Neurophysiology in diagnosis and monitoring of MS

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Evoked Potentials
“Expanded Neurological Examination”

- **Visual-VEP**
  - optic nerve
- **Somatosensory-SEP, Motor-MEP**
  - brain - spinal cord
- **Auditory-BAEP**
  - brainstem
MS functional deficits: Pathological substrates

- Segmental demyelination
- Axonal degeneration

MS pathology: functional effects (on EPs)

- Conduction slowing \((10 \text{ mm}=15-25 \text{ msec})\) (Latency)
- Temporal dispersion (Morphology)
- Increased refractory period (Amplitude)
- Conduction block \((>5\text{ mm})\) (Amplitude)

- Axonal degeneration (Amplitude)
EPs abnormalities

- **Delayed latency**
  - Demyelination
  - most often asymptomatic
    - detection of subclinical lesions
    - may be predictive of future axonal loss

- **Reduced amplitude**
  - Good correlation with clinical impairment
  - Transient
    - Conduction block (demyelination/inflammation)
  - Permanent
    - Axonal loss
Visual EPs patterns

1- Normal
2- Amplitude asymmetry
3- Latency prolongation
4- Amplitude asymmetry and latency prolongation

Anderson et al 1987
Relationship between clinical findings and EPs abnormalities

- Abnormal VEP
- Abnormal SEP
- Abnormal BAEP

Symptomatic patients
Asymptomatic patients

Comi G. et al. Multiple Sclerosis 1999; 5: 263-267
115 CIS patients followed for 5 years

<table>
<thead>
<tr>
<th></th>
<th>VEP</th>
<th>SEP</th>
<th>MEP</th>
<th>BAEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. of patients</td>
<td>115</td>
<td>114</td>
<td>93</td>
<td>109</td>
</tr>
<tr>
<td>Abnormal Eps (n)</td>
<td>54</td>
<td>77</td>
<td>47</td>
<td>19</td>
</tr>
<tr>
<td>Abnormal Eps (%)</td>
<td>47.0%</td>
<td>67.5%</td>
<td>50.6%</td>
<td>17.5%</td>
</tr>
<tr>
<td>Sensitivity (symptomatic)</td>
<td>83.3%</td>
<td>67.7%</td>
<td>58.5%</td>
<td>27.0%</td>
</tr>
<tr>
<td>Sensitivity (asymptomatic)</td>
<td>34.1%</td>
<td>67.3%</td>
<td>35.7%</td>
<td>12.5%</td>
</tr>
</tbody>
</table>

Di Maggio et al. ECTRIMS 2011
Predictive value of paraclinical tests in CIS to early evolution to CDMS

<table>
<thead>
<tr>
<th>test</th>
<th>Predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>POS</td>
</tr>
<tr>
<td>brainMRI</td>
<td>53</td>
</tr>
<tr>
<td>CSF</td>
<td>44</td>
</tr>
<tr>
<td>VEP</td>
<td>26</td>
</tr>
<tr>
<td>SEP-UL</td>
<td>50</td>
</tr>
<tr>
<td>SEP-LL</td>
<td>42</td>
</tr>
<tr>
<td>BAEP</td>
<td>50</td>
</tr>
</tbody>
</table>

97 pts avg follow-up 3 yrs

Filippini et al 1994
CIS – EPs and conversion to CDMS over 2 years

Di Maggio et al. ECTRIMS 2011
Multifocal VEPs in ON: predictive value of fellow eye abnormalities of conversion to MS after 1 year (McDonald criteria) – 48 ON pts

Klistorner et al Mult Scler 2009
Optical Coherence Tomography

Optical Coherence Tomography is a non-invasive imaging technique that uses low-coherence interferometry to capture high-resolution cross-sectional images of the internal structures of tissues, particularly in the fields of ophthalmology and dermatology. It works by emitting a beam of infrared light that is slightly below the tissue's absorption peak, allowing for deeper penetration and higher resolution images compared to other optical imaging techniques.
OCT in chronic ON
RNFL thickness correlates with VEP amplitude (axonal loss)

![Image: OCT scans of unaffected and affected eyes]

<table>
<thead>
<tr>
<th>Category</th>
<th>RNFL Thickness, μm</th>
<th>Macular Volume, mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity (logMAR)</td>
<td>+0.01 (+0.003 to +0.03)</td>
<td>+0.54 (+0.03 to +1.11)</td>
</tr>
<tr>
<td></td>
<td><em>p = 0.01</em></td>
<td>0.06b [+0.22 *p = 0.15]</td>
</tr>
<tr>
<td>Visual field mean deviation, dB</td>
<td>−1.03c (−1.66 to −0.40)</td>
<td>−4.56 (−8.69 to −0.44)</td>
</tr>
<tr>
<td></td>
<td><em>p = 0.003</em></td>
<td><em>p = 0.03</em> [-2.57 *p = 0.18]</td>
</tr>
<tr>
<td>Color vision (√FM 100-Hue score)</td>
<td>+2.93c (+2.00 to +3.87)</td>
<td>+17.93 (+11.03 to +24.83)</td>
</tr>
<tr>
<td></td>
<td><em>p &lt; 0.001</em></td>
<td><em>p &lt; 0.001</em></td>
</tr>
<tr>
<td>Whole-field VEP amplitude, μV</td>
<td>−0.10 (−0.16 to −0.03)</td>
<td>−4.62 (−7.26 to −1.98)</td>
</tr>
<tr>
<td></td>
<td><em>p = 0.006</em></td>
<td><em>p = 0.002</em></td>
</tr>
<tr>
<td>Central-field VEP amplitude, μV</td>
<td>−0.05 (−0.10 to −0.0003)</td>
<td>−2.37 (−4.49 to −0.25)</td>
</tr>
<tr>
<td></td>
<td><em>p = 0.05</em></td>
<td><em>p = 0.03</em></td>
</tr>
</tbody>
</table>

*Trip et al. 2005*
Optical coherence tomography is less sensitive than visual evoked potentials in optic neuritis.
Smith et al 1986

VEPs after high doses of steroids in MS - Optic Neuritis

basal

1 week

1 month

Smith et al 1986
VEPs in MS anti-aquaporin positive (17) and negative (84) pts
VEPs after ON in NMO spectrum disorder (19) and MS (18) pts

**NMO**
- Present VEP: 73%
- Absent VEP: 27%

**MS**
- Present VEP: 35%
- Absent VEP: 65%

**Graph**
- **NMO**: Mean 129 ms, Range 160 ms
- **MS**: Mean 143 ms, Range 140 ms

*Straffi et al ECTRIMS 2011*
FREQUENCY OF EP ABNORMALITIES (%) in clinically definite MS (n. 116: 50 RR, 48 SP, 18 PP)

PP vs RR: ° p<0.02
SP vs RR: * p<0.02; ** p<0.001
SPMS: > absent VEPs vs PPMS

even excluding previous ON

Bianco et al in prep.
EPs and longitudinal monitoring of MS
Longitudinal changes of P100 latency after acute ON

- Affected eye
- Unaffected eye

Brusa et al. 1999

6 months 3 years 6 months 3 years
Longitudinal MEPs changes (2 yrs) worsened stable

Jung et al 2008
MEPs after high doses of steroids (24 pts)

5 days

- 1 g/day
- 2 g/day

Fierro et al 2002
Somatosensory EPs – abnormalities

Normal

> N20 latency

N13 absent

N13 and N20 absent

Progression no longer detectable!

from Anderson et al 1987 - modified
EP SCORES

0 = normal

1 = abnormal latency \textit{or} amplitude

2 = abnormal latency \textit{and} amplitude

3 = absence
% EPs abnormalities: *basal vs final* (4 yrs)

<table>
<thead>
<tr>
<th></th>
<th>Basal (%)</th>
<th>Final (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEP-UL</td>
<td>51.6</td>
<td>65.6</td>
<td>0.03</td>
</tr>
<tr>
<td>SEP-LL</td>
<td>81.3</td>
<td>85.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>SEP</td>
<td>84.4</td>
<td>89.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>MEP-UL</td>
<td>68.8</td>
<td>70.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>MEP-LL</td>
<td>71.9</td>
<td>79.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>MEP</td>
<td>73.4</td>
<td>79.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>VEP</td>
<td>75.0</td>
<td>82.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>BAEP</td>
<td>40.6</td>
<td>50.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Global</td>
<td>92.2</td>
<td>96.9</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Leocani et al, JNNP 2006
<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Final</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEP</td>
<td>5.7±3.6</td>
<td>6.9±3.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MEP</td>
<td>4.1±3.0</td>
<td>4.8±3.3</td>
<td>0.0014</td>
</tr>
<tr>
<td>VEP</td>
<td>3.0±2.1</td>
<td>3.3±2.1</td>
<td>0.0081</td>
</tr>
<tr>
<td>BAEP</td>
<td>1.4±1.8</td>
<td>1.7±1.9</td>
<td>0.005</td>
</tr>
<tr>
<td>Global EP</td>
<td>12.8±7.7</td>
<td>15.9±8.8</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Leocani et al, JNNP 2006
Global basal EP* score vs EDSS

*VEP, MEP, SEP, BAEP

N=84

R=0.6
p<0.0001 (Spearmann rank correlation)

Leocani et al, JNNP 2006
Basal EPs and changes in disability at follow-up (4 yrs)

* p< 0.04, Signed ranks

Leocani et al, JNNP 2006
EPs score - time to EDSS 4.0 and 6.0
80 MS patients (62 RR, 14 PP, 4 SP)
Predicted vs observed EDSS using linear models
50 patients (47 RR, 3 CIS)

rho_{Spearman} = 0.70
p <= 0.0001
CIS: n. abnormal EPs - time to EDSS 3.0

n: 247 (out of 335)

SEP, VEP, BAEP, no MEP

Pelayo, Montalban et al. Multiple Sclerosis 2010
Predictive value of subclinical Eps abnormalities on future clinical involvement of the same FS (5 yrs)

- **VEPs**: PPV=15.8%
- **BAEPs**: PPV=55.6%
- **SEPs**: PPV=38.8%
- **MEPs**: PPV=90.0% (p=0.03)

*Di Maggio et al. ECTRIMS 2011*
Clinical usefulness of EPs in MS

DIAGNOSIS

• Detection of clinically silent lesions – SCARCE

• Indication on underlying pathology (demyelination, axonal damage/block) – VERY GOOD

MONITORING (e.g. assessing treatment efficacy)

• Detection of disease activity – SCARCE

• Objectivation of involvement of sensory/motor pathways in patients with vague symptoms (e.g. relapse confirmation) – GOOD

• Detection of disease progression – GOOD

Prediction of future disability (?)
Supervisor
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Laura Straffi

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