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-Chugai, 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

- NPSLE compared to the general population: $x_{10}$
- Compared to SLE patients without NPSLE: $x_{2-3}$

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?
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?
NPSLE & lupus

NPSLE

Neuro-Psychiatric Systemic Lupus Erythematosus
SLE is a (very) systemic disease

- Alopecia
- Fever
- Malar rash
- Photosensitivity
- Adenopathies
- Pneumonia
- Pleurisy
- Pancreatitis
- Lupus enteritis
- Raynaud’s phenomenon
- Fatigue
- Neuropsychiatric lupus
- Oral ulcers
- Rash
- Pericarditis
- Myocarditis
- Lupus nephritis
- Cytopenia
- Arthralgia / arthritis
- Myositis
SLE is a (very) systemic disease

- Alopecia
- Fever
- Malar rash
- Photosensitivity
- Adenopathies
- Pneumonia
- Pleurisy
- Pancreatitis
- Lupus enteritis
- Raynaud’s phenomenon
- Fatigue
- Oral ulcers
- Rash
- Pericarditis
- Myocarditis
- Lupus nephritis
- Cytopenia
- Arthralgia / arthritis
- Myositis

Neuropsychiatric lupus
General management of symptoms in SLE

Symptom(s)

In SLE patients

Doctor, I have SLE and I have...

« 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...)

@Lupusreference

NCI on unsplash
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? +++
- Known manifestations of SLE?
- Any other symptoms of SLE?
- Recent changes in treatment?
- Recent lack of observance?

Tests & imaging results

(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?

Tests & imaging results

Negative findings
- Exclusion of differential diagnosis
General management of symptoms in SLE

Symptom(s) of SLE

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

Tests & imaging results

• Exclusion of differential diagnosis

Probabilistic reasoning ±

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

Is this due to lupus? (versus infection, drugs, etc…)

In SLE patients
General management of symptoms in SLE

Symptom(s)

Is this due to lupus? (versus infection, drugs, etc...)

Yes → ATTRIBUTED to Lupus

No → NOT DUE TO LUPUS

Address the issue / refer the patient
General management of symptoms in SLE

NP Symptom(s)

Is this due to lupus? (versus infection, drugs, etc...)

- Yes: ATTRIBUTED to Lupus
  - NPSLE! (primary NPSLE)
  - Neuro-psychiatric manifestations

- No: NOT DUE TO LUPUS
  - Address the issue / refer the patient
  - non-NPSLE NP events
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?
NPSLE manifestations are VERY diverse

ACR classification for Neuro-Psychiatric SLE (NPSLE)

- Optic neuritis
- Myelopathy
- Cerebrovascular
- Seizure
- Neuropathy
- Acute confusion
- Headache
- Mood disorder
- Depression
- Myasthenia
- Optic neuritis
- Cerebrovascular
- Myelopathy

19+ manifestations

@Lupusreference
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
- Depression
- Myasthenia
- Optic neuritis
- Cerebrovascular disease

Cognitive dysfunction
- Acute confusion
- Neuropathy

Myelopathy
- Headache
- Chorea
- Myelopathy
- Seizure disorders
- Acute confusional state
- Anxiety disorder
- Cognitive dysfunction
- Mood disorder
- Psychosis

19+ manifestations
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

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

19+ manifestations:
- Mood disorder
- Myelopathy
- Cognitive dysfunction
- Psychosis
- Acute confusion
- Headache
- Myasthenia
- Optic neuritis
NPSLE manifestations are VERY diverse

ACR classification for Neuro-Psychiatric SLE (NPSLE)

Central nervous system
- Aseptic meningitis
- Cerebrovascular disease
- Demyelinating syndrome
- Headache
- Chorea
- Myalgia
- Acute confusional state
- Anxiety disorder
- Cognitive dysfunction
- Mood disorder
- Psychosis

Peripheral nervous system
- Optic neuritis
- Neuropathy, cranial
- Polyneuropathy
- Myasthenia gravis
- Mononeuropathy, single
- Mononeuropathy, multiplex
- Myasthenia gravis
- Neuropathy, cranial
- Plexopathy
- Polyneuropathy

None of these manifestations are SPECIFIC to SLE
NPSLE is very heterogeneous

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?
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)?
- Additional diagnostic considerations
- What is the treatment of NPSLE?
How common are NP events in SLE?

SLICC: 43 academic centres in 16 countries

Hanly et al. SLICC cohort ARD 2020

52% with NP events

1827 patients
Mean follow-up: 7.6 ± 4.6 years
Which proportion are ATTRIBUTED to SLE?

52% with NP events
Which proportion are attributed to SLE?

52% with NP events

NP events attributed to SLE = NPSLE

18-30%

Hanly et al. SLICC cohort ARD 2020
Which proportion are ATTRIBUTED to SLE?

NP events ATTRIBUTED to SLE = NPSLE

18-30%

52% with NP events

NP events NOT ATTRIBUTED to SLE > 70%

Hanly et al. SLICC cohort ARD 2020
When are NPSLE events occurring in SLE?

First SLE manifestations

NPSLE events occurring during the first 2 years

RR: 6.16 (4.96, 7.66)

2 years
When are NPSLE events occurring in SLE?

First SLE manifestations

NPSLE events occurring during the first 2 years
RR: 6.16 (4.96, 7.66)

Diagnosis of SLE

2 years

26% with ≥2 events
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?
What are the typical manifestations of NPSLE?

ACR classification for Neuro-Psychiatric SLE (NPSLE)

Central nervous system
- Aseptic meningitis
- Cerebrovascular disease
- Demyelinating syndrome
- Headache
- Chorea
- Mood disorder
- Cognitive dysfunction
- Psychosis

Peripheral nervous system
- Acute confusional state
- Anxiety disorder
- Cognitive dysfunction
- Mood disorder
- Psychosis

What are the typical manifestations of NPSLE?

Central nervous system
- Aseptic meningitis
- Cerebrovascular disease
- Demyelinating syndrome
- Headache
- Chorea
- Mood disorder
- Cognitive dysfunction
- Psychosis

Peripheral nervous system
- Acute confusional state
- Anxiety disorder
- Cognitive dysfunction
- Mood disorder
- Psychosis

None of these manifestations are SPECIFIC to SLE.

@Lupusreference
What types of events are reported in NPSLE?

- 93% CNS
- 7% PNS
- 52% with NP events

Hanly et al. SLICC cohort ARD 2020
What types of events are reported in NPSLE?

<table>
<thead>
<tr>
<th>Studies</th>
<th>NPSLE (n)</th>
<th>Total SLE (n)</th>
<th>Aseptic meningitis</th>
<th>Cerebrovascular disease</th>
<th>Demyelinating syndrome</th>
<th>Headache</th>
<th>Movement disorder</th>
<th>Myelopathy</th>
<th>Seizure disorders</th>
<th>Acute confusional State</th>
<th>Anxiety disorder</th>
<th>Cognitive dysfunction</th>
<th>Mood disorder</th>
<th>Psychosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karimifar (2013)</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murray (2012)</td>
<td>694</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cojocaru (2010)</td>
<td>47</td>
<td>78</td>
<td>3 (3.8%)</td>
<td>8 (10.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syuto (2009)</td>
<td>10</td>
<td>68</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdel-Nasser (2008)</td>
<td>26</td>
<td>32</td>
<td>1 (3.1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avcin (2008)</td>
<td>23</td>
<td>137</td>
<td>7 (5.1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fragozo-Loyo 2008</td>
<td>47</td>
<td>96</td>
<td>8 (8.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hanly (2008)</td>
<td>133</td>
<td>412</td>
<td>14 (3.4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magalhaes (2007)</td>
<td>59</td>
<td>138</td>
<td>1 (0.7%)</td>
<td>18 (13.0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steup-Beekman (2007)</td>
<td>19</td>
<td>51</td>
<td>8 (15.7%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hanly (2006)</td>
<td>15</td>
<td>65</td>
<td>3 (4.6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harrison (2006)</td>
<td>42</td>
<td>93</td>
<td>2 (2.2%)</td>
<td>16 (17.2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lapteva (2006)</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yoshio (2005)</td>
<td>50</td>
<td>70</td>
<td>6 (8.6%)</td>
<td>10 (14.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coni (2004)</td>
<td>17</td>
<td>51</td>
<td>4 (8.0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mldashi (2004)</td>
<td>74</td>
<td>130</td>
<td>19 (14.6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanna (2003)</td>
<td>185</td>
<td>323</td>
<td>47 (14.5%)</td>
<td>3 (0.9%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mok (2001)</td>
<td>96</td>
<td>518</td>
<td>25 (4.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karassa (2000)</td>
<td>32</td>
<td>128</td>
<td>1 (0.2%)</td>
<td>5 (7.6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Georgescu (1997)</td>
<td>30</td>
<td>346</td>
<td>3 (0.9%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arnett (1996)</td>
<td>30</td>
<td>394</td>
<td>9 (3.5%)</td>
<td>21 (23.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silva (1996)</td>
<td>42</td>
<td>93</td>
<td>9 (3.5%)</td>
<td>21 (23.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toubi (1995)</td>
<td>95</td>
<td>196</td>
<td>56 (28.6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>West (1995)</td>
<td>52</td>
<td>66</td>
<td>25 (37.9%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nojima (1992)</td>
<td>32</td>
<td>91</td>
<td>1 (1.5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teh (1992)</td>
<td>39</td>
<td>116</td>
<td>1 (1.5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schneebaur (1991)</td>
<td>82</td>
<td>269</td>
<td>25 (9.7%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costallat 1990</td>
<td>16</td>
<td>66</td>
<td>1 (1.5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long (1990)</td>
<td>59</td>
<td>98</td>
<td>0 (0.0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alarcon-Segovia (1989)</td>
<td>500</td>
<td></td>
<td>49 (9.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bluestein 1981</td>
<td>27</td>
<td>45</td>
<td>1 (0.2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bresnihan (1979)</td>
<td>12</td>
<td>15</td>
<td>12 (80.0%)</td>
<td>3 (20.0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Highly variable frequency

Ho et al. Autoimmun Rev 2016
What is the frequency of NPSLE manifestations

<table>
<thead>
<tr>
<th>Studies</th>
<th>NPSLE (n)</th>
<th>Total SLE (n)</th>
<th>Acute inflammatory demyelinating polyradiculoneuropathy</th>
<th>Autonomic disorder</th>
<th>Mononeuropathy</th>
<th>Myasthenia gravis</th>
<th>Neuropathy, cranial</th>
<th>Plexopathy</th>
<th>Polyneuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syuto (2009)</td>
<td>10</td>
<td>68</td>
<td>3 (3.1%)</td>
<td></td>
<td>4 (6.2%)</td>
<td></td>
<td></td>
<td>1 (1.5%)</td>
<td></td>
</tr>
<tr>
<td>Fragoso-Loyo (2008)</td>
<td>47</td>
<td>96</td>
<td>3 (4.6%)</td>
<td></td>
<td>4 (6.2%)</td>
<td></td>
<td></td>
<td>1 (1.0%)</td>
<td></td>
</tr>
<tr>
<td>Steup-Beekman (2007)</td>
<td>19</td>
<td>51</td>
<td>3 (4.6%)</td>
<td></td>
<td>2 (4.4%)</td>
<td></td>
<td></td>
<td>1 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>Hanly (2006)</td>
<td>15</td>
<td>65</td>
<td>3 (4.6%)</td>
<td></td>
<td>6 (8.6%)</td>
<td></td>
<td></td>
<td>1 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>Harrison (2006)</td>
<td>42</td>
<td>93</td>
<td>3 (4.6%)</td>
<td></td>
<td>6 (8.6%)</td>
<td></td>
<td></td>
<td>1 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>Mikdashi (2004)</td>
<td>74</td>
<td>130</td>
<td>3 (4.6%)</td>
<td></td>
<td>3 (2.3%)</td>
<td></td>
<td></td>
<td>13 (10.0%)</td>
<td></td>
</tr>
<tr>
<td>Sanna (2003)</td>
<td>185</td>
<td>323</td>
<td>3 (1.8%)</td>
<td></td>
<td>6 (1.8%)</td>
<td></td>
<td></td>
<td>13 (10.0%)</td>
<td></td>
</tr>
<tr>
<td>Mok (2001)</td>
<td>96</td>
<td>518</td>
<td>3 (1.8%)</td>
<td></td>
<td>5 (1.5%)</td>
<td></td>
<td></td>
<td>9 (2.8%)</td>
<td></td>
</tr>
<tr>
<td>Karassa (2000)</td>
<td>32</td>
<td>128</td>
<td>2 (0.5%)</td>
<td></td>
<td>5 (1.5%)</td>
<td></td>
<td></td>
<td>1 (0.2%)</td>
<td></td>
</tr>
<tr>
<td>Silva (1996)</td>
<td>42</td>
<td>93</td>
<td>2 (0.4%)</td>
<td></td>
<td>2 (0.4%)</td>
<td></td>
<td></td>
<td>4 (0.8%)</td>
<td></td>
</tr>
<tr>
<td>Bluestein (1981)</td>
<td>27</td>
<td>45</td>
<td>2 (13.3%)</td>
<td></td>
<td>3 (6.7%)</td>
<td></td>
<td></td>
<td>3 (0.6%)</td>
<td></td>
</tr>
<tr>
<td>Bresnihan (1979)</td>
<td>12</td>
<td>15</td>
<td>2 (13.3%)</td>
<td></td>
<td>2 (13.3%)</td>
<td></td>
<td></td>
<td>3 (0.6%)</td>
<td></td>
</tr>
</tbody>
</table>

Highly variable frequency

Ho et al. Autoimmun Rev 2016
**What types of events are reported in NPSLE?**

<table>
<thead>
<tr>
<th>Type</th>
<th>Cognitive dysfunction</th>
<th>Mood disorder</th>
<th>Anxiety</th>
<th>Headache</th>
<th>Seizures</th>
<th>Cerebrovascular disease</th>
<th>Psychosis</th>
<th>Acute confusional status</th>
<th>Mononeuropathy</th>
<th>Polyneuropathy</th>
<th>Myelopathy</th>
<th>Demyelinating syndrome</th>
<th>Aseptic meningitis</th>
<th>Autonomic disorder</th>
<th>AIDP (GBS)</th>
<th>Cranial neuropathy</th>
<th>Movement disorders (chorea)</th>
<th>Myasthenia gravis</th>
<th>Plexopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequent</strong></td>
<td>6.6–80 (mild)</td>
<td>7.4–65</td>
<td>6.0–40</td>
<td>12.2–28.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>7.0–20</td>
<td>8.0–15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Infrequent</strong></td>
<td>0.6–11</td>
<td>0.9–7</td>
<td>0.9–6.9</td>
<td>1.5–5.4</td>
<td>0.9–3.9</td>
<td>0.9–2.7</td>
<td>0.3–2.7</td>
<td>0.08–1.3</td>
<td>0.08–1.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>0.3–2.7</td>
<td>0.08–1.3</td>
<td>0.08–1.2</td>
<td>0.9</td>
<td>0.2</td>
<td>NR</td>
<td>1.0</td>
<td>0.9</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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?
Attribution of NP events to SLE (NPSLE)

Neuro-psychiatric manifestations in SLE patients

Attribution to SLE

☑️ SLE  ☐️ NO SLE
## What types of events are reported in NPSLE?

<table>
<thead>
<tr>
<th>Frequent ****</th>
<th>Cognitive dysfunction</th>
<th>Mood disorder</th>
<th>Anxiety</th>
<th>Headache</th>
<th>VERY COMMON IN THE GENERAL POPULATION</th>
<th>6.6–80 (mild)</th>
<th>1–3% (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>**Common ***</td>
<td>Seizures</td>
<td>Cerebrovascular disease</td>
<td></td>
<td></td>
<td></td>
<td>7.0–20</td>
<td>8.0–15</td>
</tr>
<tr>
<td>**Infrequent *</td>
<td>Psychosis</td>
<td>Acute confusional status</td>
<td>Mononeuropathy</td>
<td>Polyneuropathy</td>
<td>Myelopathy</td>
<td>Demyelinating syndrome</td>
<td></td>
</tr>
<tr>
<td>**Rare -</td>
<td>Aseptic meningitis</td>
<td>Autonomic disorder</td>
<td>AIIDP (GBS)</td>
<td>Cranial neuropathy</td>
<td>Movement disorders (chorea)</td>
<td>Myasthenia gravis</td>
<td>Plexopathy</td>
</tr>
</tbody>
</table>

# 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

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>OK (95% CI)</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACR criteria for NPSLE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1</td>
<td>42 (91%)</td>
<td>25 (56%)</td>
<td>9.5 (2.2–40.8)</td>
<td>0.46</td>
</tr>
<tr>
<td>≥2</td>
<td>37</td>
<td>10</td>
<td>7.8 (2.7–22.0)</td>
<td>0.78</td>
</tr>
<tr>
<td>≥3</td>
<td>25</td>
<td>2</td>
<td>24.0 (3.3–177.4)</td>
<td>0.96</td>
</tr>
<tr>
<td>≥4</td>
<td>10</td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Revised criteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 0</td>
<td>21</td>
<td>3</td>
<td>7.0 (2.1–23.5)</td>
<td>0.93</td>
</tr>
<tr>
<td>&gt; 1</td>
<td>9</td>
<td>0</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>6</td>
<td>0</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>&gt; 3</td>
<td>2</td>
<td>0</td>
<td></td>
<td>1.00</td>
</tr>
</tbody>
</table>

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

Ainiala et al. Arthritis Care Res 2001
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
### Lupus headache

**Lupus headache is NOT just headache in a patient with lupus**

<table>
<thead>
<tr>
<th>Disease activity index</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SLEDAI-2K</strong></td>
<td>Severe, persistent headache; may be migrainous, but <strong>must be nonresponsive to narcotic analgesia</strong>.</td>
</tr>
<tr>
<td><strong>SELENA-SLEDAI</strong></td>
<td>Severe, persistent headache; may be migrainous, but <strong>must be nonresponsive to narcotic analgesia</strong>.</td>
</tr>
</tbody>
</table>
| **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

- Optic neuritis
- Myelopathy
- Cerebrovascular
- Seizure
- Chorea
- Cerebrovascular
- Myasthenia
- Psychosis
- Aseptic meningitis
- Neuropathy
- Cognitive dysfunction
- Acute confusion
- Headache
- Mood disorder
- Depression

@Lupusreference
There are many « mimickers » of NPSLE
Attribution of NP events to SLE (NPSLE)

- Adverse effect of TREATMENTS (e.g. glucocorticoids)
- INFECTIONS

- Mood disorder
- Depression
- Myasthenia
- Psychosis
- Optic neuritis
- Aseptic meningitis
- Neuropathy
- Neuropathy
- Acute confusion
- Headache
- Seizure
- Chorea
- Cerebrovascular
- Myelopathy
- Cognitive dysfunction

Attribution of NP events to SLE (NPSLE)
Case #2 | the « brain-fog »

Adverse effect of TREATMENTS (e.g. glucocorticoids)

- Cognitive dysfunction
- Acute confusion
- Headache
- Seizures
- Chorea

INFECTIONS

- Aseptic meningitis
- Optic neuritis
- Myelopathy
- Myopathy
- Cerebrovascular

INFECTIONS

- Mood disorder
- Depression
- Myasthenia
- Psychosis

aPL/APS
Attribution of NP events to SLE (NPSLE)

- Adverse effect of TREATMENTS (e.g. glucocorticoids)
- INFECTIONS
  - Mood disorder
  - Depression
  - Myasthenia
  - Psychosis
  - Optic neuritis
  - Neuropathy
  - Aseptic meningitis
  - Cognitive dysfunction
  - Acute confusion
  - Headache
  - Seizure
  - Chorea
  - Cerebrovascular
  - Myelopathy
  - APL/APS

+ Metabolic
Attribution of NP events to SLE (NPSLE)

- Adverse effect of TREATMENTS (e.g. glucocorticoids)
- INFECTIONS
- Mood disorder
- Depression
- Myasthenia
- Psychosis
- Optic neuritis
- Acute confusion
- Headache
- Chorea
- Seizure
- NMO
- MS
- Myelopathy
- Neuropathy
- Cognitive dysfunction
- Myasthenia
- aPL/APS
- + Metabolic

@Lupusreference
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)

Adverse effect of TREATMENTS (e.g. glucocorticoids)

COMORBIDITIES

E.g. migraine

INFECTIONS

COMORBIDITIES

E.g. MS, NMO, aPL/APS, + Metabolic
Attribution of NP events to SLE (NPSLE)

COMORBIDITIES

Adverse effect of TREATMENTS (e.g. glucocorticoids)

INFECTIONS

TREATMENT IS NOT THE SAME!!!!

MS

NMO

+ Metabolic
Attribution of NP events to SLE (NPSLE)

STOP INCriminated TREATMENT

COMORBIdITIES

GC + IS

NPSLE

Averse effect of TREATMENTS (e.g. glucocorticoids)

ANTIBIOTICS ANTIVIRAL ANTIFUNGAL

COMORBIdITIES

TREATMENT OF COMORBIdITY

GC + IS

NMO

+ Metabolic

ASPIRIN VKA

@Lupusreference
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/reattrtribution if needed
Attribution of NP events to SLE (NPSLE)

Typical limbic encephalitis
The role of brain imagery

Typical limbic encephalitis
The role of brain imagery

Posterior reversible encephalopathy syndrome (PRES)
The role of brain imagery
The role of brain imagery

Normal brain MRI

+++ Does NOT RULE OUT NPSLE +++

+++ Does NOT RULE OUT NPSLE +++

+++ Does NOT RULE OUT NPSLE +++
The role of brain imagery

https://radiopaedia.org/images/3014589
The role of brain imagery

Progressive Multifocal Leukoencephalopathy (PML) ≠ NPSLE

https://radiopaedia.org/images/3014589
The role of brain imagery

Progressive Multifocal Leukoencephalopathy (PML) ≠ NPSLE

There is NO MRI image typical of NPSLE

https://radiopaedia.org/images/3014589
Cerebrospinal fluid analysis in SLE

CSF analysis is crucial to rule out an infection

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients with CNS involvement</th>
<th>Elevated CSF IgG index</th>
<th>% Oligoclonal bands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tan et al. Clin Rheumatol 2018</td>
<td>76</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>Ernerudh et al. JNNP 1985</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seibold. Semin Arthritis 1982</td>
<td>11 (of 17)</td>
<td>63%</td>
<td>81%</td>
</tr>
<tr>
<td>Hirohata. Arch Intern Med 1985</td>
<td>13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Poor quality of the literature / intratechal synthesis is commonly seen
HMPAO-SPECT
SEVERE hypofixation of tracer in:
• Inner temporal regions (bilaterally)

LIMBIC ENCEPHALITIS

Anti-NMDAR and anti-neurons antibodies were negative
Neuro-psychiatric manifestations in SLE patients

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)

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

Response to treatment | Reassessment/reattribution if needed
Attribution of NP events to SLE (NPSLE)

**Time of the onset of NP event with respect to SLE clinical onset:**
- Before (>6 months before SLE onset)
- Concomitant (within 6 months of SLE onset)
- After (>6 months after SLE onset)

**Minor or not specific NP events (as defined by Ainiala et al.):**
- Present
- Absent

**Confounding factors or not SLE-related associations (ACR glossary):**
- None or not applicable
- Present (1 confounding factor)
- Present (>1 confounding factor)

**Additional (or favouring) factors:**
- None or not applicable
- Present (1 additional or favouring factor)
- Present (>1 additional or favouring factor)

---

**Attribution of NP events to SLE:**

<table>
<thead>
<tr>
<th>Cognitive Dysfunction</th>
<th>Substance abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>- SLE disease activity</td>
<td>Medication (steroids, sedatives)</td>
</tr>
<tr>
<td>- SLE damage</td>
<td></td>
</tr>
<tr>
<td>- Past or concurrent Major NPSLE(^3)</td>
<td>History of learning disabilities</td>
</tr>
<tr>
<td>- aPL antibodies(^1)</td>
<td>History of head injury</td>
</tr>
<tr>
<td>- Heart valve disease(^2)</td>
<td>Other primary neurologic and psychiatric disorders</td>
</tr>
<tr>
<td>- Education level</td>
<td>Metabolic disturbances, particularly uremia and diabetes</td>
</tr>
<tr>
<td>- Age</td>
<td>Antiphospholipid antibody syndrome</td>
</tr>
</tbody>
</table>

---

**SLEDAI ≥16 SDI ≥1.0**
- Libman sacks endocarditis (aPL+)
- At least secondary school

**MRI or SPECT**
- Age < 50 years
- Response to IS or GC Rx
- Abnormal neuroimaging

---

\(^1\) aPL = antiphospholipid antibodies

\(^2\) ACR criteria for SLE-associated cardiovascular disease

\(^3\) NPSLE = neuropsychiatric systemic lupus erythematosus

---

Bortoluzzi et al. Rheumatology 2015
# Attribution of NP events to SLE (NPSLE)

<table>
<thead>
<tr>
<th>Cognitive Dysfunction</th>
<th>Substance abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication (steroids, sedatives)</td>
<td>History of learning disabilities</td>
</tr>
<tr>
<td>History of head injury</td>
<td>Other primary neurologic and psychiatric conditions</td>
</tr>
<tr>
<td>Metabolic disturbances</td>
<td>Antiphospholipid antibodies</td>
</tr>
<tr>
<td>Antinuclear antibodies</td>
<td>Other antinuclear antibodies</td>
</tr>
</tbody>
</table>

## Confounding factors or not SLE related associations (ACR glossary)

- None or not applicable
- Present (1 confounding factor)
- Present (>1 confounding factor)

<table>
<thead>
<tr>
<th>Attribution of neuropsychiatric symptoms (points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

## Minor or not specific NP events (as defined by Ainiala et al.)

- Present
- Absent

<table>
<thead>
<tr>
<th>Confounding factors</th>
<th>Additional (or favouring) factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>None or not applicable</td>
<td>None or not applicable</td>
</tr>
<tr>
<td>Present (1 additional or favouring factor)</td>
<td>Present (1 additional or favouring factor)</td>
</tr>
<tr>
<td>Present (&gt;1 additional or favouring factor)</td>
<td>Present (&gt;1 additional or favouring factor)</td>
</tr>
</tbody>
</table>

- Libman sacks endocarditis (aPL+)
- Age < 50 years
- Response to IS or GC Rx
- Abnormal neuroimaging

## Limited applicability in clinical practice
Neuro-psychiatric manifestations in SLE patients

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/reattrtribution if needed
Attribution of NP events to SLE (NPSLE)

Neuro-psychiatric manifestations in SLE patients

@Lupusreference

Document the involvement of CNS/PNS
CNS: Brain MRI + CSF +/- brain SPECT
PNS: EMG +/- CSF
(can be normal)

When possible, try to confirm NP event using an objective method
(can be normal)

Attribution to SLE

Search for confounding and favouring factors
Alternative diagnosis? (e.g. infection, metabolic)
Change in medications?
Previous NPSLE involvement?
(possibly 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

Now I have done all this, what do I do?
## Attribution of NP events to SLE (NPSLE)

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

<table>
<thead>
<tr>
<th>Time of the onset of NP event with respect to SLE clinical onset:</th>
<th>Weight (points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Before (&gt;6 months before SLE onset)</td>
<td>0</td>
</tr>
<tr>
<td>• Concomitant (within 6 months of SLE onset)</td>
<td>1.5</td>
</tr>
<tr>
<td>• After (&gt;6 months after SLE onset)</td>
<td>2.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor or not specific NP events (as defined by Ainiala et al.)</th>
<th>Weight (points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Present</td>
<td>0</td>
</tr>
<tr>
<td>• Absent</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Confounding factors or not SLE-related associations (ACR glossary)</th>
<th>Weight (points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• None or not applicable</td>
<td>2.5</td>
</tr>
<tr>
<td>• Present (1 confounding factor)</td>
<td>1</td>
</tr>
<tr>
<td>• Present (&gt;1 confounding factor)</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Additional (or favouring) factors</th>
<th>Weight (points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• None or not applicable</td>
<td>0</td>
</tr>
<tr>
<td>• Present (1 additional or favouring factor)</td>
<td>1</td>
</tr>
<tr>
<td>• Present (&gt;1 additional or favouring factor)</td>
<td>2</td>
</tr>
</tbody>
</table>

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

How can we decide??
**Attribution of NP events to SLE (NPSLE)**

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

<table>
<thead>
<tr>
<th>Time of the onset of NP event with respect to SLE clinical onset:</th>
<th>(points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Before (&gt;6 months before SLE onset)</td>
<td>0</td>
</tr>
<tr>
<td>• Concomitant (within 6 months of SLE onset)</td>
<td>1.5</td>
</tr>
<tr>
<td>• After (&gt;6 months after SLE onset)</td>
<td>2.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor or not specific NP events (as defined by Ainiala et al.)</th>
<th>(points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Present</td>
<td>0</td>
</tr>
<tr>
<td>• Absent</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Confounding factors or not SLE-related associations (ACR glossary)</th>
<th>(points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• None or not applicable</td>
<td>2.5</td>
</tr>
<tr>
<td>• Present (1 confounding factor)</td>
<td>1</td>
</tr>
<tr>
<td>• Present (&gt;1 confounding factor)</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Additional (or favouring) factors</th>
<th>(points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• None or not applicable</td>
<td>0</td>
</tr>
<tr>
<td>• Present (1 additional or favouring factor)</td>
<td>1</td>
</tr>
<tr>
<td>• Present (&gt;1 additional or favouring factor)</td>
<td>2</td>
</tr>
</tbody>
</table>

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

How can we decide???

Confounding factors or not SLE-related associations (ACR glossary)

Limited applicability in clinical practice
Attribution of NP events to SLE (NPSLE)

Pragmatic strategy
EXCLUSION OF NON-SLE CONDITIONS

Favoring factors for primary NPSLE
- “Major” NP manifestation
- Generalized disease activity
- Previous “major” NPSLE
- (+) aPL
- MRI: White matter hyperintense lesions or more specific findings
- CSF: lymphocytic pleocytosis, increased protein, (-)ve culture

Work-up for non-SLE-related causes
- Infections (CSF, MRI with gadolinium)
- Metabolic disturbances (blood chemistry)
- Drug adverse effects

Apply Italian attribution algorithm in doubtful cases

Infections
Metabolic
Etc...

Nikolopoulos...Bertsias. Exp Rev Clin Immunol 2021
Attribution of NP events to SLE (NPSLE)

**Pragmatic strategy**

**EXCLUSION OF NON-SLE CONDITIONS**

Favoring factors for primary NPSLE
- “Major” NP manifestation
- Generalized disease activity
- Previous “major” NPSLE
- (+) aPL
- MRI: White matter hyperintense lesions or more specific findings
- CSF: Lymphocytic pleocytosis, increased protein, (-)ve culture

Work-up for non-SLE-related causes
- Infections (CSF, MRI with gadolinium)
- Metabolic disturbances (blood chemistry)
- Drug adverse effects

Apply Italian attribution algorithm in doubtful cases

**TRIAL OF CORTICOSTEROIDS**

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?
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?

We can’t perform an MRI and do CSF analysis in ALL SLE patients reporting NP manifestations.
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
✓ What is the treatment of NPSLE?
Cognitive dysfunction in SLE

Lupus Fog and Memory Problems

By R. Morgan Griffin

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.

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

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

Cognitive dysfunction
- Mood disorder
- Psychosis

19 manifestations
Cognitive dysfunction in SLE

Frequency of CNS-involving NPSLE manifestations in various cohorts

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aseptic Meningitis</td>
<td>1 (2)</td>
<td>2 (0.4)</td>
<td>4 (2.7)</td>
<td>1 (0.4)</td>
<td>3 (0.7)</td>
<td>3 (0.7)</td>
<td>6 (10.9)</td>
<td>3 (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>7 (15)</td>
<td>15 (24)</td>
<td>13 (2.5)</td>
<td>18 (22.1)</td>
<td>40 (15.5)</td>
<td>21 (7.4)</td>
<td>68 (16.2)</td>
<td>61 (14.3)</td>
<td>16 (29)</td>
<td>44 (43)</td>
<td></td>
</tr>
<tr>
<td>Demyelinating Syndrome</td>
<td>1 (2)</td>
<td>1 (0.2)</td>
<td>1 (0.7)</td>
<td>3 (1.2)</td>
<td>2 (0.7)</td>
<td>7 (1.7)</td>
<td>3 (0.7)</td>
<td>4 (0.9)</td>
<td>1 (1.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>25 (54)</td>
<td>25 (52.5)</td>
<td>0</td>
<td>8 (2.8)</td>
<td>116 (27.7)</td>
<td>95 (22.2)</td>
<td>4 (7.2)</td>
<td>23 (23)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Movement Disorder (Chorea)</td>
<td>1 (2)</td>
<td>4 (0.76)</td>
<td>4 (2.7)</td>
<td>5 (1.9)</td>
<td>7 (1.7)</td>
<td>3 (0.7)</td>
<td>1 (1.8)</td>
<td>5 (5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myelopathy</td>
<td>4 (1.2)</td>
<td>2 (3)</td>
<td>5 (3.4)</td>
<td>10 (3.9)</td>
<td>6 (2.1)</td>
<td>1 (0.2)</td>
<td>4 (0.9)</td>
<td>2 (3.6)</td>
<td>6 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure Disorders</td>
<td>4 (9)</td>
<td>7 (11)</td>
<td>39 (7)</td>
<td>54 (20.9)</td>
<td>17 (6)</td>
<td>19 (4.5)</td>
<td>61 (24.3)</td>
<td>10 (5.5)</td>
<td>28 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Confusional State</td>
<td>3 (7)</td>
<td>15 (3)</td>
<td>39 (26.2)</td>
<td>54 (20.9)</td>
<td>17 (6)</td>
<td>19 (4.5)</td>
<td>61 (24.3)</td>
<td>10 (5.5)</td>
<td>28 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety Disorder</td>
<td>6 (13)</td>
<td>24 (7.4)</td>
<td>27 (21)</td>
<td>4 (6)</td>
<td>28 (27)</td>
<td>3 (1.1)</td>
<td>15 (3.6)</td>
<td>28 (6.6)</td>
<td>1 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive Dysfunction</td>
<td>37/46 (81)</td>
<td>35/67 (53)</td>
<td>32/61 (52)</td>
<td>32/52</td>
<td>8 (5.4)</td>
<td>22 (8.5)</td>
<td>10 (3.5)</td>
<td>61 (14.6)</td>
<td>56 (13.1)</td>
<td>6 (10.9)</td>
<td>27 (26)</td>
</tr>
<tr>
<td>- Minor</td>
<td>26/37 (70)</td>
<td>29/67 (43)</td>
<td>32/61 (52)</td>
<td>32/52</td>
<td>8 (5.4)</td>
<td>22 (8.5)</td>
<td>10 (3.5)</td>
<td>61 (14.6)</td>
<td>56 (13.1)</td>
<td>6 (10.9)</td>
<td>27 (26)</td>
</tr>
<tr>
<td>- Moderate</td>
<td>7/37 (19)</td>
<td>20/67 (30)</td>
<td>32/61 (52)</td>
<td>32/52</td>
<td>8 (5.4)</td>
<td>22 (8.5)</td>
<td>10 (3.5)</td>
<td>61 (14.6)</td>
<td>56 (13.1)</td>
<td>6 (10.9)</td>
<td>27 (26)</td>
</tr>
<tr>
<td>- Severe</td>
<td>4/37 (11)</td>
<td>4/67 (6)</td>
<td>32/61 (52)</td>
<td>32/52</td>
<td>8 (5.4)</td>
<td>22 (8.5)</td>
<td>10 (3.5)</td>
<td>61 (14.6)</td>
<td>56 (13.1)</td>
<td>6 (10.9)</td>
<td>27 (26)</td>
</tr>
<tr>
<td>Mood Disorder</td>
<td>20 (43)</td>
<td>54 (16.7)</td>
<td>25 (20)</td>
<td>30 (75)</td>
<td>22 (8.5)</td>
<td>10 (3.5)</td>
<td>67 (16)</td>
<td>49 (11.5)</td>
<td>8 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td>37/46 (81)</td>
<td>35/67 (53)</td>
<td>32/61 (52)</td>
<td>32/52</td>
<td>8 (5.4)</td>
<td>22 (8.5)</td>
<td>10 (3.5)</td>
<td>61 (14.6)</td>
<td>56 (13.1)</td>
<td>6 (10.9)</td>
<td>27 (26)</td>
</tr>
</tbody>
</table>
| Cognitive dysfunction is the most common NPSLE event

from 5 to 80% of patients !!!

Faria et al. Open Rheumatology 2017
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
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

There is **NO SPECIFIC PATTERN** of cognitive dysfunction in SLE*

- 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 impairment (<3 impaired domains**)**

*Hanly et al. Arthritis Rheum 2019
**Ainiala et al. Arthritis Care Res 2001
Cognitive dysfunction in SLE

There is NO SPECIFIC PATTERN of cognitive dysfunction in SLE*

- 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 impairment (<3 impaired domains**)

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

<table>
<thead>
<tr>
<th>NAME OF TEST</th>
<th>TIME</th>
<th>DETAILS</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SELF-ASSESSMENT BY PATIENT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive Symptom Inventory (CSI)</td>
<td>3-5 mins</td>
<td>Not correlated with objective neuro-psychological testing</td>
<td>Hanly et al. J Rheum 2012</td>
</tr>
<tr>
<td>Perceived Deficits Questionnaire 5-Item (PDQ-5)</td>
<td>3-5 mins</td>
<td>Mean value similar with/without cognitive impairment</td>
<td>Nantes &amp; Touma. J Rheum 2017</td>
</tr>
</tbody>
</table>
### Cognitive dysfunction in SLE

<table>
<thead>
<tr>
<th>NAME OF TEST</th>
<th>TIME</th>
<th>DETAILS</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SELF-ASSESSMENT BY PATIENT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive Symptom Inventory (CSI)</td>
<td>3-5 mins</td>
<td>Not correlated with objective neuro-psychological testing</td>
<td>Hanly et al. J Rheum 2012</td>
</tr>
<tr>
<td>Perceived Deficits Questionnaire 5-Item (PDQ-5)</td>
<td>3-5 mins</td>
<td>Mean value similar with/without cognitive impairment Only a low (negative) correlation with HVLT-R</td>
<td>Nantes &amp; Touma. J Rheum 2017</td>
</tr>
<tr>
<td><strong>EXTERNAL-ASSESSMENT BY PHYSICIAN</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montreal Cognitive Assessment (MoCA)</td>
<td>10-15 mins</td>
<td>PPV and LR+ similar to MMSE but NPV higher</td>
<td>Nantes &amp; Touma. J Rheum 2017</td>
</tr>
<tr>
<td>Mini Mental State Examination (MMSE)</td>
<td>10-15 mins</td>
<td>NPV lower than MoCA. <strong>Tends to miss many patients with mild CI</strong></td>
<td>Nantes &amp; Touma. J Rheum 2017</td>
</tr>
</tbody>
</table>
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 impairment.
Cognitive dysfunction in SLE

There is NO SPECIFIC PATTERN of cognitive dysfunction in SLE*

- 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 impairment (<3 impaired domains**)

*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

**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

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?
Neuro-psychiatric manifestations in SLE patients

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/reattrtribution if needed

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

@Lupusreference
The role of brain imagery

But occasionally...

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

<table>
<thead>
<tr>
<th>MRI features</th>
<th>Baseline MRI</th>
<th>Follow-up MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMHs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal/parietal</td>
<td>10 (33.3)</td>
<td>17 (56.7)</td>
</tr>
<tr>
<td>Temporal/occipital</td>
<td>2 (6.7)</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>4 (13.3)</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>Periventricular</td>
<td>9 (30.0)</td>
<td>16 (53.3)</td>
</tr>
<tr>
<td>Cerebellar/brainstem</td>
<td>1 (3.3)</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>Cerebral atrophy(^a)</td>
<td>5 (16.7)</td>
<td>10 (33.3)</td>
</tr>
<tr>
<td>Mild(^b)</td>
<td>3 (10.0)</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>Moderate(^b)</td>
<td>2 (6.7)</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>Severe(^b)</td>
<td>0</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Parenchymal defects</td>
<td>2 (6.7)</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>mMSS(^c)</td>
<td>1 (0–3)</td>
<td>2 (2–5)</td>
</tr>
</tbody>
</table>

BASELINE

50% of MRI

20 years LATER

70% !!!!

Piga et al. Autoimmun Rev 2015
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.

<table>
<thead>
<tr>
<th>MRI features</th>
<th>Baseline MRI</th>
<th>Follow-up MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMHIs</td>
<td>16 (53.3)</td>
<td>24 (80.0)</td>
</tr>
<tr>
<td>Frontal/parietal</td>
<td>10 (33.3)</td>
<td>17 (56.7)</td>
</tr>
<tr>
<td>Temporal/occipital</td>
<td>2 (6.7)</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>4 (13.3)</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>Periventricular</td>
<td>9 (30.0)</td>
<td>16 (53.3)</td>
</tr>
<tr>
<td>Cerebellar/brainstem</td>
<td>1 (3.3)</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>Cerebral atrophy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5 (16.7)</td>
<td>10 (33.3)</td>
</tr>
<tr>
<td>Mild&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (10.0)</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>Moderate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2 (6.7)</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>Severe&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Parenchymal defects</td>
<td>2 (6.7)</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>mMSS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1 (0–3)</td>
<td>2 (2–5)</td>
</tr>
</tbody>
</table>

Based on the literature
Progression of WMHIs Is related to:
- aPL+
- General CVRF
- Disease activity
- Baseline damage

Piga et al. Autoimmun Rev 2015
Based on the literature
Progression of WMHIs is related to:
- aPL+
- General CVRF
- Disease activity
- Baseline damage

Is associated with:
- New NPSLE events
- Cognitive impairment

Piga et al. Autoimmun Rev 2015
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.

<table>
<thead>
<tr>
<th>MRI features</th>
<th>Baseline MRI</th>
<th>Follow-up MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMHIs</td>
<td>16 (53.3%)</td>
<td>24 (80.0%)</td>
</tr>
<tr>
<td>Frontal/parietal</td>
<td>10 (33.3%)</td>
<td>17 (56.7%)</td>
</tr>
<tr>
<td>Temporal/occipital</td>
<td>2 (6.7%)</td>
<td>7 (23.3%)</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>4 (13.3%)</td>
<td>6 (20.0%)</td>
</tr>
<tr>
<td>Periventricular</td>
<td>9 (30.0%)</td>
<td>16 (53.3%)</td>
</tr>
<tr>
<td>Cerebellar/brainstem</td>
<td>1 (3.3%)</td>
<td>6 (20.0%)</td>
</tr>
<tr>
<td>Cerebral atrophy(^a)</td>
<td>5 (16.7%)</td>
<td>10 (33.3%)</td>
</tr>
<tr>
<td>Mild(^b)</td>
<td>3 (10.0%)</td>
<td>6 (20.0%)</td>
</tr>
<tr>
<td>Moderate(^b)</td>
<td>2 (6.7%)</td>
<td>3 (10.0%)</td>
</tr>
<tr>
<td>Severe(^b)</td>
<td>0</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Parenchymal defects</td>
<td>2 (6.7%)</td>
<td>6 (20.0%)</td>
</tr>
<tr>
<td>mMSS(^c)</td>
<td>1 (0–3)</td>
<td>2 (2–5)</td>
</tr>
</tbody>
</table>

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

✓ 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)
   ✓ 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 ++++

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients with CNS involvement</th>
<th>Elevated CSF IgG index</th>
<th>% Oligoclonal bands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tan et al. Clin Rheumatol 2018</td>
<td>76</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>Ernerudh et al. JNNP 1985</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seibold. Semin Arthritis 1982</td>
<td>11 (of 17)</td>
<td>63%</td>
<td>81%</td>
</tr>
<tr>
<td>Hirohata. Arch Intern Med 1985</td>
<td>13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Poor quality of the literature / intratechal synthesis is commonly seen

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)
  ✓ The role of Cerebrospinal fluid analysis
  ✓ The role of auto-antibodies
✓ 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

Ho et al. Autoimmun Rev 2016

For NPSLE vs SLE

aPL

Cerebrovascular events
Seizure
Chorea

2.1 (1.4-3.2)

Anti-RiboP

2.3 (1.5-3.5)

Anti-neurons
Including anti-NMDAr

9.5 (3.1-29)
Shall I search for autoantibodies in the CSF?

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

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

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

Ho et al. Autoimmun Rev 2016
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?
Treating NPSLE

Neuro-psychiatric manifestations in SLE patients
Treating NPSLE

Neuro-psychiatric manifestations in SLE patients

Is this significant?
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
Neuro-psychiatric manifestations in SLE patients

Treating NPSLE

Is this significant?
When possible, try to **confirm NP event using objective methods**
Exclude differential diagnoses such as infection or metabolic...

Attribution to SLE
Confirmed 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

Confirmed NPSLE

Treatment of 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...

Attrition to SLE

Confirmed NPSLE

Treatment of NPSLE

Patients with (severe) NPSLE are generally excluded from clinical trials
### Treating NPSLE according to its pathogenesis

<table>
<thead>
<tr>
<th>Pathogenic mechanism</th>
<th>Treatment</th>
<th>Delay of action</th>
<th>PRO’s</th>
<th>CON’s</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflammatory &amp; Immune</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glucocorticoids</td>
<td>Very fast</td>
<td>Very efficient</td>
<td>Long-term toxicity</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>10-15 days</td>
<td>Potent</td>
<td>Long-term toxicity</td>
</tr>
<tr>
<td></td>
<td>MMF</td>
<td>Weeks to months</td>
<td>Oral treatment</td>
<td>Delay of action, Well suited for maintenance</td>
</tr>
<tr>
<td></td>
<td>Rituximab</td>
<td>Weeks to months</td>
<td>Data available for refractory NPSLE</td>
<td>Delay of action</td>
</tr>
<tr>
<td><strong>Thrombotic Ischaemic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>Immediate</td>
<td>Well-suited for small vessels</td>
<td>Risk of bleeding</td>
</tr>
<tr>
<td></td>
<td>Anticoagulants</td>
<td>Immediate</td>
<td>Well suited for APS</td>
<td>Risk of bleeding</td>
</tr>
</tbody>
</table>
# Treating NPSLE according to its pathogenesis

<table>
<thead>
<tr>
<th>Pathogenic mechanism</th>
<th>Treatment</th>
<th>Delay of action</th>
<th>PRO’s</th>
<th>CON’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory &amp; Immune</td>
<td>Glucocorticoids</td>
<td>Very fast</td>
<td>Very efficient</td>
<td>Long-term toxicity</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>10-15 days</td>
<td>Potent</td>
<td>Long-term toxicity</td>
</tr>
<tr>
<td></td>
<td>MMF</td>
<td>Weeks to months</td>
<td>Data available for refractory NPSLE</td>
<td>Delay of action</td>
</tr>
<tr>
<td>Thrombotic Ischaemic</td>
<td>Aspirin</td>
<td>Immediate</td>
<td>Well-suited for small vessels</td>
<td>Risk of bleeding</td>
</tr>
<tr>
<td></td>
<td>Anticoagulants</td>
<td>Immediate</td>
<td>Well suited for APS</td>
<td>Risk of bleeding</td>
</tr>
</tbody>
</table>
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
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

Aspirin

Anticoagulants

If aPL+ or APS
Unless high bleeding risk
Neuro-psychiatric manifestations in SLE patients

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

Confirmed NPSLE

Treatment of NPSLE

- Glucocorticoids
- Cyclophosphamide IV
- MMF
- Rituximab
- Aspirin
- Anticoagulants

± Anticonvulsants

No improvement against active NPSLE

If aPL+ or APS
Unless high bleeding risk
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

Aspirin

Anticoagulants

OR

If aPL+ or APS

Unless high bleeding risk
Neuro-psychiatric manifestations in SLE patients

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

Treating NPSLE

Confirmed NPSLE

Treatment of NPSLE

Glucocorticoids
+ Cyclophosphamide IV
+ MMF
+ Rituximab
and/or
+ Aspirin
+ Anticoagulants

± IS

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

If aPL+ or APS
Unless high bleeding risk
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

Aspirin

Anticoagulants

If aPL+

Unless high bleeding risk

Thrombotic APS
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

- Glucocorticoids
- Cyclophosphamide IV
- MMF
- Rituximab
- Aspirin
- Anticoagulants

± Anticonvulsants
- NOT for all seizures
- >2 unprovoked seizures in 24h
- MRI brain lesions
- Epileptiform discharge on EEG

If aPL+
- Unless high bleeding risk

Thrombotic APS
Beware of « lupus-aggravating » drugs
Ethosuximide (Zarontin®)
Carbamazepine (Tegretol®)
=> In SLE, choose Valproate first
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
Laurent.arnaud@chru-strasbourg.fr
Twitter: @Lupusreference