Intrathecal oligoclonal IgG in MS

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SKML – sectie HIM
13-DEC 2012, 13:30-14:15
Overview

- Are OCB in MS dead?
- Vote #1
- A brief history of OCB in MS
- UK NEQAS: 16 years OCB QC experience
- Intermezzo
- A meta-analysis
- Vote #2
- Conclusion
The new diagnostic criteria in MS

**TABLE 4: The 2010 McDonald Criteria for Diagnosis of MS**

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Additional Data Needed for MS Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 attacks^a; objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack^b</td>
<td>None^c</td>
</tr>
<tr>
<td>≥2 attacks^a; objective clinical evidence of 1 lesion</td>
<td>Dissemination in space, demonstrated by:</td>
</tr>
<tr>
<td></td>
<td>≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)^d; or Await a further clinical attack^e implicating a different CNS site</td>
</tr>
<tr>
<td>1 attack^a; objective clinical evidence of ≥2 lesions</td>
<td>Dissemination in time, demonstrated by:</td>
</tr>
<tr>
<td></td>
<td>Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack^g</td>
</tr>
<tr>
<td>1 attack^a; objective clinical evidence of 1 lesion (clinically isolated syndrome)</td>
<td>Dissemination in space and time, demonstrated by:</td>
</tr>
<tr>
<td></td>
<td>For DIS: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)^d; or Await a second clinical attack^g implicating a different CNS site; and For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack^g</td>
</tr>
<tr>
<td>Insidious neurological progression suggestive of MS (PPMS)</td>
<td>1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria^h:</td>
</tr>
<tr>
<td></td>
<td>1. Evidence for DIS in the brain based on ≥1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions</td>
</tr>
<tr>
<td></td>
<td>2. Evidence for DIS in the spinal cord based on ≥2 T2 lesions; in the cord</td>
</tr>
<tr>
<td></td>
<td>3. Positive CSF (isoelectric focusing evidence of oligodonal bands and/or elevated IgG index)</td>
</tr>
</tbody>
</table>

Polman et al. ANN 2011;69:292-302
Omission of OCB provokes protest

Cerebrospinal fluid analysis in the 2010 revised McDonald's multiple sclerosis diagnostic criteria.

Galea J, Freedman MS, Thompson EJ.

Comment on
Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. [Ann Neurol. 2011]

PMID: 21789311 [PubMed - indexed for MEDLINE]

Revised McDonald criteria: the persisting importance of cerebrospinal fluid analysis.


Comment on
Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. [Ann Neurol. 2011]

PMID: 21710627 [PubMed - indexed for MEDLINE]
41 yrs, male patient:
Feb-2011 vertigo+nystagmus, MRI (A): exclusively PV located lesions
Jul-2011 ON OD (VEP P100 125 ms), MRI (B): unchanged lesions
CSF: IEF shows OCB
Before 2011: CSF OCB could substitute for radiological DIS in RRMS

Since 2011: CSF OCB cannot substitute for radiological DIS in RRMS
Vote #1

Who thinks CSF OCB should still be allowed to substitute for radiological DIS in MS?
The origin of CSF in MS

1925-1930 Arne Tiselius (Uppsala). Discovers electrophoresis - 1948 Noble prize

1942 Elvin Kabat (New York) first to use electrophoresis for CSF (70 mL !) describes an increase of gamma globulin in the CSF not seen in the serum
OCB sources

Intrathecal or central compartment

CSF

Serum

Systemic or peripheral compartment

a

b

c

d

Courtesy Dr V Chamoun
The 5 OCB pattern

OCB consensus guidelines

A pre-2005 literature review reveals a low diagnostic sensitivity for OCB in MS (45%-77%)  

This contrasts with the experience of pioneering experts in the field

Updated consensus guidelines are published  
Sensitivity of CSF OCB for MS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (n)</th>
<th>MS (n)</th>
<th>Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kostulas 1987</td>
<td>1114</td>
<td>58</td>
<td>100</td>
</tr>
<tr>
<td>McLean 1990</td>
<td>1007</td>
<td>82</td>
<td>95</td>
</tr>
<tr>
<td>Ohman 1992</td>
<td>558</td>
<td>112</td>
<td>96</td>
</tr>
</tbody>
</table>

M.S. Freedman *et al.* Arch Neurol 2005;62:865-870
UK NEQAS 2008-2011

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK NEQAS 2008</td>
<td>245</td>
<td>12</td>
<td>9</td>
<td>241</td>
<td>0.96 [0.93, 0.98]</td>
<td>0.95 [0.92, 0.98]</td>
</tr>
<tr>
<td>UK NEQAS 2009</td>
<td>243</td>
<td>7</td>
<td>22</td>
<td>254</td>
<td>0.92 [0.88, 0.95]</td>
<td>0.97 [0.95, 0.99]</td>
</tr>
<tr>
<td>UK NEQAS 2010</td>
<td>271</td>
<td>5</td>
<td>6</td>
<td>275</td>
<td>0.98 [0.95, 0.99]</td>
<td>0.98 [0.96, 0.99]</td>
</tr>
<tr>
<td>UK NEQAS 2011</td>
<td>177</td>
<td>4</td>
<td>14</td>
<td>182</td>
<td>0.93 [0.88, 0.96]</td>
<td>0.98 [0.95, 0.99]</td>
</tr>
</tbody>
</table>

Acknowledgement: Mrs D Patel & Dr W Egner, UK NEQAS
Intermezzo
Pattern training

CSF Isoelectric focusing requires only 2.5 microlitres CSF!
Pattern training

“normal”

“A classical mirror pattern”
Pattern training

<table>
<thead>
<tr>
<th>&quot;contaminated&quot;</th>
<th>Serum</th>
<th>CSF</th>
</tr>
</thead>
</table>
LHON, G3460A mutation

- 18 year old male
- Loss of vision in L eye followed by R eye 2/12 later
- No pain
- Progressive
- No other symptoms
- MRI (STIR): chiasmal hyperintensity
- CSF: ... pattern?
Wolfram's Syndrome (DIDMOAD)

- 19 year old Female
- Hx of optic atrophy & ataxia (cerebellar), deafness
- PmHx: Type I Diabetes, meningitis as child
- FHx: NIL
- Died aged 21 (suicide)
- CSF: no cells, normal proteins, ... pattern?

Positive for wolframin mutation (AR)
diabetes, deafness, optic atrophy
Morvan's Syndrom

- 18 year old male
- PmHx: Gilbert's syndrome
- 1 year Hx of fatigue, disrupted sleep pattern, constipation, hypersalivation & hyperhidrosis, painful cramps, myotonia, fasciculations
- CSF: ... pattern ?

- CK 600 U/L (n < 80 U/L)
- EMG: myokymic & neuromyotonic discharges
- No antibodies to AchR, P/Q or VGKC, Hu, Ma2
The last 5 minutes...

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Conclusion: CSF OCB in MS

Excellent GLP can be achieved (UK NEQAS)

Diagnostic sensitivity > 90%

Diagnostic specificity ~ 60% were it matters

OCB a substitute for radiological DIS?

“No, one unspecific test should not be replaced by another.”
... the end

Thank you for your attention!