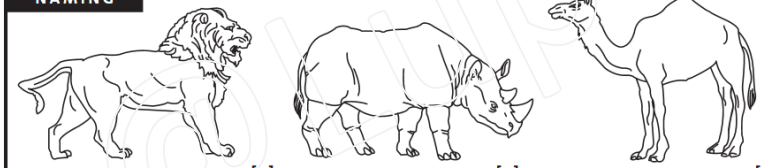


Copy cube

Draw CLOCK (Ten past eleven) (3 points)

[ ] [ ] [ ] Contour [ ] Numbers [ ] Hands __/5

NAMING



[ ] [ ] [ ] __/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

Scores on the MoCA range from zero to 30, with a score ≥26 generally considered normal. IMPORTANTLY, it may fail to identify subtle higher-level cognitive impairement.

ATTENTION	Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4 Subject has to repeat them in the backward order [ ] 7 4 2						__/2
	Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors [ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B						__/1
	Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65 4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**						__/3
LANGUAGE	Repeat : I only know that John is the one to help today. [ ] The cat always hid under the couch when dogs were in the room. [ ]						__/2
	Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words)						__/1
ABSTRACTION	Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler						__/2
DELAYED RECALL	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only __/5
Optional	Category cue						
	Multiple choice cue						
ORIENTATION	[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City						__/6

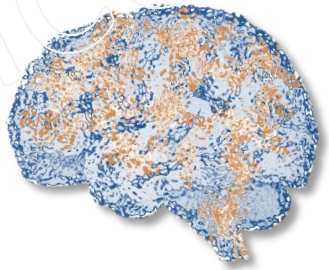
© Z.Nasreddine MD Version November 7, 2004
www.mocatest.org

Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

Cognitive dysfunction in SLE

There is NO SPECIFIC PATTERN of cognitive dysfunction in SLE*



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Cognitive complaint → **Screening tests** → **Neuropsychological full testing**

*Hanly et al. Arthritis Rheum 2019

**Ainiala et al. Arthritis Care Res 2001

Cognitive dysfunction in SLE

The ACR-SLE neuropsychological battery (1 to 2 hours)

- North American Adult Reading Test (to estimate IQ)
- Digit Symbol Substitution Test
- Trail-Making Test (Parts A & B)
- Stroop Color and Word Test
- California Verbal Learning Test
- Rey-Osterrieth Complex Figure Test (with delayed recall)
- WAIS III Letter--Number Sequencing
- Controlled Oral Word Association Test (FAS)
- Animal Naming
- Finger Tapping

Should be the « minimum » confimatory tests

Not always reimbursed by insurance

Arthritis Rheum 1999

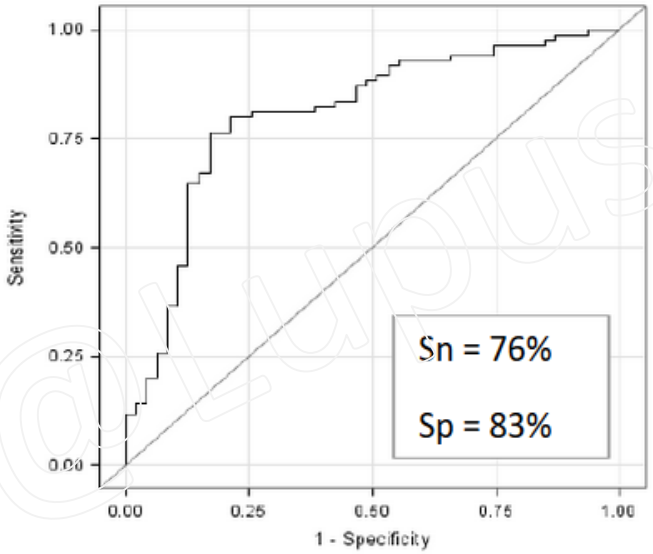
ACR Ad Hoc Committee on NPSLE Nomenclature

Cognitive dysfunction in SLE

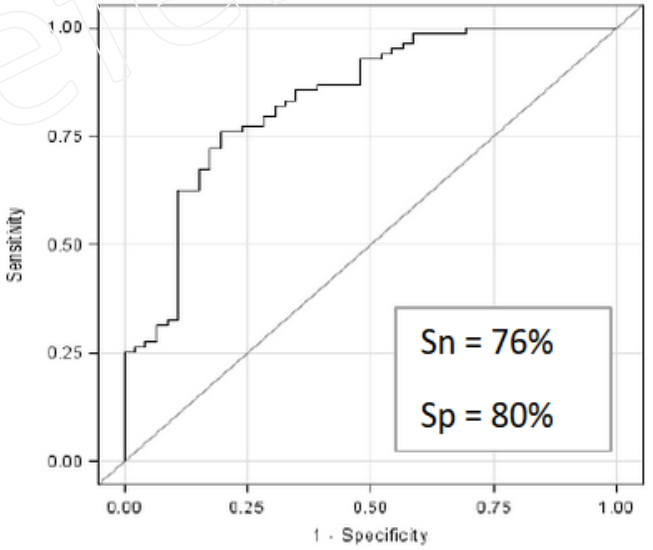
VALIDITY EVIDENCE SUPPORTS THE USE OF AUTOMATED NEUROPSYCHOLOGICAL ASSESSMENT METRICS AS A SCREENING TOOL FOR COGNITIVE IMPAIRMENT

Duration: 20 to 40 mins

Model 5 AUC = 81%



Model 6 AUC = 84%



Tayer-Shifman et al. Arthritis Care Res 2020

Today's NPSLE agenda

- ✓ What is NPSLE?
- ✓ How diverse are NPSLE manifestations
- ✓ How common is NPSLE among SLE patients?
- ✓ What are the typical manifestations of NPSLE?
- ✓ How do you attribute NP events to SLE (NPSLE)?
- ✓ **Additional diagnostic considerations**
  - ✓ **Minor complaint vs significant NP involvement**
  - ✓ **The role of brain imagery (MRI)**
- ✓ What is the treatment of NPSLE?

Attribution of NP events to SLE (NPSLE)

Neuro-psychiatric manifestations in SLE patients

@Lupusreference

When possible, try to confirm NP event using an objective method

Attribution to SLE

Document the involvement of CNS/PNS

CNS: Brain MRI + CSF

+/- brain-SPECT

+/- EEG

PNS: ENMG +/- CSF

(can be normal)

Search for confounding and favouring factors

Alternative diagnosis?

(e.g. infection, metabolic)

Change in medications?

Previous NPSLE involvement?

(can be present but play no role)

Ongoing SLE activity in other organs

Early in SLE history?

Flare in another organ ?

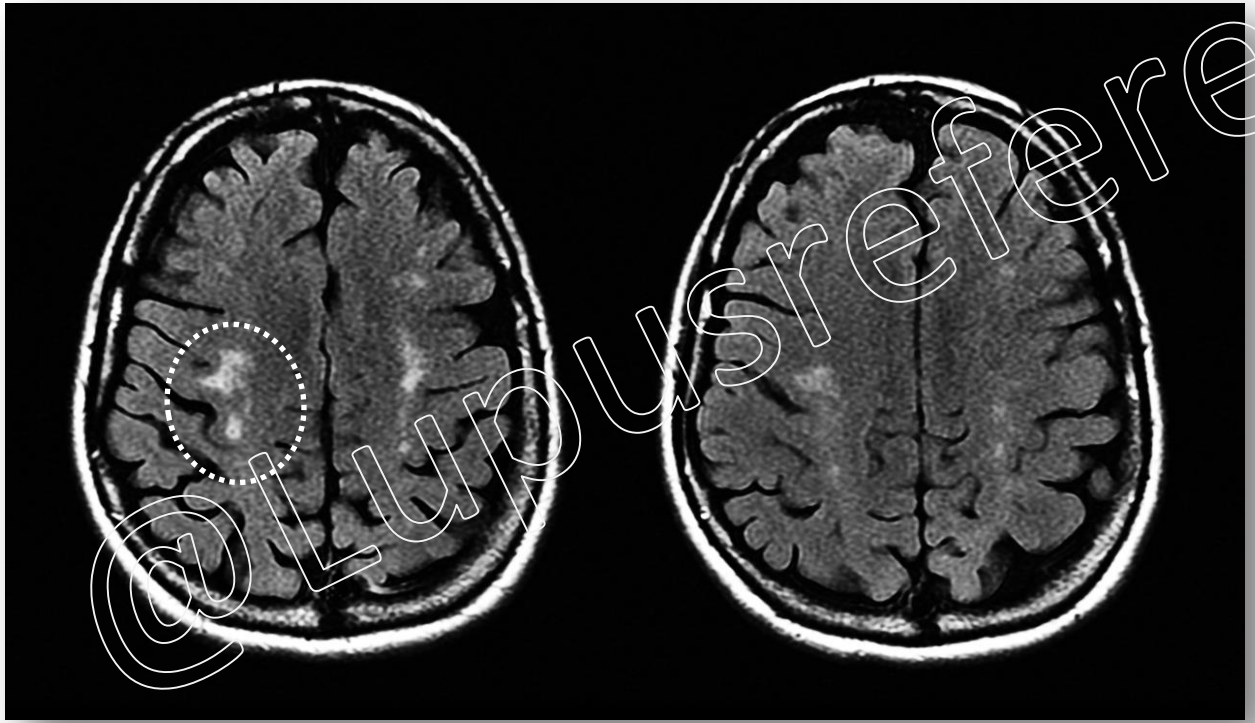
Serology (dsDNA, C3)

(isolated NPSLE flare are not uncommon)

+ Response to treatment | Reassessment/reattribution if needed

The role of brain imagery

But occasionally…



10.1594/ecr2014/C-1939

WHITE-MATTER HYPERINTENSITIES

VERY common !!!!!!

The role of brain imagery

Twenty-year brain magnetic resonance imaging follow-up study in Systemic Lupus Erythematosus: Factors associated with accrual of damage and central nervous system involvement

Distribution of MRI features at baseline and at follow-up.

MRI features	Baseline MRI	Follow-up MRI
MRI abnormalities	16 (53.3)	24 (80.0)
WMHIs	15 (50.0)	21 (70.0)
Frontal/parietal	10 (33.3)	17 (56.7)
Temporal/occipital	2 (6.7)	7 (23.3)
Basal ganglia	4 (13.3)	6 (20.0)
Periventricular	9 (30.0)	16 (53.3)
Cerebellar/brainstem	1 (3.3)	6 (20.0)
Cerebral atrophy[a]	5 (16.7)	10 (33.3)
Mild[b]	3 (10.0)	6 (20.0)
Moderate[b]	2 (6.7)	3 (10.0)
Severe[b]	0	1 (3.3)
Parenchymal defects	2 (6.7)	6 (20.0)
mMSS[c]	1 (0–3)	2 (2–5)

WHITE-MATTER HYPERINTENSITIES

BASELINE
50% of MRI

20 years LATER
70% !!!!

Piga et al. Autoimmun Rev 2015

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Based on the literature

Progression of WMHIs

Is related to:

- **aPL+**
- **General CVRF**
- **Disease activity**
- **Baseline damage**

Piga et al. Autoimmun Rev 2015

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Based on the literature

Progression of WMHIs

Is related to:

- **aPL+**
- **General CVRF**
- **Disease activity**
- **Baseline damage**

Is associated with:

- **New NPSLE events**
- **Cognitive impairement**

Piga et al. Autoimmun Rev 2015

The role of brain imagery

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Based on the literature

Progression of WMHIs Is related to:

- aPL+
- General CVRF
- Disease activity
- Baseline damage

Treatment to be discussed:

- Aspirin for primary prev
- CVRF management
- Control disease activity

Piga et al. Autoimmun Rev 2015

Today's NPSLE agenda

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  - ✓ The role of brain imagery (MRI)
  - ✓ **The role of Cerebrospinal fluid analysis**
  - ✓ The role of auto-antibodies
- ✓ What is the treatment of NPSLE?

CSF analysis in SLE

CSF analysis is crucial to rule out an infection ++++

Reference	Number of patients with CNS involvement	Elevated CSF IgG index	% Oligoclonal bands
Tan et al. Clin Rheumatol 2018	76	84%	
Ernerudh et al. JNNP 1985	17		
Seibold. Semin Arthritis 1982	11 (of 17)	63%	81%
Hirohata. Arch Intern Med 1985	13		
Winfield et al. Am J Med 1983	19	-	42%

Poor quality of the literature / **intratechal synthesis** **is commonly seen**

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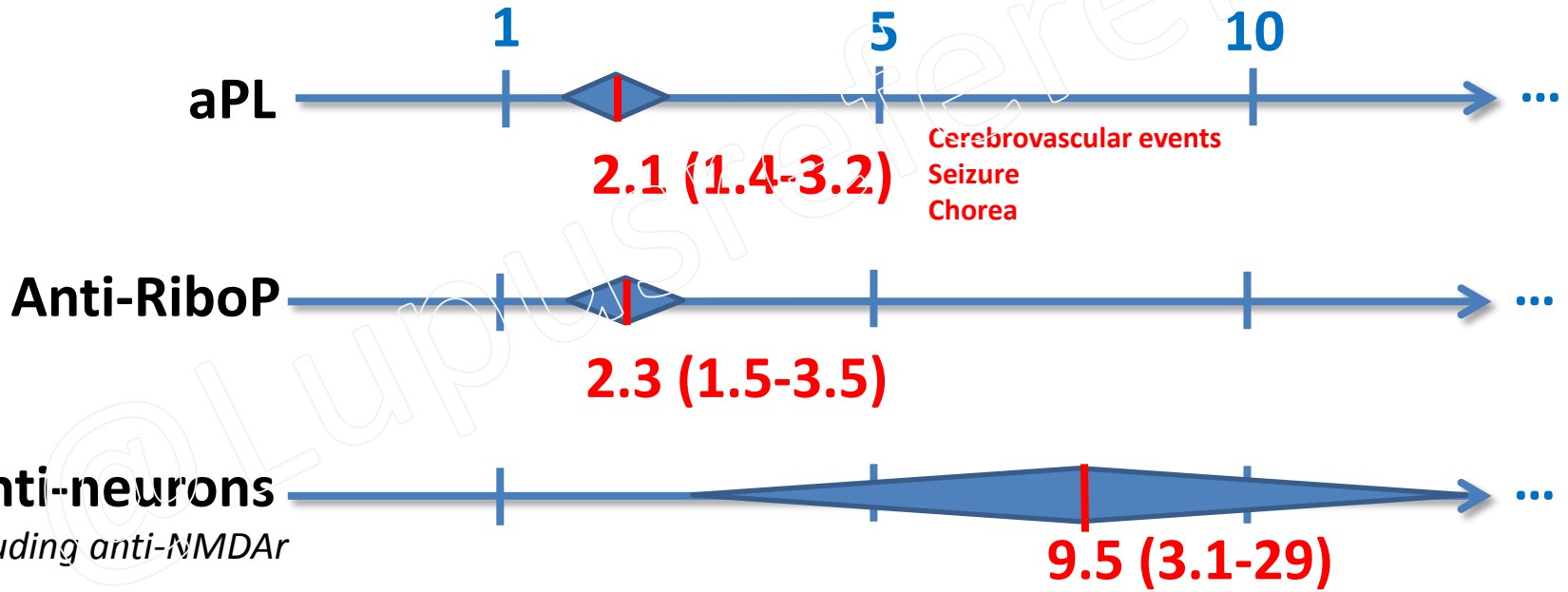
- ✓ What is the treatment of NPSLE?

Which autoantibodies are relevant in NPSLE?

A meta-analysis of serum and cerebrospinal fluid autoantibodies in neuropsychiatric systemic lupus erythematosus



For NPSLE vs SLE

Ho et al. Autoimmun Rev 2016

Shall I search for autoantibodies in the CSF?

Auto-antibodies should be searched for in the blood AND in the CSF

Sample type	Auto-antibodies	Number of studies	Pooled OR (95% CI)
Mood disorder	Anti-ribosomal P	1	0.27 (0.01–5.27)
Psychosis	Anti-ribosomal P	1	1.73(0.37–8.05)
Cerebrovascular disease	Anti-ribosomal P	1	0.10(0.01–1.82)
Seizure disorders	Total	2	**21.65 (4.62–101.49)**
	Anti-neuronal	1	10.27 (1.14–92.26)
	Anti-ribosomal P	1	45.00 (5.11–395.99)
Acute confusional state	Anti-ribosomal P	1	**36.36 (4.11–321.35)**
Myelopathy	Anti-neuronal	1	5.73(0.26–126.43)
Headache	Anti-ribosomal P	1	0.51(0.02–11.06)
Movement disorder	Anti-ribosomal P	1	**21.85(1.07–445.32)**
	Anti-neuronal	1	0.32(0.03–3.31)
	Total	2	2.36(0.04–148.28)
Aseptic meningitis	Anti-ribosomal P	1	3.00(0.55–16.38)

Anti-ribo P + anti-neurons / could be interesting markers in the CSF

Ho et al. Autoimmun Rev 2016

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Treating NPSLE

Neuro-psychiatric manifestations in SLE patients

Treating NPSLE

Neuro-psychiatric manifestations in SLE patients

Is this significant ?

Treating NPSLE

Neuro-psychiatric manifestations in SLE patients

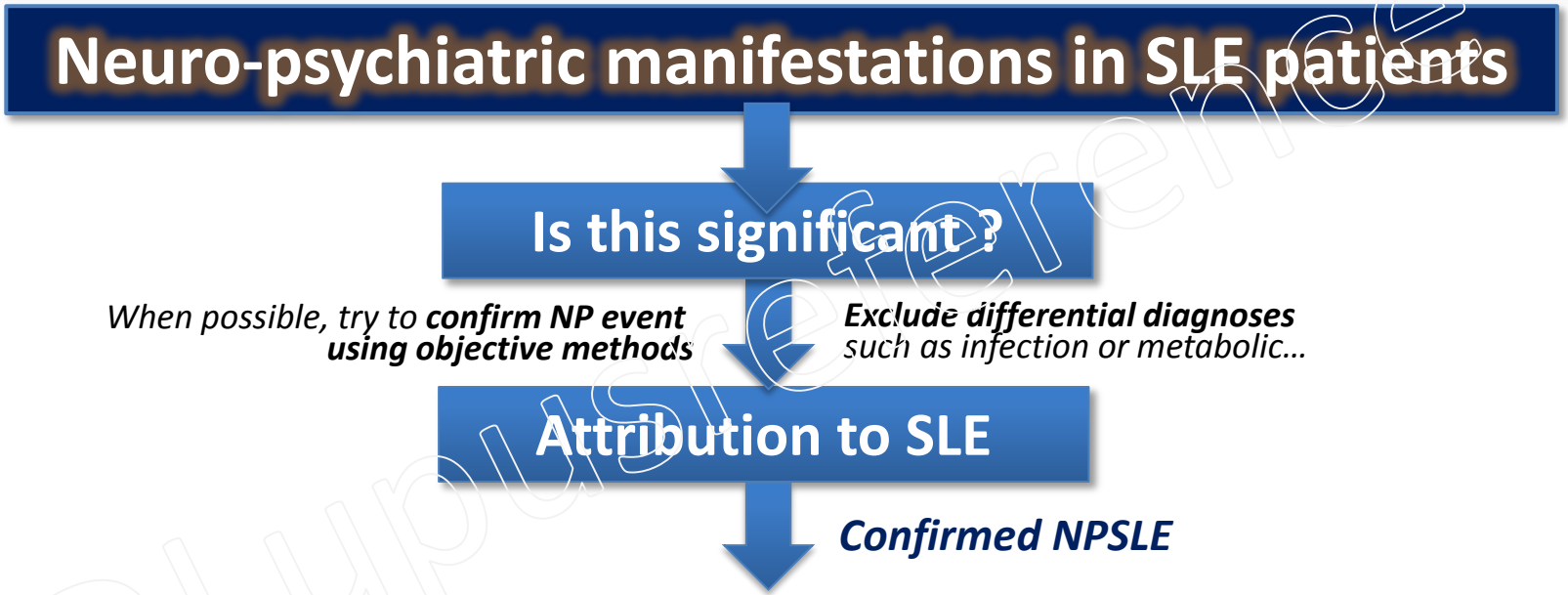
Is this significant ?

*When possible, try to **confirm NP event using objective methods***

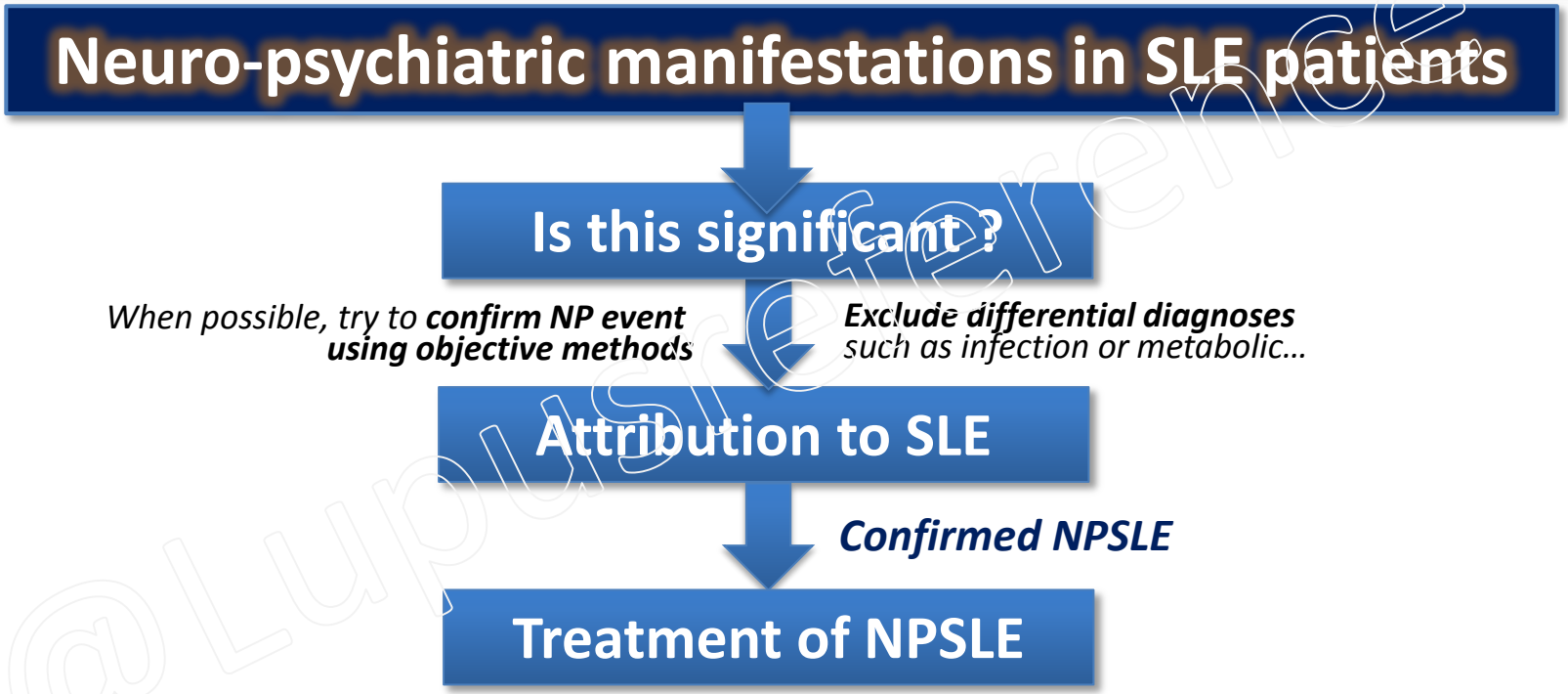
Exclude differential diagnoses *such as infection or metabolic…*

Attribution to SLE

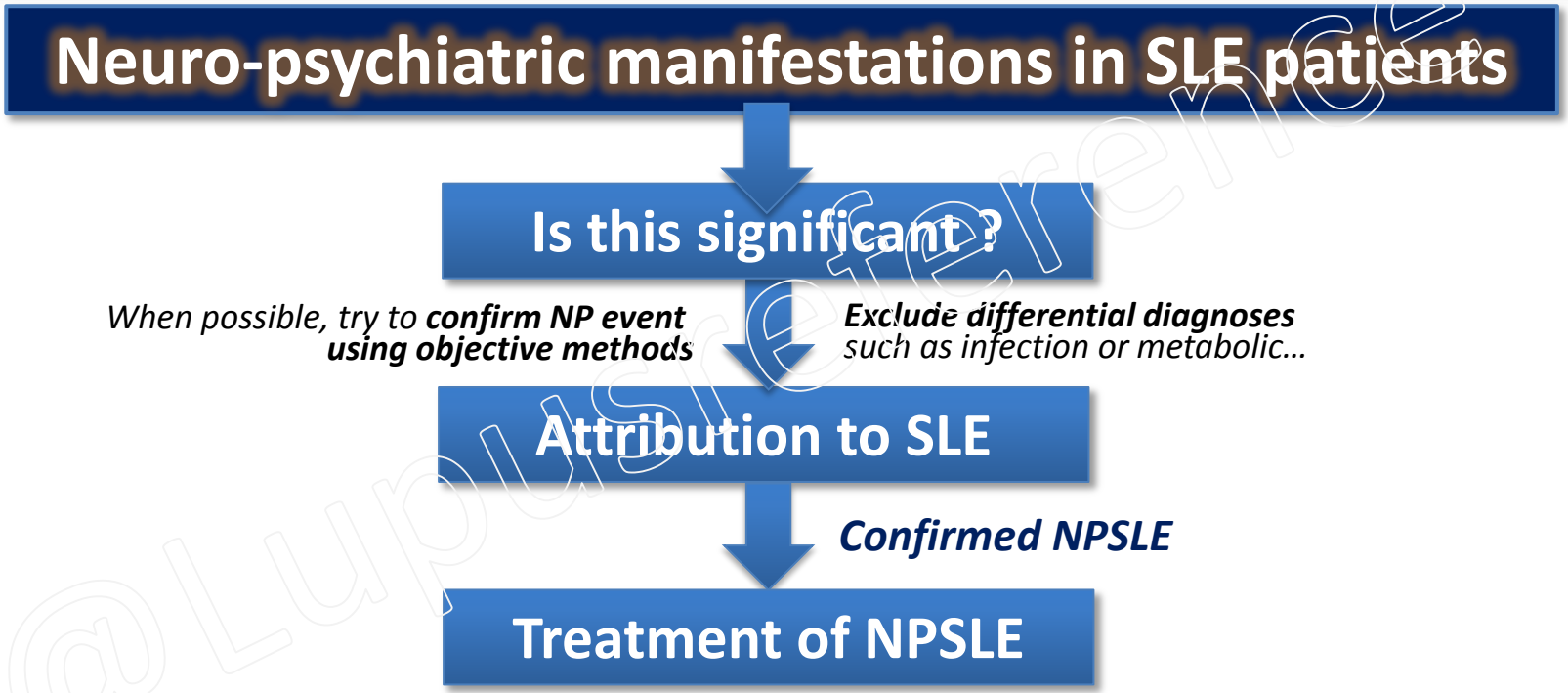
Treating NPSLE



Treating NPSLE



Treating NPSLE



Patients with (severe) NPSLE are generally excluded from clinical trials

Treating NPSLE according to its pathogenesis

Pathogenic mecanism	Treatment	Delay of action	PRO's	CON's
Inflammatory & Immune	Glucocorticoids	Very fast	Very efficient	Long-term toxicity
	Cyclophosphamide	10-15 days	Potent	Long-term toxicity
	MMF	Weeks to months	Oral treatment	Delay of action Well suited for maintenance
	Rituximab	Weeks to months	Data available for refractory NPSLE	Delay of action
Thrombotic Ischaemic	Aspirin	Immediate	Well-suited for small vessels	Risk of bleeding
	Anticoagulants	Immediate	Well suited for APS	Risk of bleeding

Treating NPSLE according to its pathogenesis

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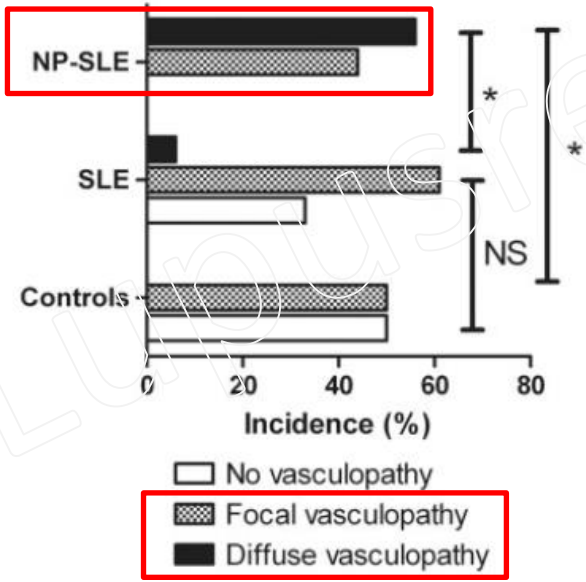
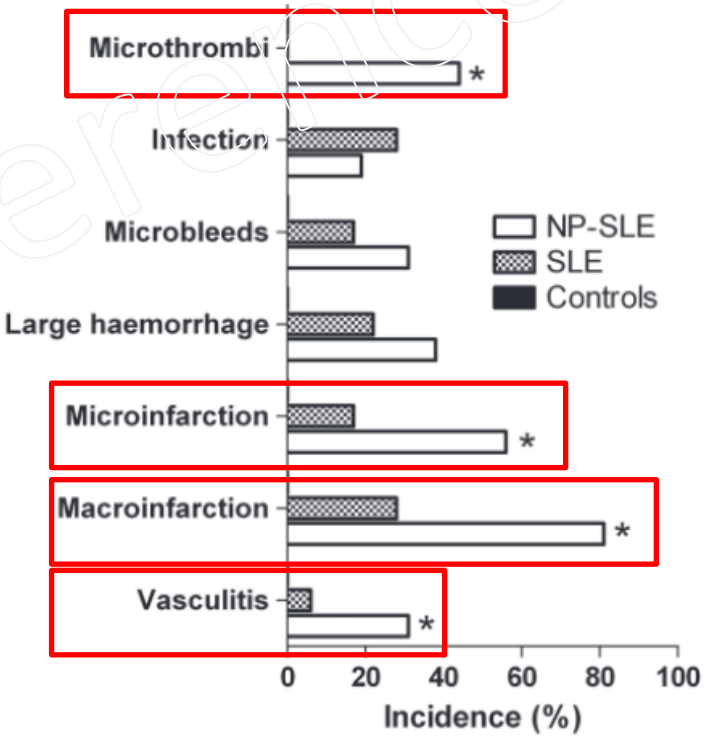
How do you make the distinction? (apart from stroke)

Treating NPSLE according to its pathogenesis

Brain histopathology in patients with systemic lupus erythematosus: identification of lesions associated with clinical neuropsychiatric lupus syndromes and the role of complement





(Thrombotic) vasculopathy is very common in NPSLE

Cohen et al. Rheumatology 2017

Treating NPSLE

Neuro-psychiatric manifestations in SLE patients

When possible, try to confirm NP event using an objective method

Attribution to SLE

Confirmed NPSLE

Treatment of NPSLE

± Anticonvulsants

Glucocorticoids

+

Cyclophosphamide IV OR **MMF** OR **Rituximab**

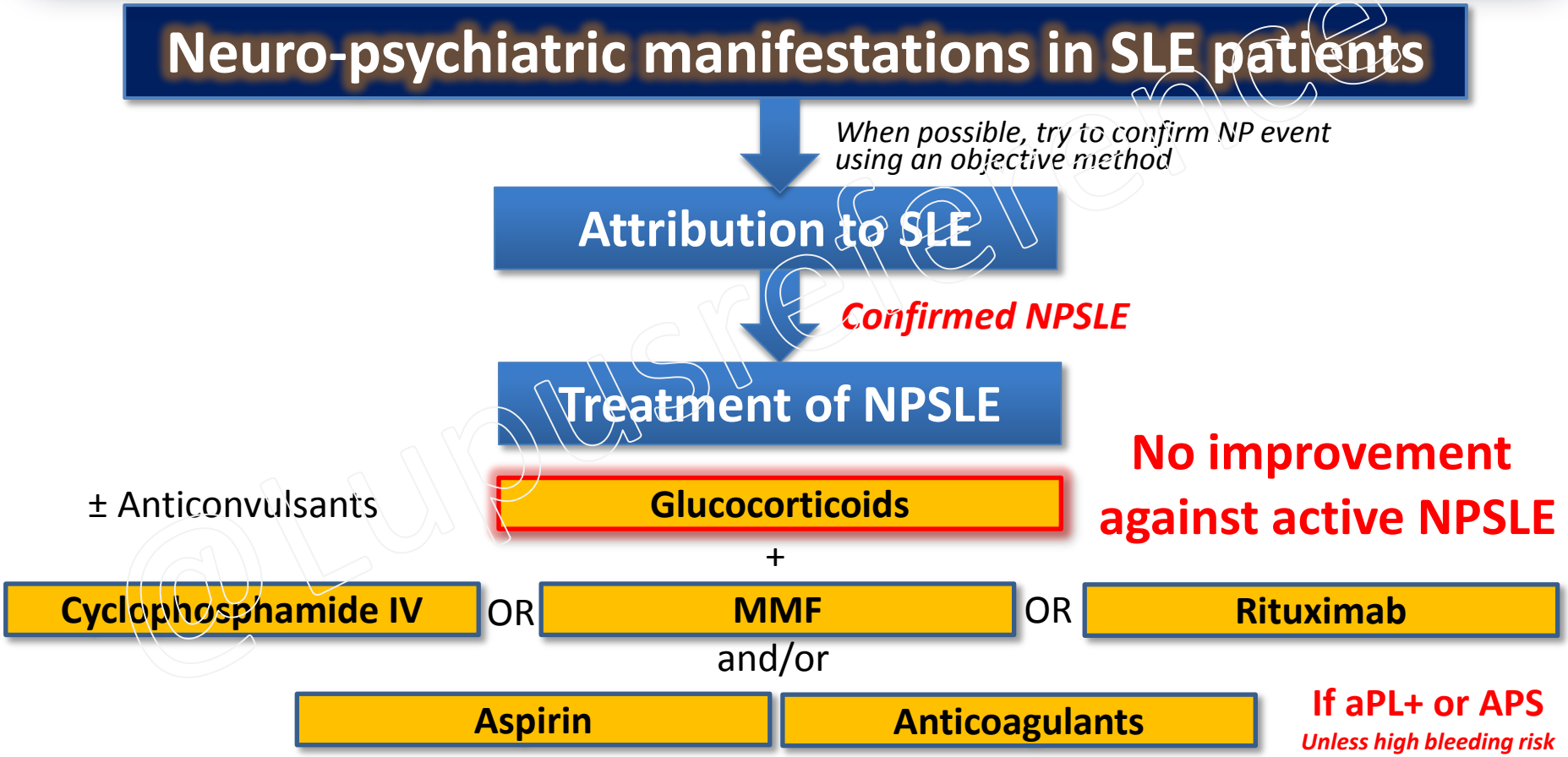
and/or

Aspirin **Anticoagulants**

If aPL+ or APS

Unless high bleeding risk

Treating NPSLE



Treating NPSLE

Neuro-psychiatric manifestations in SLE patients

When possible, try to confirm NP event using an objective method

Attribution to SLE

Confirmed NPSLE

Treatment of NPSLE

± Anticonvulsants

Glucocorticoids

± IS

+

Cyclophosphamide IV OR **MMF** OR **Rituximab**

and/or

Aspirin **Anticoagulants**

If aPL+ or APS

Unless high bleeding risk

Treating NPSLE

Neuro-psychiatric manifestations in SLE patients

When possible, try to confirm NP using an objective metho

Attribution t

Flare in any other organ? (ex. kidney?)
Specific context (eg. COVID)
Severity (CYC fastest/strongest)

± IS

…coids

+

Cyc… OR **MMF** OR **Rituximab**

and/or

Aspirin **Anticoagulants**

If aPL+ or APS
Unless high bleeding risk

Treating NPSLE

Neuro-psychiatric manifestations in SLE patients

When possible, try to confirm NP event using an objective method

Attribution to SLE

Confirmed NPSLE

Treatment of NPSLE

± Anticonvulsants

Glucocorticoids

+

Cyclophosphamide IV OR **MMF** OR **Rituximab**

and/or

If aPL+

Unless high bleeding risk

Aspirin **Anticoagulants**

Thrombotic APS

Treating NPSLE

Neuro-psychiatric manifestations in SLE patients

When possible, try to confirm NP event using an objective method

Attribution to SLE

Confirmed NPSLE

Treatment of NPSLE

± Anticonvulsants

NOT for all seizures

>2 unprovoked seizures in 24h

MRI brain lesions

Epileptiform discharge on EEG

Glucocorticoids

+

Cyclophosphamide IV OR **MMF** OR **Rituximab**

and/or

If aPL+

Unless high bleeding risk

Aspirin **Anticoagulants**

Thrombotic APS

Table 1 List of the 118 drugs associated with drug-induced lupus in VigiBase, by decreasing IC_{025}

Substance	IC_{025}	Substance	IC_{025}	Substance	IC_{025}
Procainamide	7.48	Golimumab	1.22	Interfe	
Hydralazine	6.63	Esomeprazole	1.21	Alendr	
Aesculus extract	4.98	Flecainide	1.18	Riociguat	
Minocycline	4.75	Epoprostenol	1.17	Selexip	
Ethosuximide	4.60	Estrogens conjugated, medroxyprogesterone	1.16	Tocilizu	
Quinidine	3.43	Folic acid	1.15	Electro	
Infliximab	3.39	Desoximetasone	1.12	Phenel	
Tocainide	3.32	Macitentan	1.11	Lansop	
Acebutolol	3.06	Treprostinil	1.11	Perphe	
Corticotropin	2.92	Romiplostim	1.09	Estroge	
Phthalylsulfathiazole	2.79	Etanercept	1.07	Fluoxet	
Labetalol	2.57	Celiprolol	1.00	Anastr	
Penicillamine	2.55	Propafenone	0.97	Cevime	
Methyldopa	2.53	Ethinylestradiol, etonogestrel	0.94	Bisopro	
Propylthiouracil	2.45	Hepatitis a vaccine, hepatitis B vaccine	0.88	Chlorpr	
HHR	2.40	Oxybate sodium	0.87	Medro	
Terbinafine	2.33	Hydrochlorothiazide, telmisartan	0.83	Pindolol	0.31
Sulfasalazine	2.29	Alendronic acid	0.81	Cinnarizine	0.29
Disopyramide	2.24	Hydrochlorothiazide, triamterene	0.81	Vaccines	0.27
Carbamazepine	2.07	Interferon beta-1a	0.79	Blood substitutes and perfusion solutions	0.26
Hepatitis b vaccine	1.96	Pravastatin	0.78	Omeprazole	0.26
Ambrisentan	1.95	Lamotrigine	0.77	Valproic acid	0.25
Dihydralazine	1.91	Ticlopidine	0.77	Cyproterone, ethinylestradiol	0.21
Lovastatin	1.72	Hydrochlorothiazide, methyldopa	0.75	Captopril	0.20
Bosentan	1.70	Oxprenolol	0.75	Imiquimod	0.17
Primidone	1.68	Eculizumab	0.70	Isotretinoin	0.16
Adalimumab	1.66	Atenolol	0.65	Teriparatide	0.15
Thiamazole	1.60	Fluvastatin	0.60	Diltiazem	0.14
HPV vaccine	1.59	Interferon alpha	0.60	Nitrofurantoin	0.13
Certolizumab pegol	1.58	Pregabalin	0.60	Cetirizine	0.12
Carteolol	1.52	Altizide, spironolactone	0.58	Interferon alpha-2b	0.11
Oxcarbazepine	1.52	Rofecoxib	0.58	Denosumab	0.07
Practolol	1.41	Gemfibrozil	0.54	Alprenolol	0.06
Abatacept	1.40	Mexiletine	0.54	Fosinopril	0.04
Propranolol	1.40	Prazosin	0.54	Simvastatin	0.03
Lyme disease vaccine	1.39	Isoniazid	0.52	Carbimazole	0.01
Leflunomide	1.38	Ethinylestradiol, levonorgestrel	0.51	Nomegestrol	0.01
Estrogens conjugated	1.35	Griseofulvin	0.51		
Mesalazine	1.27	Iloprost	0.51		
Phenytoin	1.24	Efalizumab	0.48		
Felbamate	1.22				

EPIDEMIOLOGICAL SCIENCE

Drug-induced systemic lupus: revisiting the ever-changing spectrum of the disease using the WHO pharmacovigilance database

Laurent Arnaud,[1,2] Philippe Mertz,[1,2] Pierre-Edouard Gavand,[2,3] Thierry Martin,[2,3] François Chasset,[4] Martine Tebacher-Alt,[5] Aude Lambert,[5] Charlotte Muller,[5] Jean Sibilia,[1,2] Bénédicte Lebrun-Vignes,[6] Joe-Elie Salem[6]

Beware of « lupus-aggravating » drugs

Ethosuximide (Zarontin®)

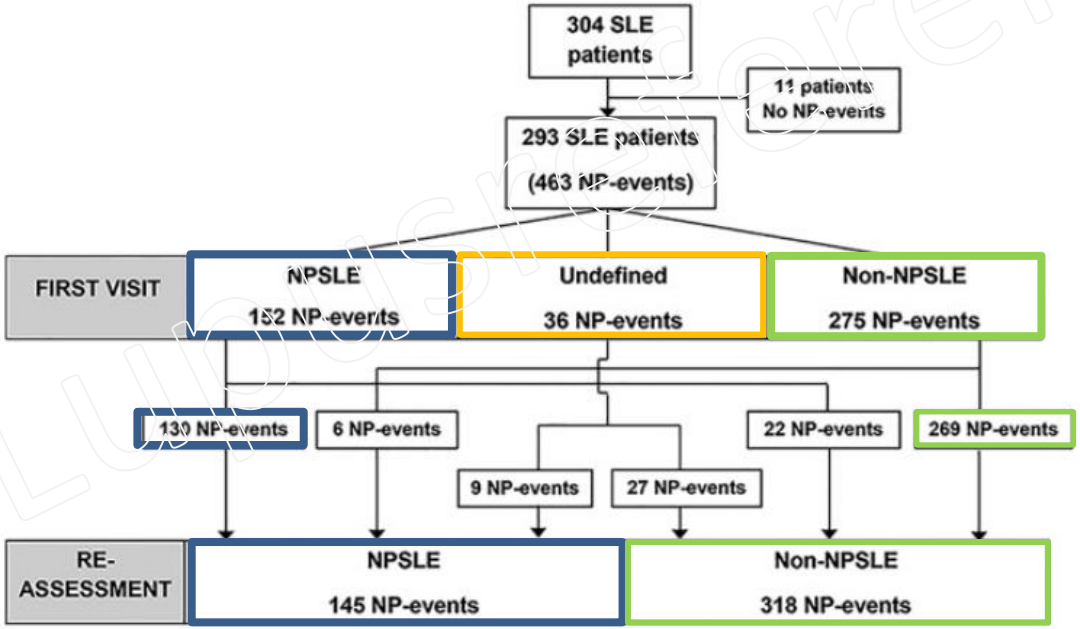
Carbamazepine (Tegretol®)

=> In SLE, choose Valproate first

Arnaud et al. ARD 2019

Let's keep an open mind ☺

Value of multidisciplinary reassessment in attribution of neuropsychiatric events to systemic lupus



It is very important to reassess whether it is NPSLE

Magro-Checa et al. Rheumatology 2017

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