Teaching Course 11

Differential diagnoses

Chairs:  

S. Fredrikson (Stockholm, SE)  
A. Siva (Istanbul, TK)

49  Diagnostic and differential diagnostic aspects in MS  
S. Fredrikson (Stockholm, SE)

32  Multiple Sclerosis Differential diagnoses MRI - diagnostic possibilities and pitfalls  
A. Siva (Istanbul, TK)

33  Blood and CSF Biomarkers in the Diagnostic Process  
F. Sellebjerg (Copenhagen, DK)
Diagnostic and differential diagnostic aspects of multiple sclerosis

Teaching course 11, ECTRIMS 2016, London

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Department of Clinical Neuroscience
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"Multiple sclerosis is what a good clinician would call multiple sclerosis”

John Kurtzke, 1970

"Nothing shuts off critical neurological thought processes faster than a diagnosis of multiple sclerosis”

Semin Neurol 1985:5 94-98
Some possible pitfalls and problems

- There is no definitive diagnostic test for MS
- Misdiagnosis estimated to be 5-10% (or higher?, up to 35% reported)
- Diagnosis is based on (changing) criteria – what is the interrater reliability of the criteria for atypical cases?
- The occurrence of “preclinical” diagnosis based on MRI findings
- A broad spectrum of (treatable) differential diagnoses
- Coincidence of MS and psychiatric/psychological problems (and the latter symptoms constitute the major part of the functional disability)

Key Steps in the Diagnostic Process

- History:
  - Previous episodes
  - Other diseases
  - Family history
- Comprehensive physical examination:
  - ‘Objective evidence’
  - Other lesions
- Additional tests:
  - MRI
  - CSF
Figure 3. Overview of the Indications for MRI in published cohorts, n=394. 4,6 –12,23,26 ...

Radiologically isolated syndrome (RIS)

- Approximately two-thirds of persons with RIS show radiological progression and one-third develop neurological symptoms during mean follow-up times of up to five years. Cervical cord lesions are important predictors of clinical conversion.

Radiologically isolated syndrome--incidental magnetic resonance imaging findings suggestive of multiple sclerosis, a systematic review.
What is a Clinically Isolated Syndrome?

- A clinically isolated syndrome (CIS) is a first acute or subacute episode of neurological dysfunction with a high suspicion of development of multiple sclerosis.
- A CIS is usually the first clinical event in an MS patient.
- Magnetic resonance imaging (MRI) findings compatible with:
  - No or minimal oedema/mass effect
  - T2-hyperintense lesions
  - Contrast enhancing lesions
  - Location of lesion
- Spontaneous or steroid responsive remissions

To exclude other pathologies that may underly the same syndrome (Always look for RED FLAGS, Miller DH, Mult Scler 2008:14:1157-74)

Multiple sclerosis and diagnosis

- The main principle: dissemination in time (DIT) and space (DIS)
- Schumacher 1965
- Poser 1983
- McDonald 2001
- Reviderate McDonald 2005 (Polman)
- Reviderate McDonald 2010 (Polman)

- Demonstration of DIS and DIT with MRI:
  - Paty 1988
  - Barkhof 1997
  - Reviderate Barkhof (Tintoré) 2000
  - Swanton 2006

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Additional Data Needed for MS Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Discord*</td>
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<tr>
<td></td>
<td>Dissemination in time, demonstrated by:</td>
</tr>
<tr>
<td></td>
<td>- Two lesions in at least 2 of 4 CNS</td>
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<tr>
<td></td>
<td>regions (both hemispheres, both sides)</td>
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<td>- One or more lesions in the spinal cord</td>
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<td>Discord*</td>
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<td>Dissemination in space and time, demonstrated by:</td>
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Incident neurologic progression suggests MS (SPMS)

1 year or more progression (subjectively or objectively demonstrated) and at least 1 of the following criteria fulfilled:
- Two lesions in the MS-dominant, precentral, jampso, or thalamus region
- Evidence for DMS in the spinal cord based on 2 or 1 T2 lesions in the cord
- MRI with lesions in spinal cord, brainstem, or optic nerve

Ann Neurol 2011:69:292-
Recent radiological classifications for MS lesions

<table>
<thead>
<tr>
<th>MRI article</th>
<th>McDonald 2010</th>
<th>McDonald 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiological Classification</td>
<td>Revised-Third</td>
<td>Revised-Third</td>
</tr>
<tr>
<td>Demonstrated demyelination of DMS</td>
<td>At least 1 out of 3</td>
<td>At least 1 out of 3</td>
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<tr>
<td></td>
<td>1. Brainstem lesions</td>
<td>1. Brainstem lesions</td>
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<tr>
<td></td>
<td>2. Inflammatory or gadolinium-enhancing lesions</td>
<td>2. Inflammatory or gadolinium-enhancing lesions</td>
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<tr>
<td></td>
<td>3. Multiple T2 lesions</td>
<td>3. Multiple T2 lesions</td>
</tr>
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<td></td>
<td>3. Multiple T2 lesions</td>
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Diagnostic criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria


*Activity determined by clinical relapses assessed at least annually and/or MRI activity (contrast-enhancing lesions; new and unequivocally enlarging T2 lesions).

**Progression measured by clinical evaluation, assessed at least annually. If assessments are not available, activity and progression are indeterminate.

MS = multiple sclerosis; PP = primary progressive; PR = progressive relapsing; SP = secondary progressive.
Oligoclonal bands

The utility of cerebrospinal fluid analysis in the diagnosis of multiple sclerosis: a consensus report

CSF is of particular value in patients:
- older than 50 years
- with vascular risk factors
- with migraine
- with non-specific neurologic symptoms

Differential diagnosis based on presenting symptoms from the brainstem, spinal cord, optic nerves or cerebrum.

Frequencies of abnormal CSF variables in clinically definite MS

- Oligoclonal IgG in CSF: >95%
- Increased IgG index: 70-80%
- Increased cell count: 50%
- Abnormal albumin ratio: 12%

CSF is of particular value in patients:
- older than 50 years
- with vascular risk factors
- with migraine
- with non-specific neurologic symptoms

Differential diagnosis based on presenting symptoms from the brainstem, spinal cord, optic nerves or cerebrum.

Mult Scler 2008:14:1157-74
### Brain stem presentation

<table>
<thead>
<tr>
<th>MS</th>
<th>Less common</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internuclear ophthalmoplegia</td>
<td>Facial palsy, facial myokymia</td>
<td></td>
</tr>
<tr>
<td>Ataxia and multidirectional nystagmus</td>
<td>Deafness</td>
<td>Vascular territory syndrome, e.g., lateral medullary</td>
</tr>
<tr>
<td>Sixth nerve palsy</td>
<td>One-and-a-half syndrome</td>
<td>Third nerve palsy</td>
</tr>
<tr>
<td>Facial numbness</td>
<td>Trigeminal neuralgia</td>
<td>Progressive trigeminal sensory neuropathy</td>
</tr>
<tr>
<td></td>
<td>Paroxysmal tonic spasms</td>
<td>Focal dystonia, torticollis</td>
</tr>
</tbody>
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### Optic nerve presentation

<table>
<thead>
<tr>
<th>MS</th>
<th>Less common</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral</td>
<td>Bilateral simultaneous optic neuritis</td>
<td>Progressive optic neuropathy</td>
</tr>
<tr>
<td>Pain on eye movement</td>
<td>No pain</td>
<td>Severe, continuous orbital pain</td>
</tr>
<tr>
<td>Partial and mainly central visual blurring</td>
<td>No light perception</td>
<td>Persistent complete loss of vision</td>
</tr>
<tr>
<td>Normal disc or mild disc swelling</td>
<td>Severe disc swelling</td>
<td>Neuroretinitis (optic disc swelling with macular star)</td>
</tr>
<tr>
<td></td>
<td>Uveitis (mild, posterior)</td>
<td>Uveitis (severe, anterior)</td>
</tr>
</tbody>
</table>

### Spinal cord presentation

<table>
<thead>
<tr>
<th>MS</th>
<th>Less common</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial myelopathy</td>
<td>Complete transverse myelitis</td>
<td>Anterior spinal artery territory lesion (sparking posterior column only)</td>
</tr>
<tr>
<td>Lhermitte's symptom</td>
<td>Radiculopathy, radicula</td>
<td>Cauda equina syndrome</td>
</tr>
<tr>
<td>Deafferented hand</td>
<td>Segmental loss of pain and temperature sensation</td>
<td>Sharp sensory level to all modalities &amp; localized spinal pain</td>
</tr>
<tr>
<td>Numbnesses</td>
<td>Partial Brown-Squard syndrome sparing posterior columns</td>
<td>Complete Brown-Squard syndrome</td>
</tr>
<tr>
<td>Urinary urgency, incontinence, erectile dysfunction</td>
<td>Facial incontinence</td>
<td>Acute urinary retention</td>
</tr>
<tr>
<td></td>
<td>Progressive spastic paraplegia (asymetrical)</td>
<td>Progressive sensory ataxia (posterior column)</td>
</tr>
</tbody>
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Cerebral presentation

<table>
<thead>
<tr>
<th>MS</th>
<th>Less common</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild subcortical cognitive impairment</td>
<td>Epilepsy</td>
<td>Encephalopathy (obtundation, confusion, drowsiness)</td>
</tr>
<tr>
<td>Hemianopia</td>
<td>Cortical blindness</td>
<td></td>
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<tr>
<td>Hemiparesis</td>
<td>Chorea, myoclonus</td>
<td>Generalized movement disorder or Parkinsonian syndrome</td>
</tr>
</tbody>
</table>

Some differential diagnosis to MS

- ADEM, NMO, AHL, PML, Balo
- Systemic: Sarcoidosis, SLE, Behcet, Sjögren, Wegener
- Vascular: Stroke, Vasculitis, CADASIL, anti-phospholipid syndrome, AV-malformations, hemangioma
- Metabolic: Leukodystrophies (metachromatic/adreno-), mitochondrial disorders (MERFF, MELAS, Leber), B12-deficiency
- Genetic: SCAs, Friedreich, HSP
- Neoplastic: Lymphomas, paraneoplastic syndromes
- Infection: HIV, syphilis, Borrelia, herpes, Whipple
- Psychiatric
- Others (toxic, compression, neuromuscular (MG) etc)

RED FLAGS

- Lung involvement
- Multiple cranial neuropathies or polyneuropathy
- Periperal neuropathy
- Mucosal ulcers
- Hemorrhages/subarachnoid hemorrhages
- Extrapyramidal features: Movement disorders
- Livedo reticularis
- Retinopathy
- Cerebral venous sinus thrombosis
- Cardiac disease
- Myopathy
- Renal involvement
- Hematological manifestations
- Clotifications on CT scan
- Bone lesions
- Hodgkinson disease
- Increase serum lactate level
- Selective involvement of the anterior temporal and inferior frontal lobe
- Hematological manifestations
- Lacunar infarcts
- Mucosal ulcers
- Myoarthropathy
- Hypothalamic disturbance
- Recurrent spontaneous abortion or thrombotic events
- Simultaneous enhancement of all lesions
- Rash
- Arthritis, polyarthalgias, myalgias
- Amyotrophy
- Headache or meningismus

REMEMBER:
- Age?
- Abrupt onset?
- Short duration or poor recovery?
- Lack of typical symptoms?
- Nonspecific symptoms?
- Family history?
- Normal examination?
- Normal MRI/CSF?
What differ age related changes on MRI from MS?

<table>
<thead>
<tr>
<th>MS lesions</th>
<th>Balancing degenerative lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger patients (15-40 years)</td>
<td>Older patients (&gt; 40 years)</td>
</tr>
<tr>
<td>Often female</td>
<td>Males predominance</td>
</tr>
<tr>
<td>Periventricular lesions relating to corpus callosum</td>
<td>Lesions in watershed areas</td>
</tr>
<tr>
<td>Corpus callosum lesions and atrophy</td>
<td>Lack of lesions in MS prodromal stages</td>
</tr>
<tr>
<td>Microvascular lesions</td>
<td>Spreading of the U-fibers and corpus callosum</td>
</tr>
<tr>
<td>Intraventricular lesions affecting the middle cerebellar peduncles</td>
<td>No contrast-enhancing lesions</td>
</tr>
<tr>
<td>Contrast-enhancing lesions</td>
<td>No enhancement</td>
</tr>
</tbody>
</table>

Red flags on MRI

- Persistent Gd-enhancement and continued enlargement of lesions
- Persistently unifocal manifestations
- Large and infiltrating brainstem lesions
- Predominance of lesions at the cortical/subcortical junction
- Meningeal enhancement
- T2-hyperintensity in the dentate nuclei
- No "black holes"
- Large lesions
- Marked asymmetry of WM lesions
- No enhancement

Blood tests in MS diagnosis???
In conclusion…

MS remains a diagnosis requiring an expert neurologist

Differential diagnosis are many, but they can usually be excluded by considering “red flags”

Although a disease specific marker does not exist, a robust diagnosis can usually be established early after onset in most cases based on compatible clinical-, CSF- and MRI-data

Atypical MRI changes should be interpreted cautiously

References

Multiple Sclerosis
Differential diagnoses and diagnostic dilemmas
MRI - possibilities and pitfalls in diagnosis of MS

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ECTRIMS - 14 - 17 September 2016, London

Disclosure
- Received research grants to my department from The Scientific and Technological Research Council Of Turkey - Health Sciences Research Grants numbers: 1096070 and 1125052; and also unrestricted research grants from Merck-Serono to our Clinical Neuroimmunology Unit
- Honoraria or consultation fees and/or travel and registration coverage for attending several national or international congresses or symposia, from Merck Serono, Teva, Novartis, Genzyme, Roche, Bionet Idec/Gen Pharma of Turkey and Bayer-Schering AG
- Educational presentations at programmes & symposia prepared by Excemed internationally and at national meetings and symposia sponsored by Merck-Serono; Novartis and Teva; Bionet Idec/Gen Pharma of Turkey

Diagnostic criteria in “MS”
- Schumacher et al, 1965
  “a clinical disease disseminated in time and space”
- Poser et al, 1983
  “additional paraclinical and/or laboratory evidence: neuroimaging, neurophysiology & CSF (IgG/OCB)"
- McDonald et al, 2001 & revised McDonald; Polman et al, 2005
  “evidence for dissemination in time and space supported by MRI”
- No better explanation to account for symptoms and signs (or alternative neurological disease)

Diagnosing MS
MS is a neuro-inflammatory demyelinating disease with neurodegeneration of the CNS, in which...
- Evidence of dissemination in space (multifocality)
  Clinical sx & signs + DIS by MRI
- Evidence of dissemination in time
  Clinical relapses or steady progression + DIT by MRI
- No better explanation to account for symptoms and signs and/or MRI findings
  Clinical & MRI: no alternative neurological disease

Diagnosis and Differential Diagnosis of MS
Patients are admitted to neurology outpatient clinics because of...
- Clinical Symptoms & Signs suggestive of “MS”
- Imaging Cranial & Spinal MRI suggestive of “MS”
- Clinical & Imaging findings suggestive of MS
- RIS CIS RRMS PMS
MS variants, mimics or not so rarely something else!
A first concern!

In a patient who is admitted with symptoms and/or MRI findings suggestive of MS or MS Spectrum / related disorders:

- **MS**
- **Not MS**

Difficulties in **MS** diagnosis

- Evaluation of diagnostic outcomes in patients referred to a university-based MS center for possible MS
  
  **# 281 pts → Final MS diagnosis: 33%** (McDonald-I)
  
  pts referred on the basis of clinical dx: MS in 46%
  
  pts referred on the basis of MRI dx: MS in 11%

  **Non-MS dx:**
  
  Other neurologic disorders: 31.5 %
  
  Probable psychiatric diagnoses: 22.5 %
  
  No clear diagnosis made: 12.5 %

  *Carmosino et al. Arch Neurol. 2005

For **MS experts & in MS centers** it is relatively common to see patients diagnosed as MS, who in fact don’t have MS, with a significant number of these misdiagnosed cases being on DMD!

*Solomon et al. Neurology, 2012

The most common alternative diagnoses in patients misdiagnosed with MS*

- NSWMA - nonspecific white matter abnormalities **81.7 %**
- SVD - small vessel ischemic disease **46.8 %**
- Migraine **50 %**
- Psychiatric disease **44.8 %**
- Fibromyalgia **31 %**
- NMO - Neuromyelitis optica **40.5 %**
- Misdiagnosed patients on DMD for MS **26 %**

*Solomon et al. Neurology, 2012

In 5 - 35 % of people diagnosed as MS, the ultimate diagnosis is not MS!!!

migraine - fibromyalgia - psychiatric conditions

vague neurologic symptoms with

non-specific white matter abnormalities on brain MRI

misinterpretation and misapplication of radiographic diagnostic criteria

Difficulties in MS diagnosis

Diagnosing MS may be challenging!
- Vague neurologic symptoms in young people
- Insignificant neurological findings
- Nonspecific white matter abnormalities on brain MRI
- False neuroimaging (MR) reports
- The urge (!) to diagnose MS early
- MS and its masquerades

May cause over / false - diagnosis of MS!!!

MRI pitfalls in MS diagnosis

MRI criteria for MS diagnosis are not developed to differentiate MS from other conditions
- but to identify high risk CIS patients for converting to MS
In the setting of clinical findings suggestive of MS
overreliance on MRI interpretation
- is the major cause of misdiagnosis


MRI - possibilities and pitfalls in diagnosis of MS

How to improve the role of MRI in the differential diagnosis of MS?
- Revealing the perivenular distribution pattern of MS lesions
  - most MS lesions show a central vein
- Detection of increased iron deposition within MS-related lesions
  - most chronic focal and some acute focal lesions show increase in iron deposition
- Demonstration of cortical lesions
  - Cortical lesions are abundant in patients with MS


MS diagnosis

Steps to MS Dx
- Clinical history
- Neurological examination
  - Neuroimaging - MRI
  - other laboratory testing (CSF & EP)

MRI - possibilities and pitfalls in diagnosis of MS

In a patient who has been referred with a "clinical diagnosis" of probable MS
- MRI may confirm the clinical diagnosis of MS
- MRI may be suggestive of an alternative diagnosis
- MRI sometimes may cause further diagnostic confusion!

MRI - possibilities and pitfalls in diagnosis of MS

How to improve the role of MRI in the differential diagnosis of MS?
- Further studies are needed before detection, the 'central vein sign', or within lesions can be incorporated
  - MS (at standard field strength)
  - Those require: high field strength
  
The Spectrum of MS and related disorders

<table>
<thead>
<tr>
<th>MS sub-clinical phenotypes</th>
<th>MS variants</th>
<th>MS related disorders (once upon a time MS!)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIS</td>
<td>Tumefactive MS</td>
<td>ADEM</td>
</tr>
<tr>
<td>CIS</td>
<td>Balo's</td>
<td>NMO / NMOSD</td>
</tr>
<tr>
<td>SAMS</td>
<td>Marburg's</td>
<td>aMOG-related syndromes</td>
</tr>
<tr>
<td>SAPMS</td>
<td>Schilder's?</td>
<td>Others - Ab unknown? - atypical CNS inflammatory disorders?</td>
</tr>
<tr>
<td>RRMS</td>
<td></td>
<td></td>
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<tr>
<td>2PMS</td>
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<tr>
<td>PPMS</td>
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</table>

The diagnostic spectrum of MRI in MS

- RIS
- CIS
- Clinically definite MS - RRMS / SPMS
- PPMS
- MS variants
- NMO/NMOSD
- ADEM & other autoimmune inflammatory 
- Non-MS CNS diseases
- Non-specific white matter abnormalities

MRI - possibilities and pitfalls in diagnosis of MS

- A proper MRI reading:
  - may confirm the clinical diagnosis of MS
  - may be suggestive but not confirmative, further w/up & f/up for MS
  - may not be conclusive and leads for further non-MS other neuro-inflammatory demy.
  - may exclude the clinical diagnosis of MS and alternative diagnosis

MRI - possibilities and pitfalls in diagnosis of MS

- In a patient who has been referred with an "MRI diagnosis" of probable MS (radiology report/non-expert reading)
  - confirmative
  - suggestive
  - explorative
  - eliminative

MRI - possibilities and pitfalls in diagnosis of MS

- In a patient who is diagnosed and followed as MS
  - MRI will also assist the clinician to
    - decide when to start long term treatment
    - decide whether the patient is a treatment responder
    - decide to change a DMD
    - predict the clinical course and prognosis - to a certain extent

MRI - possibilities and pitfalls in diagnosis of MS

- Defining the clinical course of multiple sclerosis - the 2013 revision

- Treatment decisions are based on either clinical activity / progression

MRI - possibilities and pitfalls in diagnosis of MS

- When to re-scan?
  - CIS/RIS! - Follow-up brain imaging
  - When to scan after an initial brain MRI is suggestive but not diagnostic by McDonald 2010 MRI criteria
  - optimal interval is 3-6 months
  - if new lesions at F-up scans
    - a third scan 6-12 months later, then at 12 - 18 months

*Lubin et al Neurology, 2014

When to re-scan?

**RRMS on DMD**
- Follow-up brain imaging depends on availability and reimbursement
- Within the first month of the onset of the given drug efficacy!
  (i.e. 3-4th months after initiating INF-beta drugs & oral 6-7th months of GA) - this may serve as the baseline/reference MRI
  - in the absence of any clinical episode first f/up MRI at month 12
  - if months 6 - 12, then at 18 - 24 months; and then eventually every other year x 2; afterwards longer intervals.

**RRMS not on DMD (is it possible? It may...) not active** - Follow-up brain imaging
  - Depends on the duration of the disease and for how long the patient is clinically & by imaging inactive and the MRI load!
  - The longer duration & lower MRI load safer to scan at longer intervals - first at 6 - 12, then at 18 - 24 months; and then every 3 years or until a new clinical episode occurs.


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**McDonald 2010 - MRI diagnostic criteria**

**DIS - Dissemination in space**
- ≥ 1 T2 lesions in ≥ 2 regions of the following CNS areas
  - juxtaocular
  - periventricular
  - infratentorial
  - spinal cord

**DIT - Dissemination in time**
- ≥ 1 asymptomatic Gd enhancing lesion/s in the initial MRI
- New T2 lesion/s (GdØ) on follow-up MRI

*Polman et al, Ann. Neurol. 2011*
McD 2010 MS diagnostic MR findings – DIS
juxtacortical & periventricular & post fossa & spinal cord

1. Juxtacortical
2. Periventricular
3. Post fossa
4. Spinal cord

McD 2010 MS diagnostic MR findings – DIT*

DIT – Dissemination in time
- ≥ 1 asymptomatic Gd enhancing lesion/s in the initial MRI
- New T2 lesion/s (Gd-Ø) on follow-up MRI

*Polman et al, Ann. Neurol 2011

MS suggestive MR findings
Gadolinium enhancing lesions

Open ring pattern
Nodular enhancement

MS suggestive MR findings
Gadolinium enhancing lesions

Ring pattern
Nodular enhancement

McD 2010 MS diagnostic MR findings
spinal cord lesions

Spinal cord lesions

MR findings in MS
"black holes!"

(T1) black holes
MR findings in MS
"cerebral atrophy"

Severe atrophy of the corpus callosum

2001/07, 35, M; New Dx
Sx: Visual blurring
EDSS: 1

2001/OT, 35, M; SPMS
On DMD since 03/02
at 10 yrs: EDSS: 6
2015 EDSS: 6.5

An update on MRI criteria for the diagnosis of MS the 2016 MAGNIMS consensus guidelines

We propose an increase in the number of lesions necessary to confirm involvement of the periventricular area from one to three, and to add an additional cardinal CNS location, the optic nerve.


An update on MRI criteria for the diagnosis of MS the 2016 MAGNIMS consensus guidelines

Clinically MS & MR consistent with MS

A young man with dizziness, numbness in hands and T2 lesions on MRI

32, M admitted because of dizziness & numbness in hands
he receives an MRI diagnosis (radiologic report) of MS.
The clinician agrees with this diagnosis and starts a DMD!
A year later continues to describe the same symptoms - no change on MRI
But accepted as a non-responder (!) and his DMD is changed
About another year later he comes for another opinion to our center...
Neuroexam normal; MRI unchanged; CSF normal no OCBs
Further work up including vasculitis/collagen disease panel & serology all normal

Not all white spots seen on MRI are MS!!!
Lesions are bilateral & semi-symmetrical & largely subcortical

Patient was seen again about 3 years later in Apr 2014 because of dizziness and tension type headache - he was fine over the years with the exception of a few episodes of dizziness closely related to life events! He was given duloxetine in 05.2014 and responded well. His neuro-exam is normal and a f/up MRI done on 02/15 was unchanged

Follow up MRI: no change - no enhancement - no atrophy - no T1 Black holes
No posterior fossa and no spinal cord lesions

A young man with dizziness, numbness in hands and T2 lesions on MRI

His final diagnosis is not MS
or any other significant neurologic disease
This individual is someone who turns out to have
"NSWMA - nonspecific white matter abnormalities" on his MRI
He also has an anxiety disorder and a tendency for somatization
His MRI changes are unlikely to be related to his symptoms
or to any other disorder
He was overdiagnosed with MS
and received unnecessary treatments

Difficulties in MS diagnosis by MRI

• Never rely on a radiologist's report (whom you don't know!)
• A clinical neurologist should understand neuro-imaging and be able to read what MRI abnormalities may say...
• When you are not sure about what MRI abnormalities may mean, then find a good neuroradiologist (whom you trust) to consult...

MRI possibilities and pitfalls in MS diagnosis
RIS & CIS & MS
Other inflammatory demyelinating disorders
MRI mimics of MS

MS diagnosis by MRI
clinical diagnosis should come first!

• the interpretation of MRI abnormalities and the imaging differential diagnosis always should be based on "clinical grounds" (Hx & Sx & signs)
• The clinical impression and diagnosis comes first!
  ➢ imaging/MRI and all other lab tools should be used to confirm or to exclude a clinical diagnosis!
• The MRI may lead you to a clinical diagnosis, only when it’s highly suggestive of a certain disease (i.e. MS) and when your mind isn’t clear clinically!

A young man with dizziness, numbness in hands and T2 lesions on MRI
The Spectrum of MS and related disorders

<table>
<thead>
<tr>
<th>MS sub-clinical phenotypes</th>
<th>MS variants</th>
<th>MS related disorders*</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIS</td>
<td>Tumefactive MS</td>
<td>ADEM</td>
</tr>
<tr>
<td>CIS</td>
<td>Balo's</td>
<td>NMO / NMOSD</td>
</tr>
<tr>
<td>SAMS</td>
<td>Marburg's</td>
<td>aMOG-related syndromes</td>
</tr>
<tr>
<td>SAPMS</td>
<td>Schilder's?</td>
<td>Others -Ab unknown? - atypical CNS inflammatory disorders?</td>
</tr>
<tr>
<td>RRMS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2°PMS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPMS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Other inflammatory demyelinating disorders

MRI possibilities and pitfalls in MS diagnosis

Other inflammatory demyelinating disorders

- Acute disseminated encephalomyelitis (ADEM)
- Multiple CNS large lesions with simultaneous enhancement
- Neuromyelitis optica spectrum disorders (NMO/NMOSD)
- Single symptomatic spinal lesion - long / LETM & nonspecific lesions
- MOG-Ab related inflammatory demyelinating syndromes
- ADEM-suggestive lesions / multiple spinal lesions!
- Idiopathic transverse myelitis
- Single symptomatic spinal lesion - short / no other lesions
- Isolated - idiopathic ON
- Single symptomatic optic nerve lesion / no other lesions

Pink Flags!!!

MRI - possibilities and pitfalls in diagnosis of MS differential diagnosis

Neuro-imaging

In a patient, in whom the clinical symptoms are suggestive of MS
The MRI may disclose
- A normal study
- Atypical findings
- MS suggestive findings
- Findings fulfilling MS criteria
- Non-MS pathology (i.e. vasculopathies; neoplastic disorders...)

MRI - possibilities and pitfalls in diagnosis of MS differential diagnosis

Neuro-imaging

In a patient, in whom the clinical symptoms are not suggestive of MS
The MRI may disclose
- MS suggestive findings
  - incidental - it may be RIS!
  - consider re-taking a detailed Hx - it may be MS!
**MRI - possibilities and pitfalls in diagnosis of MS**

"think twice"

In an individual with MRI abnormalities suggestive of MS:

- MRI findings atypical for MS - less likely to be MS
- Very small lesions (<3 mm)
- Absence of ovoid lesions
- Absence of posterior fossa & corpus callosum lesions
- Peripheric - subcortical - localization of white matter lesions rather than periventricular
- Symmetrical/semi-symmetrical lesions
- Unproportionally large corpus callosum lesions

**Another young man with T2 lesions on MRI**

A young man with non-significant neurologic symptoms gets an unnecessary MRI scan that reveals the below lesions - then he receives a diagnosis of MS, is given IVMP and suggested to go on long term treatments!

Follow up MRI x 3 - over 3 years
- no change - no enhancement - no atrophy - no T1 black holes
- No posterior fossa and no spinal cord lesions
- Most lesions are subcortical, semi-symmetrical and frontal

**Semi-symmetrical semi-specific white matter lesions**

**CADASIL**

*Characteristic MRI lesions in the ant temporal & frontal poles, U-fibres, the basal ganglia, external capsule, lesional regions and lacunar-like infarcts within the corona radiata and SC regions.

*Frequent sparing of corpus callosum and cerebellum

**MS and its mimics**

Unproportionally large corpus callosum lesions

**Susac's syndrome**

Clinical triad
- Encephalopathy, Retinopathy, Hearing

**Susac's Syndrome**

*It is an autoimmune endotheliopathy affecting the precapillary arterioles of the brain, retina, and inner ear

*Remacle et al. / Journal of the Neurological Sciences 2010

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*Remacle et al. / J Neurol Sci 2010*
**MRI - possibilities and pitfalls in diagnosis of MS**

*think twice*

MRI abnormalities which may cause further confusion?
- MRI findings - not to be mistaken as MS lesions
  - large and multiple "perivascular spaces"
  - vascular lesions (e.g., venous developmental anomalies) may be mistaken as enhancing demyelinating lesions
  - stable, punctate, patchy, and diffuse nonenhancing white matter lesions with relatively few touching the ventricles should be considered indeterminate

In an individual with MRI abnormalities suggestive of MS?
- Neurological imaging - MRI - atypical / unexpected in MS
  - No change in successive MRIs - all MRIs are the same!
  - No gadolinium enhancement in any MRI
- Family members with similar / identical MRIs!
  - Up/downward (edematous) extension of large brainstem les.
  - Lesions with prominent mass effect
  - Longitudinally extensive optic nerve lesions ≠ chiasmal involv
  - Longitudinally extensive spinal cord lesions
  - All possible in MS, but other diseases should be R/o first!

**MS and its mimics - intraaxial (CNS) NBS***
Up/downward extension of large brainstem lesions

* NBS Neuro-Behcet Syndrome

**MS vs NBS - differential diagnosis***

<table>
<thead>
<tr>
<th>MS</th>
<th>CNS - NBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>MRI</td>
</tr>
<tr>
<td>- PV &amp; SC lesions (+++)</td>
<td>- PV &amp; SC lesions (+)</td>
</tr>
<tr>
<td>- BS lesions: small, discrete, extension (-)</td>
<td>- BS lesions: large, diffuse, extension (+)</td>
</tr>
<tr>
<td>- spinal cord lesions (±)</td>
<td>- spinal cord lesions (±)</td>
</tr>
<tr>
<td>- CSF</td>
<td>- CSF</td>
</tr>
<tr>
<td>- Inflammatory changes (-)</td>
<td>- Inflammatory changes (+)</td>
</tr>
<tr>
<td>- OCB (-) (&gt;90%)</td>
<td>- OCB (-) (&gt;20%)</td>
</tr>
</tbody>
</table>

* Siva & Saj. J Neurol, 2009

**MS and its clinical and MRI masquerades**

Cerebral vasculopathies, which may mimic MS both clinically and on MRI!
- CADASIL
- Susac
- Fabry
- PCNSA
- Neuro - Behcet
- SLE
- Sjogren

These are disorders seen uncommonly either some of their clinical or MRI features will be atypical for MS!
MRI possibilities and pitfalls in MS diagnosis
“Tumefactive lesions” when they may be MS and when not?

Tumefactive lesions

What could they be?
- Brain neoplasms
- CNS lymphoma
- Abscesses
- PML
- Vasculitic disorders & NBS!
- Tumefactive demyelinating lesions (TDL)

Clues to the diagnosis of TDL include*
- Less mass effect than expected for their size
- Open ring enhancement
- No increased perfusion
- Visualisation of veins coursing through the lesion

*Taschier 2014

Tumefactive lesions - MS or not?

Tumefactive demyelinating lesions are well-demarcated, hyperintense on T2, hypointense on T1-wMRI. Ring enhancement with Gd is characteristic, open ring, the open portion abuts the GM of the cortex (or BG). Size of the lesion (>20mm), the relative lack of mass effect, and edema are helpful radiological findings.

Tumefactive lesions - MS

“Tumefactive MS” lesions may be seen with other MS suggestive lesions when the diagnosis becomes easier. However, it should be kept in mind that MS and brain tumors although highly unlikely may be seen together in an unfortunate individual.

MS and its MRI mimics - multifocal glial tumors

MS and its mimics - multifocal glial tumors

Brain biopsy: multifocal glioma
### MRI possibilities and pitfalls in MS diagnosis

**multiple brain lesions**

**Multiple CNS lesions +/- enhancement**
- Metastatic tumors
- CNS lymphoma
- Acute disseminated encephalomyelitis (ADEM)
- (HIV related) CNS toxoplasmosis
- CNS tuberculosis
- CNS cystisercosis
- CNS hydatid cysts
- Other CNS infections

### Other inflammatory demyelinating disorders

**ADEM** is an acute monophasic disease with poly-symptomatic presentation that generally includes encephalopathy. It requires early anti-inflammatory treatment, whereas long-term immunomodulatory therapies are considered unnecessary due to the self-limiting nature of the disease.

**Acute Disseminated Encephalomyelitis**

- MRI shows diffuse, poorly demarcated, large, >1-2 cm lesions involving predominantly the cerebral white matter
- The subcortical and deep white matter is more often affected than periventricular regions
- Lesions are not oriented perpendicular to the lateral ventricles
- All lesions have same age - show simultaneous enhancement
- One third of cases show additional cord lesions
- Lesions are new - there are no black holes
- Deep grey matter (thalamus, basal ganglia) lesions may be seen
- No new MRI findings after 3 months of the incident ADEM

**Acute Disseminated Encephalomyelitis**

- MRI possibilities and pitfalls in MS diagnosis
- Other inflammatory demyelinating disorders

- Acute disseminated encephalomyelitis (ADEM)
- Multiple CNS large lesions with simultaneous enhancement
- Neuromyelitis optica spectrum disorder (NMOSD)
- Single symptomatic spinal lesion - long / LETM & nonspecific lesions
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- Single symptomatic optic nerve lesion / no other lesions

**Acute Disseminated Encephalomyelitis**

- MRI shows multiple relatively large edematous WM lesions with simultaneous enhancement.

**Acute Disseminated Encephalomyelitis**

- MRI shows diffusion, poorly demarcated, large, >1-2 cm lesions involving predominantly the cerebral white matter.

**Acute Disseminated Encephalomyelitis**

- MRI shows multiple relatively large edematous WM lesions with simultaneous enhancement.

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13.10.2005

13.10.2005

13.10.2005

13.10.2005
MRI possibilities and pitfalls in MS diagnosis

- Longitudinally extensive optic nerve lesions with/without chiasmal involvement
- Neuromyelitis optica spectrum disorder (NMOSD)

Other inflammatory demyelinating disorders - NMOSD

- Much of the optic nerve
- A trend to more posterior involvement of the optic nerve including chiasm
- Simultaneous bilateral disease

Kim et al. Neurology 2015

41 F; with recurrent ON
05/2012 painful L-ON
limited improvement with IVMP
05/2013 painful R-ON
MRI - enhancing longitudinal optic nerve lesion extending to chiasma
CSF-OCB (-); AQP-Ab (+)

Neuromyelitis Optica - optic nerve imaging

MRI - possibilities and pitfalls in diagnosis of MS

“think twice”

In an individual with parenchymal spinal MRI abnormalities suggestive of inflammatory pathology, possibilities are:

- When it is a “small spinal cord lesion” (<3 segments)
  - MS
  - Transverse myelitis
  - Short segment or recovering NMO / NMOSD – myelitis
  - Myelitis associated with systemic vasculitic or collagen tissue disorders
  - Tumors (i.e. astrocytoma; ependymoma)
  - Infectious disorders

MRI - possibilities and pitfalls in diagnosis of MS

“think twice”

In an individual with parenchymal (intra-axial) spinal MRI abnormalities suggestive of inflammatory pathology, possibilities:

- When it is a “longitudinally extensive spinal cord lesion” (>3 segments)
  - NMO / NMOSD – myelitis
  - Transverse myelitis
  - MS – multiple small lesions in contiguity suggestive of a single LETM lesion
  - Myelitis associated with systemic vasculitides & collagen tissue disorders
  - Spinal venous dural fistula
  - Tumors (i.e. astrocytoma; ependymoma)
  - Infectious disorders (i.e. viral, tbc, lyme)
  - Granulomatous disorders (i.e. Sarcoidosis)

Longitudinally extensive spinal cord lesions suggestive of NMO

widespread Gd enhancement
MRI possibilities and pitfalls in MS diagnosis

Other inflammatory demyelinating disorders - NMOSD

MS - Spinal cord lesions
- do not extend over more than three vertebral segments
- are eccentric / laterally located (on axial images)
- may have focal (nodular or peripheral) gad-enhancement

NMOSD - Spinal cord lesions
- extend over more than three vertebral segments
- are centrally located (on axial images)
- may have patchy or long-extensive gad-enhancement
- bright spotty cord lesions
- short segmental lesions, may be seen at onset and during periods of recovery
- if present other CNS lesions are nonspecific

MOG-Ab+ related inflammatory demyelinating syndromes

NS, 49 F - 29 01 2007 Dx. APS & SLE & MS? NMOSD? AQP4-Ab all times negative
Rx with oral AC + mycophenolate mofetil (MMF) + GA - stable
MOG-Ab recently was detected (+)
No specific pattern
To be suspected in pts with ADEM-like lesions or Tumefactive lesions or in pts with no or atypical cerebral lesions and multiple spinal cord lesions ± dorsocaudal LETM

Longitudinally extensive spinal cord lesions
2° to dural fistules

NS, 49 F - 29 12 2006 Dx. APS & SLE & MS? NMOSD? AQP4-Ab all times negative
Rx with oral AC + mycophenolate mofetil (MMF) + GA - stable
Longitudinally extensive spinal cord lesions

MRI possibilities and pitfalls in diagnosis

Inflammatory granulomatous disorders - Neurosarcoïdosis

Neurosarcoïdosis
- Basal meningitis / Leptomeningeal enhancement in about 40%
- Hydrocephalus
- Hypothalamic involvement and/or pituitary fossa involvement
- Parenchymal - non-specific lesions - areas of increased T2 signal with or without enhancement at SC and/or PV regions
- Intraparenchymal lesions exhibit Gad enhancement that persists without treatment!
- Sarcoid myelitis can be longitudinally extensive. Root involvement as well as linear and/or nodular enhancement along the surface of the spinal cord ± intramedullary extension suggests sarcoidosis

MRI possibilities and pitfalls in MS diagnosis

Inflammatory granulomatous disorders - Neurosarcoïdosis

Neuromyelitis Optica - Area postrema involvement

A.G. 18y F
- 03/2015 develops nausea and vomiting with hiccup:
  - Hosp in gastro clinic! No Dx!
  - Discharged without improvement,
  - Develops numbness, itching, burning sensation and allodynia in extremities and part of body
  - Lhermitte & tonic spasms!!
- Neuro - first time; MR+
- AQP4-Ab (+++)

MR lesions in NMO/NMOSD are closely correlated with aquaporin-4 expression

Strange looking brain abnormalities!

Neuromyelitis Optica

Brain lesions were detected in 36 patients (60%)
Most were non-specific, but 6 patients (10%) had MS-like lesions, usually asymptomatic.
Another 5 patients (8%), mostly children, had diencephalic, basal brain, periventricular or cortical lesions, typical for MS
Strange looking brain abnormalities!
NMO & NMOSD

Cortical and leptomeningeal involvement in NMO - rare but possible
“Cloud-like enhancement” on postcontrast T1W images - as multiple patchy enhancement with blurred margin in adjacent regions

MRI possibilities and pitfalls in MS diagnosis
Other inflammatory demyelinating disorders - NMOSD

Distinction of AQP4-Ab+NMOSD & MS brain lesion distribution
Brain lesions
- 100% patients with RRMS
- 63% of the patients with NMOSD
- 27% of the pts with NMOSD fulfilling Barkhof DIS criteria
Distinguishing RRMS from NMOSD
- at least one T2 PV lesion in both the inf temp lobe WM and adjacent to the body of the lateral ventricle (MS+)
or
- either a juxtacortical U-fiber-shaped lesion or an ovoid lesion perpendicular to the lateral ventricle - Dawson finger (MS+)

*Matthews et al Neurology 2013

No MRI finding should be interpreted independent from the clinical presentation
There is only one exception! The “Radiologically Isolated Syndrome”

MRI possibilities and pitfalls in MS diagnosis
Other inflammatory demyelinating disorders - NMOSD

Distinction of AQP4-Ab+NMOSD & MS brain lesion distribution
Brain lesions
- 100% patients with RRMS
- 63% of the patients
- 27% of the pts with NMOSD fulfiling Barkhof DIS criteria
Distinguishing RRMS from NMOSD
- at least one T2 PV lesion in both the inf temp lobe WM and adjacent to the body of the lateral ventricle (MS+)
or
- either a juxtacortical U-fiber-shaped lesion or an ovoid lesion perpendicular to the lateral ventricle - Dawson finger (MS+)

PV T2 lesions
Dawson fingers (avoid lesions perpendicular to the lateral ventricle)
Juxtacortical U-fiber-shaped lesions
Lesions are highly suggestive of MS

*Matthews et al Neurology 2013

Radiologically Isolated Syndrome - dx criteria*

Barkhof criteria for DIS - 3 of 4:
≥9 T2 lesions or 1 Gd+
≥3 PV / ≥1 PF / ≥1 JC

No clinical symptoms or signs suggestive MS
At least 3/4 Barkhof criteria for DIS
MRI criteria for RIS should we need to update it according to the new McDonald 2010 criteria?

MRT anomalies not associated with any other known disease or in any other reason
MRT abnormalities not attributed to any inflammatory process or to any other reason

Okuda et al Neurology, 2009
A 37F patient presents with non-specific neurologic symptoms & non-specific white matter abnormalities on MRI. She has received a number of DMD over many years. "Radiologically Isolated Syndrome" improving radiological diagnosis!

All pts whose condition was eventually diagnosed as MS had central veins visible in the majority of brain lesions at baseline. T2W7-T MRI had 100% positive and negative predictive value for the diagnosis of MS. Clinical application of this technique could improve existing diagnostic algorithms.

* Mistry et al. JAMA Neurol. 2013

Subclinical - incidental lesions on MRI in young people what else to think?

MRI possibilities and pitfalls in MS diagnosis

MRI mimics of MS

Single gene disorders that share clinical & radiologic characteristics with MS
- lysosomal storage disorders
- neurometabolic disorders
- various mitochondrial diseases
- several other miscellaneous disorders


ZC, 26 F
Attacks of visual & sensorial aura, followed by a migrainous headache
In some aura without headache
Past family Hx: Mother alive/well & HT
Father A/Well - has migraine
Sister A/Well - has migraine

Work-up?
TTE / TEE to R/o - PFO & ASA
Doppler
R/o embolic showers!
**MRI possibilities and pitfalls in diagnosis**

Single gene disorders sharing clinical & radiologic characteristics with MS

Presence of the following findings - not suggestive of MS...
- Symmetrical WM involvement of the cerebral hemispheres
- Cerebral involvement limited to long tracts (post int cap & brain stem)
- Spinal cord involvement limited to long tracts - longitudinal lesions
- TI hyperintensities of thalamic pulvinar
- T2 (symmetric) hyperintensities of dentate nucleus
- Multiple cystic cavitations
- Absence of the following findings - not likely in MS...
  - Lack of ovoid lesions
  - Lack of spinal cord involvement
  - Lack of Gad-enhancement (exception - adrenoleucodystrophies)

*Weisfeld-Adams et al. Brain, 2015*

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**MS and Its Masquerades**

32 F: Admitted with a diagnosis of MS!

Hx: Subacute onset of weakness in both legs at age 30. Paraparesis progressing to significant gait difficulty over a month; then shows a fluctuating course with limited progression + affected with major depression.

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**MS and Its Masquerades**

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**MS and Its Masquerades**

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**MS and Its Masquerades**

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**MRI possibilities and pitfalls in MS diagnosis**

This is a group of rare multisystem disorders caused by a variety of genetic defects affecting the mitochondrial metabolism

- Multisystem involvement
- Clinical presentation
- A positive family history
- Cortical & deep gray matter involvement in a non-vascular pattern
- Asymmetrical or symmetrical white matter non-specific involvement
- Calcified cerebral lesions might be the clue

Leber’s hereditary optic neuropathy, chronic progressive ophthalmoplegia and mitochondrial encephalomyelopathy, lactic acidosis and stroke-like episodes (MELAS) might be difficult to distinguish radiologically from MS

---

**MRI possibilities and pitfalls in diagnosis**

Shortcomings that may lead to erroneous diagnoses in patients who are suspected to have MS

- MRI examinations -that- are nonstandardized and often of inadequate quality
- scans -that- might be read by radiologists lacking expertise in this field and without consideration of relevant clinical and laboratory data
- the simplified and less-restrictive McDonald's 2010 MRI criteria -that- might compromise diagnostic specificity leading to overdiagnosis

*Rovira et al. Nature Reviews Neorlogy, 2015*

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**Incorrect MRI reports and its consequences**

Incorrect radiological-MRI reports
- False T1 Gd+ lesions
- Incorrectly reported additional T2 lesions
- Overreadings...

Such incorrect reports may result in unnecessary IVMP treatments and/or inappropriate DMT switches!!

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**MRI possibilities and pitfalls in diagnostic mitochondrial disorders**

- Multisystem involvement
- Clinical presentation
- A positive family history
- Cortical & deep gray matter involvement in a non-vascular pattern
- Asymmetrical or symmetrical white matter non-specific involvement
- Calcified cerebral lesions might be the clue

Leber’s hereditary optic neuropathy, chronic progressive ophthalmoplegia and mitochondrial encephalomyelopathy, lactic acidosis and stroke-like episodes (MELAS) might be difficult to distinguish radiologically from MS
Problem areas in MRI diagnosis of MS

Technical
- Having f/up MRI studies at different centers / with dif MRs
- Lack of standardization of MRI studies
- Lack of knowledge of MS MRI protocols at the study centers
- Different slice thicknesses / different sequences
- Application of Gd-contrast at low dose
- Scanning without waiting after giving the Gd-contrast media

Incorrect MRI evaluations – radiologist related causes
- Lack of knowledge – lack of proper training
- Lack of experience
- Overload of work – too many MRI reports / too little time
- The non-professional understanding of "I will report everything I see - or I think I see - and will leave it to the clinician to decide what they are!"

Problem areas in MRI diagnosis of MS

Incorrect MRI evaluations – neurologist related causes
- Not looking to the images – just reading the report!
- Not interpreting the MRI her/him-self, lack of neuroradiology training!
- The unfortunate changes in the healthcare and educational systems, in which the "patient centric evaluation and care" understanding is losing grounds or completely forgotten!

Not likely to be MS!

Normal CSF & (-) OCBs ⇒ think twice!
Normal MRI* ⇒ unlikely to be MS
Normal MRI & CSF ➢ can’t be MS!!!

*MRI of brain and spinal cord

Abnormal CSF ⇒ (+) OCBs not always MS!
Abnormal MRI ➢ not always MS
or not clinically significant "MS!"

The other side of the coin!
Differential diagnoses: Blood and CSF biomarkers in the diagnostic process

Finn Sellebjerg

Danish Multiple Sclerosis Center, Department of Neurology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Introduction

Although widely used in the diagnostic process, blood biomarkers are not included in current diagnostic criteria for multiple sclerosis (MS). In the Poser criteria for the diagnosis of MS, which preceded the currently used McDonald criteria, laboratory support for the diagnosis could be provided by the finding of intrathecal IgG synthesis by cerebrospinal fluid (CSF) analysis. Today CSF analysis is still used to support the MS diagnosis, especially in patients with a progressive onset of disease, although the use of CSF analysis has clearly decreased with the development of modern imaging criteria for the diagnosis.

Diagnostic criteria for MS

- Poser, Ann Neurol 1983
  - “The manifestations of the disease must be shown to be characteristic of MS and not attributable to another condition”
  - Dissemination in space
  - Dissemination in time
  - Laboratory support (IgG oligoclonal bands or increased production of IgG)

Conensus criteria for CSF analysis

The most consistent CSF feature of MS is the presence of intrathecal synthesis of IgG, which can be detected in at least 90% of patients. The detection of IgG oligoclonal bands by isoelectric focusing and immununodetection is the most sensitive method, and is preferred over quantitative methods, i.e., IgG-index and intrathecal IgG synthesis rate calculations. IgG oligoclonal bands are also a
common finding in patients with neuroinfections or inflammatory diseases, and may be an unexpected finding in some 5-10% of controls without neurological diseases. Thus, the isolated detection of IgG oligoclonal bands should not prompt extensive diagnostic investigations. Lack of oligoclonal bands are considered a “red flag” which should lead to reconsideration of the diagnosis. However, the 5-10% of MS patients without oligoclonal bands do not show major differences in clinical disease course compared to oligoclonal bands negative patients. Furthermore, some patients who are initially oligoclonal bands negative may develop oligoclonal bands on follow-up.

Minor increases in CSF mononuclear cell counts are often observed, especially in younger patients, whereas the CSF protein content and the CSF-serum glucose ratio is usually normal. Thus, CSF cell counts > 50 cells/µl, the presence of granulocytes in the absence of blood contamination, an increase in CSF protein concentration above 1 g/l or a markedly increased CSF-serum albumin concentration quotient, and a low CSF-serum glucose ratio are also considered “red flags” which may indicate an alternative diagnosis such as infection, sarcoidosis or lymphoma.

---

**Recommended Standard of Cerebrospinal Fluid Analysis in the Diagnosis of Multiple Sclerosis**

A Consensus Statement

Mark S. Freedman, MS, MD, FRCP; Edward J. Thompson, DSc; Florian Dischehammer, MD; Gavin Giovannoni, PhD; Gay Grimsley, PhD; Geoffrey Kett, PhD; Sven Olhman, PhD; Michael K. Racke, MD; Mohammad Shatie, PhD; Christian J. M. Sindel, MD, PhD; Finn Solberg, MD, PhD, DMSc; Wallace W. Trelleto, MD, PhD

- IgG oligoclonal bands (isoelectric focusing and immuno detection)
  - Nearly 100% of patients, 5-10% of controls
- Some increase in CSF leukocyte count (mononuclear cells)
  - Rarely > 50 cells/µl
- Rarely increased CSF protein (> 1 g/l) or CSF-serum albumin quotient
- Normal CSF-serum glucose ratio

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**Table 2. Sensitivity and Specificity of Isoelectric Focusing for Multiple Sclerosis**

<table>
<thead>
<tr>
<th>Source</th>
<th>Total No. of Patients</th>
<th>No. of Patients With MS</th>
<th>Sensitivity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kochkin et al.</td>
<td>1114</td>
<td>58</td>
<td>105</td>
</tr>
<tr>
<td>McLean et al.</td>
<td>1007</td>
<td>82</td>
<td>99</td>
</tr>
<tr>
<td>Olman et al.</td>
<td>558</td>
<td>112</td>
<td>94</td>
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<tr>
<td>Beer et al.</td>
<td>189</td>
<td>98</td>
<td>87</td>
</tr>
<tr>
<td>Paulson et al.</td>
<td>44</td>
<td>28</td>
<td>81</td>
</tr>
</tbody>
</table>

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**Freedman, Arch Neurol 1983**

**CSF analysis in diagnostic criteria**

As mentioned above the Poser criteria allowed for “laboratory support” for diagnosing MS. Laboratory support allowed for a diagnosis of “laboratory-supported definite MS” in patients where evidence of either dissemination in time or dissemination in space was lacking (Poser 1983).
In the original McDonald criteria the term “laboratory support” was omitted, but the presence of intrathecal IgG synthesis was still used to support the diagnosis in cases where the imaging findings did not fulfill the strict criteria for dissemination in space in the original criteria (McDonald 2001). Furthermore, intrathecal IgG synthesis was mandatory for the diagnosis primary progressive MS (PPMS).

**McDonald criteria**

- **McDonald criteria**
  - 2000 (McDonald, Ann Neurol 2001)
    - Some role for CSF analysis in RRMS diagnosis
    - Mandatory for PPMS diagnosis
  - 2005 (Polman, Ann Neurol 2005)
    - No role for CSF analysis in RRMS diagnosis
    - Included in criteria for PPMS diagnosis
  - 2010 (Polman, Ann Neurol 2011)
    - Maintained in criteria for PPMS diagnosis
In the 2005 revision the combination of imaging criteria and CSF analysis was no longer used in the general criteria (Polman 2005). Furthermore, intrathecal IgG synthesis was no longer mandatory for the PPMS diagnosis, but was included in the criteria along with brain and spinal cord imaging findings. In the 2010 revision the presence of intrathecal IgG synthesis is still one of the three criteria used to support the diagnosis PPMS (Polman 2011).

**McDonald criteria 2010 revision**

<table>
<thead>
<tr>
<th>PPMS May Be Diagnosed in Subjects With:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. One year of disease progression (retrospectively or prospectively determined)</td>
</tr>
<tr>
<td>2. Plus 2 of the 3 following criteria⁴:</td>
</tr>
<tr>
<td>A. Evidence for DIS in the brain based on ≥1 T2⁰ lesions in at least 1 area characteristic for MS (periventricular, juxtacortical, or infratentorial)</td>
</tr>
<tr>
<td>B. Evidence for DIS in the spinal cord based on ≥2 T2⁰ lesions in the cord</td>
</tr>
<tr>
<td>C. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)</td>
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*Polman, Ann Neurol 2011*

**Ruling out alternative explanations**

Perhaps the most important factor in the diagnostic process is ruling out alternative explanations. Already in the Poser criteria, it was emphasized that in patients with a typical age at onset, typical symptoms, and typical findings at the neurological examination, the skilled neurologist would often find diagnosing MS quite simple. Thus, in an otherwise healthy young woman of Northern European ancestry with a history of previous optic neuritis now presenting with an internuclear ophthalmoplegia, the diagnosis of a demyelinating disorder should be obvious. Conversely, in a young woman of Eastern Mediterranean ancestry with a history of arthralgia and oral ulcerations, the same presentation with internuclear ophthalmoplegia would immediately suggest the diagnosis Behçet’s disease. Although the CSF analysis and imaging findings should discriminate between these diagnoses, it is important to emphasize that it is often the clinical setting and imaging findings that should suggest alternative diagnoses rather than CSF or blood biomarker studies.
In an extensive effort an international panel previously developed a scheme for MS differential diagnoses as an aid in the diagnostic process (Miller 2008). This scheme provides a set of clinical and imaging “red flags” and suggests alternative diagnosis for a large number of settings. The panel also suggested a diagnostic process, which should lead to classification of patients either into the category prototypic MS (including clinically isolated syndromes), other demyelinating disorders, or non-demyelinating diseases.

**Ruling out alternative explanations?**

- Often unlikely with typical age, symptoms, MRI and CSF findings
- Vascular disorders
  - Stroke, vasculitis
- Hereditary diseases
  - Episodic, e.g., CADASIL
  - Progressive, e.g., SCA or HSP
- Metabolic/toxic diseases
  - Copper or vitamin B12 deficiency
- Inflammatory diseases
  - Neuro lupus, sarcoidosis, Behçet’s, paraneoplastic disease
- Infectious diseases

**MS differential diagnosis**

Miller, Mult Scier 2008
Blood biomarkers in the diagnostic process

It should be clear that it is not necessary to use extensive blood biomarker screening in each and every patient presenting with typical symptoms, signs and imaging findings suggestive of MS. On the other hand, most clinicians would probably request a standard battery of tests which would also be needed for establishing baseline conditions, e.g., normal leukocyte counts and liver function tests, before the initiation of disease-modifying therapy. Additional analyses can then be added to this battery, but this should be guided by the clinical context and imaging findings as well as the results of the CSF analysis as rare differential diagnosis might otherwise be missed.

Blood tests for differential diagnosis

- Routine blood tests (hematology, liver, thyroid, kidney)
- Serology depending on clinical context
  - E.g., varicella-zoster virus, HIV, HTLV-1
- Autoantibodies?
  - Anti-aquaporin 4, anti-myelin oligodendrocyte glycoprotein (MOG)
  - Anti-nuclear antibodies, anti-cardiolipin, etc...
- Other tests
  - E.g., B12, angiotensin-converting enzyme
- Genetic testing depending on clinical context
- Baseline tests for disease-modifying therapy

References


