Case 3: Multiple Sclerosis (MS)

Ms. Murielle Plum is a 38-year-old woman whose neurological problems first began in college. At that time, she developed ascending numbness and weakness from her feet upward. Eventually, over several weeks, her arms became weak as well, and she developed pins-and-needles sensations in all her limbs. Her chest felt “frozen” and there was a tight, band-like sensation across her torso. Recovery from this episode was essentially complete but took more than six months. In retrospect, she had had a six-week episode in high school in which she developed loss of sensation in both feet; this had resolved spontaneously.

Several years later, she had a six-to-eight-week episode of blurry vision in her left eye, which caused particular trouble with her ability to remain steady while walking. There was no pain behind the eye, but merely blurriness of vision in the left eye. The right eye appeared normal.

In her early 30’s, she began noticing problems with word-finding. Sometimes she would come up with the wrong word, or have trouble writing or spelling a word. Over time this has persisted and continues to be a problem currently.

In 2002, she developed a loss of dexterity and temperature sensation in her hands bilaterally, as well as a “frozen” feeling in her chest and abdomen, all worsening over a couple of weeks and resolving spontaneously over several weeks more.

Between 2006 and 2008, she developed several recurrences of neurological problems: First she developed decreasing hearing in the right ear, decreased balance, and a weak left leg. The following year she noticed severely decreased dexterity of the hands, left worse than right. She was treated with intravenous methylprednisolone and improved. Similar symptoms recurred the following month and she was treated again and recovered partially with the same methylprednisolone treatment. Two months later she developed left leg weakness, treated similarly. In June 2009, loss of dexterity of the left hand recurred.

Over these recent years, she did not return entirely to normal functioning after each of these episodes; instead, she would accumulate persistent neurological problems that would not completely resolve after each exacerbation. In 2011 now she continues to be troubled by decreased dexterity in the hands, left worse than right; burning dysesthesias in the hands, helped by cooling the hands; word-finding and naming difficulties; a spastic gait with left leg weakness and footdrop; exertional fatigue; and occasional slurring of speech.

The most prominent trigger for her worsening neurological symptoms is heat; the summer is typically quite difficult for her, and sometimes the sensory symptoms in her upper extremities have been relieved by application of ice.
Patient Exam:
Social history: Ms. Plum is from the South Shore of Massachusetts originally and currently lives in Brookline with her husband. She is a sales representative for a large pharmaceutical company. She has no history of cigarette smoking, illicit drug use, or excessive alcohol.

Neurological examination:

Mental status: No abnormalities of cognition, language, prosody, or behavior noted.

Cranial nerves: Visual acuity was intact (with correction) in both eyes. Color vision was intact in both eyes. Pupils were 4 mm and reactive, bilaterally, but a relative afferent pupillary defect was seen in the left eye. Both optic discs were pale. Pursuit and saccadic eye movements were intact. Other cranial nerves were all intact.

Motor: No atrophy, fasciculations, abnormal movements, or abnormal posturing were noted.

- In the right upper extremity, no spasticity was noted and strength was full. In the left upper extremity, there was some spasticity seen and slight weakness of wrist extension and intrinsic hand muscles.

- Both lower extremities showed signs of significant spasticity. Other movements were full strength.

Reflexes: There were hyperactive reflexes in both upper extremities at brachioradialis and triceps and in addition, on the left, in biceps. Both patellar reflexes were hyperactive. The right ankle jerk was hyperactive and on the left there was clonus at the ankle.

- Babinski sign was present on the left but not on the right. The Babinski sign can indicate upper motor neuron lesion constituting damage to the corticospinal tract.

Sensory: Sensation to light touch, position sense, pinprick, temperature, and vibration were normal.

Coordination: Finger-to-nose movements demonstrated moderate left and mild right dysmetria. Heel-to-shin testing revealed mild dysmetria bilaterally. Rapid alternating movements were performed poorly on both sides, worse on the left.
Hospital tests and results: (1) Imaging:
(2): Laboratory Data

2a- Cerebrospinal fluid (CSF) analysis:

<table>
<thead>
<tr>
<th>Appearance of fluid</th>
<th>Clear, colorless</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cells (per mm$^3$)</td>
<td></td>
</tr>
<tr>
<td>Red</td>
<td>41 first tube, 1 last tube</td>
</tr>
<tr>
<td>White</td>
<td><strong>13</strong></td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>68</td>
</tr>
<tr>
<td>Protein (mg/dl)</td>
<td><strong>83</strong></td>
</tr>
<tr>
<td>Albumin (mg/dl)</td>
<td>24.7</td>
</tr>
<tr>
<td>Stained smears</td>
<td>No tumor cells or microorganisms</td>
</tr>
<tr>
<td>Culture</td>
<td>Negative (remained sterile)</td>
</tr>
</tbody>
</table>

2b- Protein electrophoretic pattern: oligoclonal bands present. IgG Index: 2.1
(3) Clinical Electrophysiology

Visual evoked potentials were performed. (Stimulus is a flash of light & evoked potential is recorded by electrodes placed on the scalp over the posterior part of the head.) Visual evoked potentials are used to measure conduction along the visual pathways in response to visual stimuli presented to one eye at a time.

Right: normal $P_{100}$ (Latency: 100 ms; Amplitude: 10μV).

Left: slow and reduced in amplitude.
**Diagnosis:** Multiple Sclerosis

**Treatment:**
Currently she takes intravenous methylprednisolone every two months, extended-release tolterodine, clonazepam, and recently started natalizumab infusions.

Past medications tried include beta-interferon 1a, beta-interferon 1b, azathioprine, modafinil, gabapentin, and baclofen.

She is in discussions with her physician to possibly join new clinical trials for Avonex or Daclizumab.
Session 1: Case presentation (including diagnostics and treatments)
- Two students will present the case and discuss the diagnostics (points 1-3)
- Two students will be assigned to go over the treatments (see point 4-5 below)

1. What is MS?

2. Compare and contrast: different types of MS

3. Diagnostic tools:
   - Western blots
   - CSF analysis
   - MRIs
   - New diagnostic tools?

4. Treatments
   - methylprednisolone
   - interferon treatment
   - monoclonal antibodies

5. In the pipeline- clinical trials
   - clinical trials and pipeline drugs

Session 2: Our understanding of the molecular basis for MS

- One student will be assigned to go over the genetics MS
- Two student will be assigned to go over the animal models, have we learned anything?
  Are they useful for new therapies? There are many from fish to non-human primates

Points to cover in this session:
   - genetics involved, the role of genetics in MS
   - the focus on the discussion should be on the animal models and the ways to study the disease. There are many models, one that has historically been favored: why? Is this still the best way to model the disease?

Session 3: Where to go next from what we know

All 8 students will brainstorm: if they were going to work on this disease what would they do next, what are novel targets/therapies to examine?

Points to discuss in this session: What is MS and what are the causes? Neurodegeneration vs Autoimmune disease

*Note: there are a lot of unknowns in the field of MS, identifying them and discussing how to attack the problem should be the main part of the discussions.*

   - New therapeutics should also be discussed here as there are a lot in the pipeline.
• MS is traditionally viewed as autoimmune disease that leads to neurodegeneration, recently more scientists are considering the opposite view and considering MS’s causes as neurodegenerative leading to BBB break and immune infiltration.
• Role of the BBB in MS: what happens to it?
• These should also be discussed: can a different perspective lead to novel breakthroughs?
• The variable clinical presentation of MS and the lack of diagnostic laboratory tests lead to delays in diagnosis and the impossibility of predicting diagnosis
• The need for biomarkers that distinguish between medication responders and nonresponders
References:

General articles about MS:


• Multiple sclerosis
  Alastair Compston, Alasdair Coles


Genetics of MS:


Treatments:
• Long-term follow-up of clinical trials of multiple sclerosis therapies.
  Freedman MS.

• Therapy of MS.
  Vosoughi R, Freedman MS.

• Development of biomarkers in multiple sclerosis.
  Bielekova B, Martin R.

• Functional treatments in multiple sclerosis.
  Courtney AM, Castro-Borrero W, Davis SL, Frohman TC, Frohman EM.

• Multiple sclerosis: current treatment algorithms.
  Rio J, Comabella M, Montalban X.

Animal Models:
• Experimental models of multiple sclerosis.
  Pachner AR.

  't Hart BA, Laman JD, Bauer J, Blezer E, van Kooyk Y, Hintzen RQ.

• The value of animal models for drug development in multiple sclerosis.
  Friese MA, Montalban X, Willcox N, Bell JI, Martin R, Fugger L.

• Zebrfish myelination: a transparent model for remyelination?
  Buckley CE, Goldsmith P, Franklin RJ.

• Restoring the balance between disease and repair in multiple sclerosis: insights from mouse models.
  Miller RH, Fyffe-Maricich SL.
A. History:

1. What does the episodic nature of symptoms suggest?

2. Where do you localize blurred vision in one eye only?

Pre-chiasmatic, so the eye itself or the optic nerve.

3. What is the meaning of her blurry vision affecting her ability to remain steady while walking?

Suggests a problem with ascending proprioceptive systems (dorsal columns & spinocerebellar tracts) as she is dependent upon visual cues for balance.

4. What neurological test might be appropriate?

Test for Romberg’s sign.

5. What might be the source of word finding problems?

Aphasia. Localizes to the left hemisphere.

6. What systems do her symptoms from 2006-08 invoke?

Hearing: auditory-unilateral so right cochlear nerve or nuclei (technically, pure cranial nerve lesion not expected in MS, a central demyelinating condition)
Balance: vestibular/cerebellar/proprionceptive
Burning paresthesias: spinothalamic or possibly dorsal column (which when lesioned can lead to paresthesias)
Weakness, spasticity & diminished dexterity: Cortico-spinal
Slurring of speech: cranial nerve/nuclei or cerebellar
B. Neurological Exam:

1. **What is a “relative afferent pupillary defect” and where is the lesion?**
   Normally, a pupil will constrict more prominently when directly stimulated with light than when consensually constricting in response to light shone in the other eye. Optic nerve lesions on one side will sometimes lead the ipsilateral pupil to retain ability to constrict directly and consensually, but the pupil may actually constrict less prominently to direct stimulation than consensual (an afferent defect). This is tested by swinging the flashlight from the unaffected eye to the affected eye, which leads to a paradoxical dilation of the pupil when light is swung onto it.

2. **What do the motor & reflex exams indicate?**
   Muscle, peripheral nerve & lower motor neurons intact (no atrophy or fasciculations). Spasticity and hyperreflexia suggest an upper motor neuron problem.

3. **What does the coordination testing indicate?**
   Cerebellar (or proprioceptive) involvement.

C. Imaging & Data:

1. **Identify the main structures shown in the images and the sites of the lesions.** FLAIR imaging is used because it attenuates the signal from the CSF allowing us to see the pathology in the periventricular white matter more easily.

2. **What is the significance of the CSF analysis and the protein electrophoresis?**
   Elevated white cells & protein are consistent with an inflammatory response. The oligoclonal bands are due to a spike in production of monoclonal antibodies.

   **IgG Index:** \[\text{CSFIgG} / \text{Serum IgG}] / [\text{CSF albumin} / \text{Serum albumin}] In this case it is > 0.7 and indicates there is elevation of IgG synthesis in the CNS. This is consistent with but not at all exclusive to MS.

3. **What do the visually evoked potentials indicate?**
   Slowing of nerve conduction in the left optic nerve. Consistent with demyelination.
D. Medications:

**Alteration of the Natural Course.** The primary goal of drug treatment is to alter the natural course of the disease. In MS clinical trials, this means reduction in the frequency and severity of relapses, preventing the chronic progressive phase, and slowing the progression of disability. The activity of disease seen on MRI is often used as a secondary outcome. Many different immunosuppressive and immunomodulating therapies have been evaluated, and several other studies are in progress.

- **methylprednisolone:** a dehydrogenated analogue of cortisol with the same actions and uses as cortisol. Used as an anti-inflammatory agent.

- **tolterodine:** antimuscarinic often used to relieve urinary difficulties, including frequent urination and inability to control urination

- **natalizumab:** (Tysabri) a monoclonal antibody adhesion-molecule inhibitor. The drug works by blocking the integrin molecule and preventing immune cells from migrating through blood vessels in the brain to areas of inflammation; however the specific mechanism by which it exerts its effects in multiple sclerosis have not been fully defined. Has returned to clinical use only recently after being withdrawn due to highly publicized cases of progressive multifocal leukoencephalopathy (PML), a viral infection of oligodendrocytes associated with immunocompromise.

- **beta-interferon:** interferons are a class of peptides that have antiviral and immunoregulatory functions.

- **azathioprine:** immunosuppressive agent

- **modafinil:** dopamine re-uptake inhibitor. Used to treat fatigue and to promote wakefulness.

- **gabapentin:** Used to treat neuropathic pain. Its mechanism is uncertain but likely to involve inhibition of calcium channels thereby reducing transmission.

- **baclofen:** GABA receptor agonist. Used to treat spasticity.
Appendix 1: From Netter Anatomy textbook:
Sudden unilateral blindness, self-limited (usually 2 to 3 weeks). Patient covering one eye, suddenly realizes other eye is partially or totally blind.

Visual fields reveal central scotoma due to acute retrobulbar neuritis.

Brainstem and/or cerebellar manifestations:
- Wide-based gait. Patient teeters back and forth and sideways.
- Exaggerated, repetitive knee jerk.

Spinal cord manifestations:
- Spastic gait. Patient needs help walking.
- Lhermitte’s sign: sudden sensation of electric shock down spine and along arms when patient flexes neck.