The Diagnosis Of Multiple Sclerosis

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There is no path gnomonic or perfect laboratory test which may be used in isolation to reliably diagnose MS.

The key to correct diagnosis is typicality.

The duck test is important, (is this a duck, it looks like a duck, walk like and quacks like a duck, then it is probably a duck.)
Question One

- What is the most common mistake during MS diagnosis?

- The most common mistake during MS diagnosis is a false positive attribution that is making a diagnosis of MS in patients who don’t have MS. Often this error is the result of uncritical or causal reliance on MRI without appropriate clinical correlation.
62 patients assessed by general neurologists and reassessed by other general neurologists using Mc Donald’s criteria and found 51% of MS patients were not confirmed.

Mc Hugh et al Multiple sclerosis 2008,14:81-85
<table>
<thead>
<tr>
<th>Initial symptom</th>
<th>Time to MS diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980-1984</td>
<td>7 y</td>
</tr>
<tr>
<td>1985-1989</td>
<td>5.3 y</td>
</tr>
<tr>
<td>1990-1994</td>
<td>3.7 y</td>
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<tr>
<td>1995-1999</td>
<td>1.8 y</td>
</tr>
<tr>
<td>&gt; 2000</td>
<td>0.63 y</td>
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Marie et al Neurology 2005,65;1066-1070
Question 2

- What is the definition and gold standards in the diagnosis of MS?

1- Evidence of dissemination in space (multifocality).

2- Evidence of dissemination in time (recurrent attacks or steady progression).

3- No better explanation to account for signs and symptoms.
Clinically isolated syndromes are not MS.

This could be optic neuritis, myelitis, or brain stem dysfunction. CIS is not MS. This is very analogous to first attack of convulsions.

CIS may or may not evolve to MS. This depends on follow up using McDonald's criteria (paraclinical MRI evidence).
ACIS = Atypical clinically isolated syndrome
Like parasthesias or clumsiness.

Some suggested the use of early treatment in MS and some types of CIS
Frahman et al Arch. Neurol. 2006; 614-618
Question 3

- What are the Mc Donald's criteria?
- The first or ground floor, without which the structure can’t exist, is the clinical assessment (history, neurologic examination the goal of which is:
  1. DIS (dissemination in space)
  2. DIT (dissemination in time)
  3. NBE (no better explanation)

  Schmacher et al Ann NY acad sci 1965 , 12:522-568
  Poser et al , Neurosurg, 2004; 106 : 147-158.
Definition of MS attack according to Mc Donald's 2001:

1. Clinical event of type seen in MS.
2. Event lasts at least 24 hours.
3. Objective findings must be present.
4. The event shouldn’t be pseudo attack (temporary worsening due to fever or infection)
5. The onset should be at least 40 days after onset of previous attack.
6. Single paroxysmal attack eg muscle spasm is not countable, but multiple paroxysmal events occurring over a period of 24 hours.
A patient who presented with ON, experience a second attack one month later (DIT) with bilateral INO (DIS) and there are no atypical features (NBE).
Revised (2005) Mc Donalds criteria for (DIS) and (DIT)

A-DIS  at least 3 of the following must be present
1- At least one gadolinium enhancing lesion or nine T2 hyperintense lesions. 2-At least one infratentorial lesion
3-At least one juxta cortical  
4- At least 3 periventricular.

NB one spinal lesion  may be used to fulfill criteria
1+2.Spinal lesions at least 3 mm in size ,less than 2 vertebral segments occupying only part of the cross section of spinal cord .CSF oligoclonal bands  and 2 typical MRI lesions can establish the diagnosis of MS
The presence of new lesion (gadolinium enhanced) not corresponding to site implicated with initial event if the scan done 3 months after the event.
MRI Lesions similar to MS.

- 1-SLE
- 2- SJOGREN S
- 3- SARCOIDOSIS
- 4- ADEM
- 5- ANTIPHOSPHOLIPID ANTIBODY SYND
- 6- LEBER OPTIC ATROPHY
- 7- CADASIL
- 8- SUSAC SYNDROME
- 9- USHER SYNDROME
- 10- VIT E DEFICIENCY
- 11- LYMPHOMA
SUSAC SYNDROME

Was first described in 1975 sufferers often experience personality changes and bizarre and develop paranoid behavior. Speech can be affected and many experience severe headaches and migraine. Some hearing and visual loss which might correct itself in a matter of 5 years. Diagnosis MRI multifocal supratentorial lesions most lesions are small ones 3-7 mm which might affect grey matter and show meningeal enhancement which never found in MS NOR ADEM. Pathogenesis vasculitis, hypercoagulable, or viral infection. Treatment hyperbaric o2, ivig, iv steroids
 usher syndrome

- Is a leading cause ion is of deaf blindness is an autosomal recessive condition. The vision is described as doughnut vile vision where central and peripheral visions are spared while impaired in an annulus around central vision. Three types were described: 1&2 are born with disease while 3 acquired loss of vision and hearing. Treatment gene therapy.
Question 4

What are the best clinical keys for MS diagnosis?

A- Typical time course of an attack of MS. Usually the attack takes a gradual progressive course with peak at 3-4 weeks with gradual decline and recovery at 6 weeks differing from epilepsy and migraine attacks which resolves in 24 hours.
- B-Typical history
- Using schumacher criteria 1965 involving DIT, DIS, and NBE.
C- Red flags

This means negative criteria diagnosing NOT MS.

1- Neurological red flags.

2- Genetic red flags.

3- Psychiatric red flags.

4- MRI red flags.
1- Neurological red flags.

- Absence of eye signs like ON, or INO
- Absence of clinical remission.
- Absence of sensory finding or bladder disturbance.
- Localized disease in one brain region.
- Absence of typical CSF changes

2-Genetic red flags.

- Family history of MS (first degree relative)
- Early age of onset (less than 15 years old)

Natawicz and Bejjani, Am. J. Genetics, 1994;46 149-169
3- Psychiatric red flags.

- Marked disproportion of psychiatric symptoms relative to objective neurological signs.
- Prior history of major psychiatric illness

- Parson GW, South Med J 1969;89;301-304
4- MRI red flags

MRI finding

- Think over

Brain

Symmetrical lesions → ADEM, or adult leukodystrophy

Absent activity on → ADEM or chronic meningitis

Serial scans

Infarcts → SLE, lacunes

Predominant juxta → small vessel disease.

Cortical lesions

Normal brain MRI in spite → Neuromyelitis optica

Severe cord and optic nerve lesions
- Spinal MRI  
  - Think over
- More than 3 segments  
  - NMO, SS, ADEM,
- TS myelitis
- Diffuse posterior column  
  - vit B 12 def,
- acquired cu def
- Meningeal enhancement  
  - Susac syndrome
- primary CNS angitis
- Behcet, Lymes, sarcoid
Question 5

- Is the population suspected to have MS are homogenous?
- In fact the population suspected to have MS constitute a heterogeneous groups many of them will ultimately be found to have MS, and some of whom may have other neurological diseases which mimic MS.
Stratification of MS suspected into subgroups on basis of typicality.

- **Group 1**: finding typical of MS. MS is likely a diagnosis.
- **Group 2**: atypical with normal finding's is very unusual
- **Group 3**: atypical with minimal definite findings, MS is possible
- **Group 4**: atypical with major unusual findings, wide DD
Example of group 1

- Female 18 y, presented with rt eye pain and blurring of vision she was diagnosed as ON and treated with steroids and recovered partially in one month. Two y later (DIT) she developed over a period of week RT UL parasthesia and weakness with spontaneous resolution over a month (DIS) on /ex severe optic atrophy, brisk DTR RT side with bilateral subtle ataxia. MRI numerous T2 periventricular hyperintesties (NBE). Disease modifying therapy was initiated (DMT) in the form of interferons.
Example of group 2

- Female 28 y she underwent hysterectomy for cervical dysplasia 2 days later she developed weakness and shooting pains in her LLs. Work up was negative and she recovered completely in 6 weeks with physiotherapy. Succeeding 5 y she continued to experience transient non specific pains, mental stress, fatigue, cramps, tingling in non anatomical patterns. Her past medical history was notable for depression and fibromyalgia and bimonthly severe occipital headache which was not associated with nausea or vomiting or scintillating scotomata. Assessment by her primary neurologist revealed NAD all investigations were negative apart from some white spots (punctuate) in the left cerebrum.
Example of group 3

- (possible or probable MS) a male 27 y, noted electric like shocks on neck flexion, these symptoms recurred for 2 months and stopped but recurred again at the age of 33y (DIT). His past medical history showed transient left arm pain at age of 30y with notably no specific diagnosis. Significantly, his family history revealed documented MS in older sister and perhaps in mother. Comment essentially this gentleman presents with recurrent lehermitte sign and strong FH. Over the course of one decade he had no major progression this remained possible due to lack of (DIS) and lack of objective neurological signs. Finally at age of 37y he developed sub acute sensory loss in LLs and CSF was +ve and MRI was classic of MS he received pulsed steroids with good response and he started DMT.
Example group 4

- Atypical patient presents with major but unusual finding here other neurological disease is possible.
Question 6

- What are the MS variants?
- 1- Neuromyelitis optica NMO
- 2- Tumefactive MS (tumor like course)
- 3- Fulminate acute MS (Marburg)
- 4- Balo concentric sclerosis.
- 5- Myelinoclastic diffuse sclerosis (Schilder disease)
NMO is considered when patient presents acutely with severe bilateral optic ON for the first time or presenting with unusually severe myelitis, MRI head minimal atypical changes, spinal MRI shows longitudinal more than 3 segments extensive lesion. and CSF shows +ve monoclonal bands in 25% and +ve autoantibody NMO IgG with sensitivity of 73% and 90% specificity and is directed against aquaporin water channels present on astrocytic foot process. CSF also shows granulocytic increase rather than lymphocytic increase. It has bad response to DMT.
Question 7

- What is the role of lab in MS?

- 1- Screening tests like MRI, cbc, ANA, vit b 12, RPR (rapid plasma reagin for syphilis)

- 2- CSF for oligoclonal bands, IgG index and synthesis, VER, SS-A, SS-B, SER, ANCA, anticardiolipin, lyme serology, thyroid function, serum antibodies in NMO, serum copper in case of unexplained myelopathy, serum long chain fatty acids, DNA, for cadasil, aryl sulphatase and ACE for sarcoidosis.
Accuracy of MRI

- Application of MRI according Mc Donald's criteria has yielded high sensitivity of 75% and specificity of 85% for prediction of CDMS during approximately 2 years of observation for patients with CIS. ANN (2003) published guidelines for the use of MRI in diagnosis of MS. Saying that 3 characteristic white matter lesions are more sensitive predictor of CDMS in CIS patients than complex Mc Donald's criteria.
What are major pitfalls in MS diagnosis?

1- Atypical MS: This is CDMS with some unusual features like
   a- Acute attacks with abrupt onset.
   b- Fixed relationship to menses
   c- Late onset
   d- Prominent cognitive, or psychiatric symptoms early in disease
2- Inconvenient MS.
Where MS patient has only one inconvenient lab test e.g. very high ANA in the absence of rheumatologic disease, or CSF with marked pleocytosis.

3- Partial MS. These cases represent intermediate between CIS and CDMS.
THANK YOU