Clinical Case Study Discussion of Demyelinating Diseases

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August 6, 2011
• No financial disclosures

• Will discuss use of non-FDA approved medication
CONTENT

• Case 1- discuss current diagnosis criteria and treatment options
• Case 2- discuss current diagnosis criteria and treatment options
• Case 3- discuss differential diagnosis
• Case 4- discuss differential diagnosis
Case 1

- 26 yo F was evaluated initially in 2001. She awakened with blurry vision in left eye (almost no vision) and pain in left eye. Was treated with iv steroids and vision improved over the next month. On examination she had hyperreflexia.

- Brain MRI showed multiple-T2 hyperintense lesions, with one lesion enhancing with Gad in right centrum semiovale

- As prior history she reported numbness in legs for one year, but she was not evaluated at that time

- She refused CSF analysis

- Labs: ANA, sed rate, ACE, Lyme Ab: negative.
What is the diagnosis?

What treatment should be considered?
DIAGNOSIS- 2010 McDonald

• Before a definitive dx of MS at least 1 attack must be corroborated by findings on neurological examination, VEP response in patients reporting prior visual disturbances, or MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms

• Original criteria, 2001 and 2005 are still valid

• Key changes recommended are related to use and interpretation of imaging criteria

ANN Neurol 2011; 69:292-302
DIS can be demonstrated by $\geq 1$ T2 lesion in at least 2 of 4 areas of CNS:

- Periventricular
- Juxtacortical
- Infratentorial
- Spinal cord

-Gad enhancement of lesions not required for DIS
-If subject has a brainstem or SC syndrome, the symptomatic lesions are excluded
DIAGNOSIS- 2010 McDonald

• MRI Criteria for DIT

DIT can be demonstrated by:

1. A new T2 and/or Gad-enhancing lesions (s) on follow up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI

or

2. Simultaneous presence of asymptomatic Gad-enhancing and non-enhancing lesions at any time
• It was considered a clinical isolated syndrome with high probability to develop multiple sclerosis and was offered to start Avonex based on CHAMPS study results.

What choices for treatment will she have based on diagnosis made by 2010 Mc Donald criteria?
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<th>DMA</th>
<th>Indication</th>
<th>Dose</th>
<th>Frequency</th>
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<tr>
<td>Interferon beta-1a</td>
<td>RR, CIS</td>
<td>30µg IM</td>
<td>QW</td>
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<td>44µg SC</td>
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<td>250µg SC</td>
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<td>(Betaseron, 1993)</td>
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<td>Glatiramer acetate</td>
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<td>Natalizumab</td>
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<td>300mg IV</td>
<td>Q4W</td>
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<td>(Tysabri, 2004)</td>
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<td>Mitoxantrone</td>
<td>worsening RR, SP</td>
<td>12mg/m²IV</td>
<td>Q3M</td>
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<td>(Novantrone, 2000)</td>
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<tr>
<td>Fingolimod</td>
<td>RR</td>
<td>0.5mg PO</td>
<td>QD</td>
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<td>(Gilenya, 2010)</td>
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Case 1-continuation

• She had one relapse in 2001 and intermittent new symptoms

• A repeat brain MRI in 2002 showed new enhancing lesions

What will be the next step in treatment?
Case 1-continuation

- Assess for compliance
- Check neutralizing antibodies
- Change DMT?
Case 1-continuation

- 2003 started Rebif

- 2004 two episodes of diplopia, pleural empyema and another episode of vertigo for which she took oral steroids

- 2005 had 3 exacerbations (increased dizziness, episode of numbness in extremities)
  Brain MRI showed more lesions, some Gad+
Case 1-continuation

• Assess for compliance

• Change DMT? What options?
Case 1-continuation

- 2008 continued to have multiple enhanced lesions
- 2009 switched to Copaxone
- Continued to have episodes of exacerbation and brain MRI showed new enhancing lesions
Case 1-continuation

- Assess for compliance

- Change DMT? What options?
Case 1-continuation

- Started on natalizumab in November 2009
- Had another exacerbation 2 month after starting natalizumab
- 6 month MRI showed numerous enhancing lesions
Case 1-continuation

• What to do at this point?
Case 1-continuation

- CSF negative for PML
- Anti-natalizumab Ab were present
- Had two more relapses
- Tysabri was stopped

Any other option for treatment?
Case 1 - continuation

- Patient refused to go back on any injectable medication, although had less relapses on Copaxone, refused mitoxantrone
- Had a few relapses and monthly solumedrol was used
- Repeat MRI showed new-enhancing lesions
- 2011 Gilenya was started

Case 2

51 yo F with history of recurrent left and right ON (4 episodes) in the prior 4 years presented to the hospital after a fall complaining of generalized, progressive weakness and inability to empty her bladder. On examination she had a normal mental status, bilateral optic pallor on fundi examination, right upper extremity wrist drop, strength in LE was 0/5, and a sensory level was found at T4.
Case 2-continuation

CSF analysis:

- IgG CSF 4.7mg/dL
- IgG index 0.6
- Oligoclonal bands negative
- Protein: 54, glucose 58, WBC 15 (0-5), neutrophils 17% (0-6), lymphocytes 57%

Labs: Lyme, ACE, DsDNA, ANCA, SSA/SSB, MPEV: normal
Case 2-continuation

What is the presumptive diagnosis?

Any other test?
Case 2-continuation

NMO-IgG was positive
NEUROMYELITIS OPTICA- criteria for diagnosis

NMSS task force on differential diagnosis of MS (2008):

Major criteria required, but may be separated by an unspecified interval:

1. ON in one or two eyes
2. TM, clinically complete or incomplete, but associated with radiological evidence of SC lesion extending over three or more spinal segments on T2-weighted MRI images and hypointensities on T1 when obtained during an acute episode of myelitis and no evidence for sarcoidosis, vasculitis, or other explanation

Minor criteria from which at least one must be fulfilled:

1. Most recent brain MRI must be normal or may show abnormalities not fulfilling revised McDonalds diagnosis criteria for MS
2. Positive test in serum or CSF for NMO-IgG antibodies
NEUROMYELITIS OPTICA - diagnosis

EFNS guidelines 2010:

- Course: recurrent, severe attacks of myelitis and/or uni- or bilateral ON with incomplete recovery.

- ON with severe visual loss and in rapid succession may be indicative of NMO. Complete TM is typical for NMO. Expansion of the SC lesion may lead to brainstem symptoms and life-threatening complications.

- The most characteristic MRI finding is a spinal cord lesion expending over three or more vertebral segments on T2-weighted images, occupying most of cross-sectional are, frequently hypointense on T1-weighted images and displaying Gad+.

- CSF findings with a lymphomononuclear pleocytosis >50 cells/µl, occasional presence of neutrophils/eosinophils, and lack of OCB may be indicative of, but not specific for NMO.

- Testing for NMO-IgG antibodies is an important element in work-up of NMO and NMO spectrum disorders
Case 2-continuation

What treatment will you consider at this time?
Patient was started on IV methylprednisolone 1 g X5 days. There was no improvement and plasmapharesis was considered next. During the first plasmapharesis session patient became diaphoretic, systolic BP was 72. Treatment was aborted.

IVIG was next considered and after IVIG was finished, patient was continued on prednisolone and started on azathioprine.

Patient was discharged to rehab. Exam on discharge: Alert, Ox3, CN II - XII intact except optic nerve atrophy, RUE 3/5 except wrist extensor 1/5, LUE 4/5, LE B/L 0/5, sensory level at T4, not ambulating.
Case 2-continuation

• Patient was discharged 3 months later from rehab, wheelchair bound.

• 4 month later she was able to use a walker for short distances.

• 3 month later she was using a cane and bilateral AFO for ~30m. Prednisone was slowly tapered down over the next few months.

• 3 month later she was able to walk with cane for ~100m, and was stable on azathioprine and 5mg prednisone. Prednisone was stopped after another 2 months due to weight gain.

• One month later patient had an episode of ON.

What to do next?
Case 2-continuation

• Receive IV solumedrol X5 days and azathioprine was increased to 125mg.

• Continued prednisone 10mg and azathioprine. Over the next 4 month her walking improved at the point that she was not using any more the wheelchair for longer distances. Strength was 5/5 in LE with exception of right hamstring and bilateral toe dorsiflexion +4. Prednisone was stopped at patient request.

• 4 years later patient remains stable, using a cane for walking outside home, no further exacerbations, and continues with azathioprine.
Neuromyelitis optica- treatment

• No clinical trials have been conducted

• Therapeutic recommendations are based on case series

• Relapse therapy:
  - high dose IV methylprednisolone
  - plasma exchange (2 to 5 courses)
  - IVIG

• Prevention therapy:
  - early and maintenance immunosuppressive treatment
  - azathioprine
  - mycophenolate mofetil, methotrexate
  - mitoxantrone
  - anti-CD20 treatment (rituximab)
Case 3

• 57 yo F presented to discuss Copaxone treatment for recent diagnosis of multiple sclerosis

• Her initial symptom was ~ 3 years ago. She reported slurred speech for 30 seconds. 2 ½ years ago she developed “spells”. All the spells were similar: “she hears a conversation in her head followed by a hissing sound and then pain on top of her head”. A spell will last a few seconds, but she may have multiple spells at night. Examination was normal.

• Had EEGs, cardiac work up which were negative

• A brain MRI showed extensive white matter abnormalities mostly in the right hemisphere.
Case 3-continuation
Case 3-continuation

What to do next?
Case 3-continuation

• She had CSF analysis:
  - normal IgG, IgG index, no oligoclonal bands
  - myelin basic protein 1.13 (upper limit 1.10)

• 6 months repeat brain MRI was stable

• Labs: B12, folate, Sjogrens Ab, Lyme Ab, ACE, ANA in normal limits
Case 3-continuation

Does she have multiple sclerosis?
Case 4

• 63 year old women presented for second opinion on dx of demyelinating disease.

• In December developed dizziness and inability to stand up. Was evaluated in ED and was told that she has depression.

• In January was found to be confused by family members. Was admitted to a hospital for a few days and was told that she has seizures. Was started on Keppra.

• In March was admitted to HFH because she continued to have episodes of confusion and episodic difficulties with speech. On EEG she had “Frequent broad based sharp wave discharges over the left hemisphere, usually with fronto-temporal maximum that appeared almost quasi-periodic in sleep” felt to be an expression of localization-related epilepsy.
Case 4-continuation

PAST MEDICAL HISTORY
Hypertension.

PAST SURGICAL HISTORY
Cholecystectomy, splenectomy after an MVA in 2004.

FAMILY HISTORY
Father with diabetes. Grandmother with diabetes. There is no neurological disease in her family.

SOCIAL HISTORY
She stopped smoking in 2004. She stopped drinking in January. She was drinking 2 glasses of wine a day. She does not have children. She is single.

NEUROLOGICAL EXAMINATION
Patient is alert, oriented to time, place, and person. Her speech is scant, but fluent. She is not able to give a good history of her present illness. CN intact with exception of left naso-labial fold flattening. Normal tone, normal strength. Vibration slightly decreased in toes. She has tremor in her arms and legs upon extension, but at times seems to have a few beats of asterixis. She has mild dysmetria for finger-to-nose and mild-to-moderate dysmetria for heel-to-shin. Reflexes normal. Truncal and gait ataxia upon standing and walking. Needs bilateral assistance for walking.
Case 4-continuation

• MRI brain showed: numerous multifocal foci of T2 hyperintensity identified throughout the cerebral white matter bilaterally. Additional areas were seen within the left temporal lobe primarily at the subcortical white matter junction as well as within the pons bilaterally. No enhancing lesions.
Case 4-continuation

- CSF: protein 58.1 (upper normal 55), glucose normal, IgG CSF normal
- IgG index 1.1 (upper normal 0.7), WBC 13 (0-5), lymphocytes 94%
- 4 or more oligoclonal bands present
- cytology negative for malignant cells

- Labs: Lyme, ACE, ANA normal
Case 4-continuation

What to do next?
Does she have multiple sclerosis?
Thank you