Clinical Case Discussion

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CUSOM

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CAMPBELL UNIVERSITY | Jerry M. Wallace School of Osteopathic Medicine

A 34-year-old woman presents to urgent care with complaints of left leg numbness and stiffness over the last week.

She describes awakening about a week ago feeling fatigued. When she tried to get out of bed, she had difficulty feeling her left leg. She denied weakness in her leg. She has slight difficulty walking around as a result of the leg numbness.

She is otherwise healthy. She is physically active: she runs outside most days of the week and plays soccer twice weekly at her local community center. She does admit to frequent muscle pulls. She also describes recent low back pain.

She works full time at a local bank. She is single. There is no history of tobacco, alcohol or drug abuse.

On exam, her VSS are stable. She has no spinal tenderness. Her only abnormal neurologic finding is decreased sensation to light touch over her left leg. She has 2+ left patellar and left ankle reflexes and 1+ right patellar and right ankle reflexes.

She is diagnosed with a mild herniated nucleus pulposis of the lumbar spine. She is prescribed ibuprofen 600 mg po tid and is instructed to avoid heavy lifting. Her symptoms completely resolve one week later. She has no primary physician and therefore never follows up.

Six months after her first presentation, the patient develops acute vertigo which persists over two days. On the third day of vertigo, she presents again to urgent care. She denies fevers, chills, changes in appetite or weight; headache, visual changes or focal weakness.

On exam, she has mild horizontal nystagmus but no other abnormal neurologic or general findings.

She is prescribed meclizine 25 mg po tid prn dizziness. She stays home from work for one day and by the following weekend, her symptoms have completely resolved.

Again, she never follows up.

One year after her first presentation, the patient develops lower abdominal pain; pain with urination, and a sensation of incomplete bladder emptying and goes back to urgent care.

She complains of a low grade fever and fatigue. Otherwise, she has no new symptoms. She is having regular menstrual periods. She is not sexually active.

On exam, she has mild suprapubic tenderness and a palpable bladder.

A UA shows positive leukocyte esterase, 20-30 wbc/hpf, 5-10 rbc/hpf and 2+ bacteria.

She is prescribed Bactrim for three days with resolution of her symptoms.

Two days later, a urine culture grows pansensitive E coli.

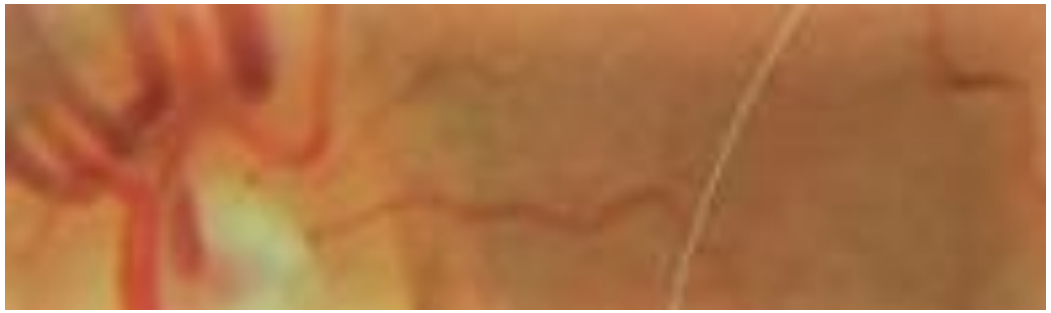
However, four days later, she has recurrent pain with urination and a sensation of incomplete bladder emptying. She returns to urgent care and is given a seven-day course of Bactrim and three days of pyridium with resolution of her symptoms.

Two years after her first presentation, the patient presents to the emergency room with decreased vision and pain in one eye. She describes waking up that morning with fatigue and seeing a "punched out" area of blackness the upper outer field of vision in her left eye. She also has mild difficulty with slurred speech.

She is admitted due to concern for stroke.

On exam, she has mildly slurred speech and decreased visual acuity in the left eye. You see a "sliver" of the optic disc with your ophthalmoscope. . .

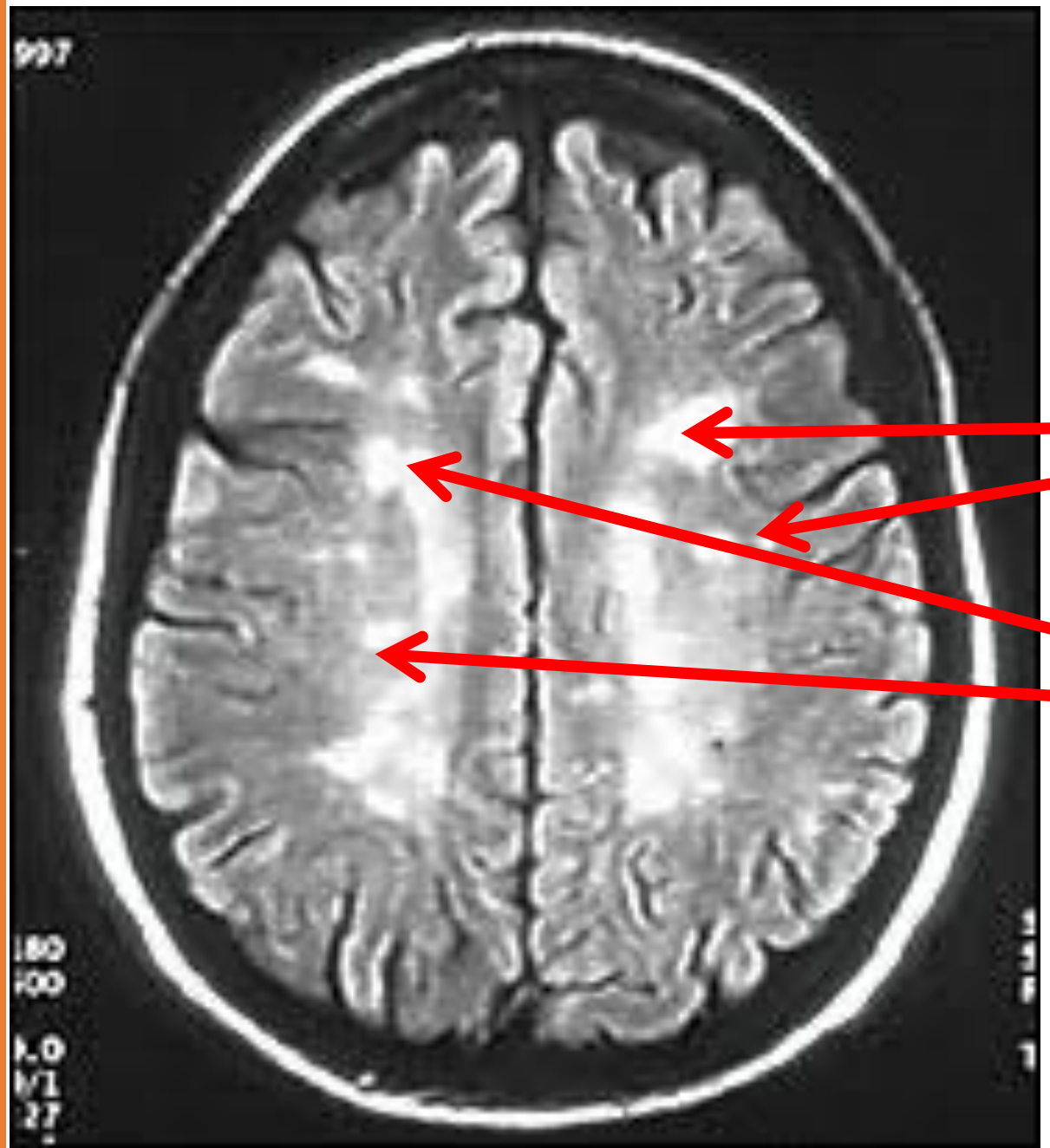
Normal fundoscopic exam



Patient's fundoscopic exam

R. Riordan-Eva, J. J. Augsburger: Vaughan & Asbury's General Ophthalmology, Nineteenth edition.

A brain MRI is performed . . .



Increased signal intensity lesions, periventricular region

aafp.org

She is diagnosed with multiple sclerosis.

She is treated with methylprednisolone 250 mg IV every 6 hours for three days. Her vision improves and she is discharged.

She follows up with a neurologist and begins maintenance therapy with Natalizumab infusions 300 mg every 4 weeks.

She has no further symptoms and returns to work full-time.

Three years after her first presentation, she presents to her neurologist with three days of worsening fatigue, gait imbalance and new onset spasticity in her left leg.

She is directly admitted to the hospital and an MS exacerbation is confirmed.

She is treated with methylprednisolone 1000 mg IV daily for 3 days. Her walking and left leg spasticity gradually improve. She is discharged home with outpatient PT/OT twice weekly.

Six weeks after her hospitalization, she is back to baseline, with no further symptoms. She continues her maintenance infusions every 4 weeks.

Clinical Definition of Multiple Sclerosis (MS)

- Immune-mediated inflammatory demyelinating disease of the central nervous system resulting in neurologic signs and symptoms separated in space and time.

Epidemiology of MS

(Cross AH, in Cecil's Essentials of Medicine, 10th Edition; Calabresi PA, in Goldman-Cecil Medicine, 27th edition)

- 600,000 to 900,000 patients in the US
- Estimated 2.3 million people affected worldwide.
- Second only to trauma as the most common cause of neurologic disability in young adults
- Most commonly presents in third and fourth decades

Epidemiology of MS

(Cross AH, in Cecil's Essentials of Medicine, 10th Edition; Calabresi PA, in Goldman-Cecil Medicine, 27th edition)

- Some patients present in the teen years or in the 50's
- 2 to 2.5 times more frequent in women than men
- Most common among people of Northern European descent

What causes MS?

(Cross AH, in Cecil's Essentials of Medicine, 10th Edition; Calabresi PA, in Goldman-Cecil Medicine, 27th edition)

- Concordance rate of MS between identical (monozygotic) twins is only 15 to 50%
- There appears to be an unidentified environmental factor
- Other risk factors: Smoking
- Other "negative" risk factors (ie. Associated with lower risk of MS)
  - High vitamin D levels
  - High levels of sunlight exposure (ie. Sunburns)

Initial Clinical Presentation of MS

(Olek MJ and Howard J, UpToDate 2024)

- Unilateral optic neuritis
  - Painful, monocular vision loss
  - Visual blurring
  - Scotoma: specific area of decreased or absent vision
- Diplopia (double vision)
  - Internuclear ophthalmoplegia
  - Cranial nerve VI palsy
- Transverse myelitis
  - Brown-Sequard Syndrome
    - One side: paralysis and loss of proprioception
    - Other side: loss of pain and temperature sensation
- Lhermitte sign
  - Electrical sensation radiating from the back to the limbs
  - Precipitated by neck flexion

Initial Clinical Presentation of MS

(Olek MJ and Howard J, UpToDate 2024)

- Bladder symptoms: Urge incontinence/urinary retention
- Bowel dysfunction
- Erectile dysfunction

Clinical Course of MS

(Olek MJ and Howard J, UpToDate 2024)

Subtype	**Characteristics**
Relapsing-Remitting 85-90% of patients	•Clearly defined exacerbations •Full or incomplete recovery •Minimal disease progression between exacerbations
Secondary Progressive	•Retrospectively diagnosed •Initially relapsing-remitting subtype •Gradual and steady worsening of disease usually 10 to 20 years after disease onset
Primary Progressive 10% of patients	Progressive accumulation of neurologic disability from disease onset

Initial Presentation of Relapsing-Remitting MS

(Olek MJ and Howard J, UpToDate 2024)

- Symptoms develop over hours to days
- Gradual improvement over weeks to months
- Improvement may not be complete
- Symptoms can be the result of one or more lesions in the CNS

Clinical manifestations of MS

(Olek MJ, Narayan RN, Frohman EM, UpToDate 2024)

Manifestation	Prevalence	Description
Sensory	Nearly 100%	•Numbness •Tingling •Tightness •Coldness
Motor: spasticity	About 85%	•Legs most commonly affected •Neck, pelvic floor, others

Clinical manifestations of MS

(Olek MJ, Narayan RN, Frohman EM, UpToDate 2024)

Manifestation	**Prevalence**	**Description**

Motor: Incoordination	About 45% (with tremor)	•Gait imbalance
		•Ocular problems
		  •Nystagmus
		  •Internuclear ophthalmoplegia
		  •Optic neuritis
		•Vertigo
		•Speech

Clinical manifestations of MS

(Olek MJ, Narayan, RN, Frohman EM, UpToDate 2024)

Manifestation	**Prevalence**	**Description**
Bladder dysfunction	75%	•Urinary retention •Urinary incontinence
Bowel dysfunction	50%	•Constipation •Stool incontinence

Clinical manifestations of MS

(Olek MJ, Narayan, RN, Frohman EM, UpToDate 2024)

Manifestation	Prevalence	Description
Fatigue	86%	•Rated as the worst symptom causing distress by 65% of patients
Heat sensitivity	60 to 80%	•Small increases in body temperature transiently worsen MS symptoms and signs

Clinical manifestations of MS

(Olek MJ, Narayan, RN, Frohman EM, UpToDate 2024)

Manifestation	Prevalence	Description
Pain	63%	•Neurogenic: burning or cold dysesthesias of feet, hands, limbs, trunk •Non-neurogenic: musculoskeletal and soft tissue
Depression	66% of patients have a affective disorder	•Contributing factors: pain, anxiety, fatigue, substance abuse, cognitive impairment

Clinical manifestations of MS

(Olek MJ, Narayan, RN, Frohman EM, UpToDate 2024)

Manifestation	Prevalence	Description
Sexual dysfunction	70%	•50% of patients become completely sexually inactive due to MS •20% of patients become less sexually active
Sleep disorders	Likely common but exact prevalence unknown	•Restless legs syndrome •Periodic limb movements in sleep •Obstructive sleep apnea

Clinical manifestations of MS

(Olek MJ, Narayan, RN, Frohman EM, UpToDate 2024)

Manifestation	Prevalence	Description
Cognitive impairment	70% when confirmed with neuropsych testing	•Attention •Executive function •Abstract thinking •Short term memory •Dementia is RARE, less than 5% of patients
Epilepsy	2-3% of patients	•Generally benign •Effectively treated with antiepileptic medication or requires no treatment

What else look like multiple sclerosis? . . .
Differential diagnosis

Differential Diagnosis of MS: Other Demyelinating Diseases (MKSAP 18;NINDS.NIH.gov)

Diagnosis	Key Points
Acute Disseminated Encephalomyelitis (ADEM)	• Can follow viral or bacterial infections, or rarely vaccination for measles, mumps, or rubella. • Rapid onset • Improves within six days in most patients • Some patients recover over months
Neuromyelitis optica (Devic disease)	• Autoimmune disease of the optic nerves and spinal cord with antibodies against aquaporin-4 channels • Brain not involved; extensive spinal cord lesions • Severe CSF leukocytosis
Idiopathic Transverse Myelitis	• Often post-infectious spinal cord inflammation

Differential Diagnosis of MS: Systemic Inflammatory Diseases (MKSAP 18)

Diagnosis	Key Points
Systemic lupus erythematosus	• White matter changes on brain MRI • Some patients have encephalopathy
Sjogren's Syndrome	• Can present like neuromyelitis optica plus with cranial neuropathies
Sarcoidosis	• Granulomatous inflammation of the parenchyma and meninges of the brain and spinal cord • May be associated with myelopathy

Differential Diagnosis of MS: Metabolic Disorders (MKSAP 18)

Diagnosis	Key Points
Adult-onset leukodystrophies	• White matter changes and progressive neurologic symptoms • Family history often present
Vitamin B12 deficiency	• Optic neuropathy • Cognitive changes • Subacute combined degeneration of the spinal cord: spasticity, weakness, loss of vibratory sensation and joint proprioception
Copper deficiency	• Myelopathy similar to vitamin B12 deficiency • Can follow gastric bypass surgery, malabsorption, excessive zinc ingestion

Differential Diagnosis of MS: Infections (MKSAP 18)

Diagnosis	Key Points
HIV infection	• Encephalopathy • Myelopathy
Lyme disease	• See above
Syphilis	• See above
Human T-lymphotrophic virus (HTLV)	• Progressive myelopathy • Thoracic cord atrophy • More common in patients living in equatorial latitudes

Differential Diagnosis of MS: Vascular disorders (MKSAP 18)

Diagnosis	Key Points

Sporadic and genetic stroke syndromes	• Hypercoagulability disorders
	• Hyperviscosity disorders
	  • Polycythemia vera
	  • Multiple myeloma

CNS Vasculitis	• Can be diagnosed by conventional cerebral angiography and biopsy • Can present with changes similar to stroke plus meningeal enhancement on contrast MRI.
Susac Syndrome	• Small vessel arteriopathy of retina and cochlea • Corpus callosum lesions on MRI

Differential Diagnosis of MS (MKSAP 18)

Diagnosis	Key Points

Migraine	• Subcortical and white matter lesions often confused with MS lesions
	• Cerebral Autosomal Dominant Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy (CADASIL)(NINDS.nih.gov)
	  • Mutation of Notch3 gene alters walls of small arteries in the brain
	  • Migraine headaches
	  • Multiple strokes
	  • Dementia
	  • Seizures
	  • Vision problems
	  • Psychiatric illness

Diagnosis of MS: History (Olek MJ and Howard J, UpToDate 2024)

- Detailed description of current neurologic symptoms, AND past symptoms which may represent unrecognized prior exacerbations.

Diagnosis of MS:
Review of associated symptoms:

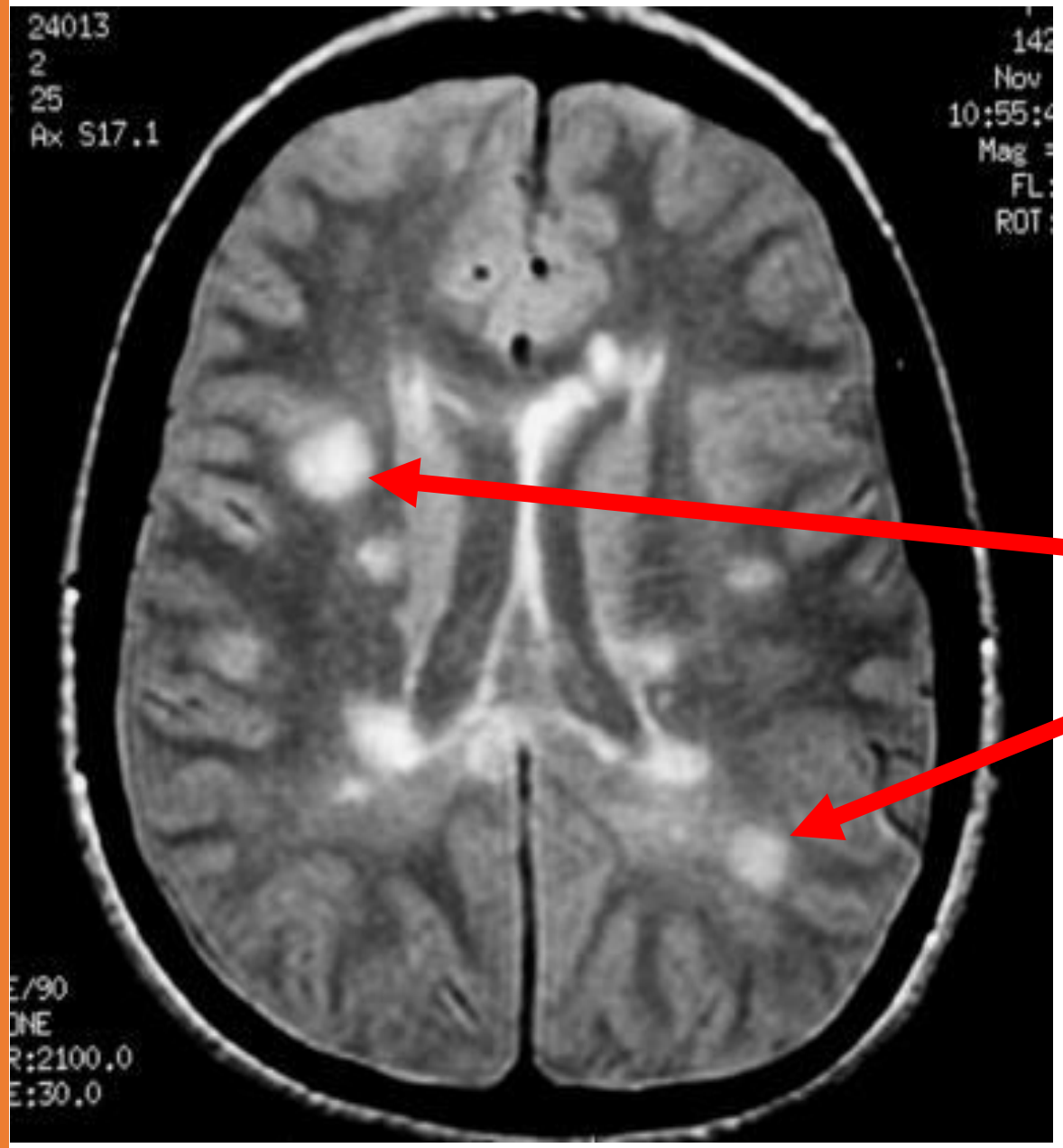
- Fatigue
- Heat sensitivity
- Bowel and bladder dysfunction
- Unexplained chronic pain (neuropathic and non-neuropathic)
- Depression
- Sleep disorder
- Sexual dysfunction
- Cognitive impairment
- New onset seizures

Diagnosis of MS: Physical Examination

- Vision
- Extraocular movements
- Spasticity
- Hyperreflexia
- Babinski sign
- Gait disturbance
- Hemisensory loss
- Paresthesias

Diagnosis of MS: Imaging

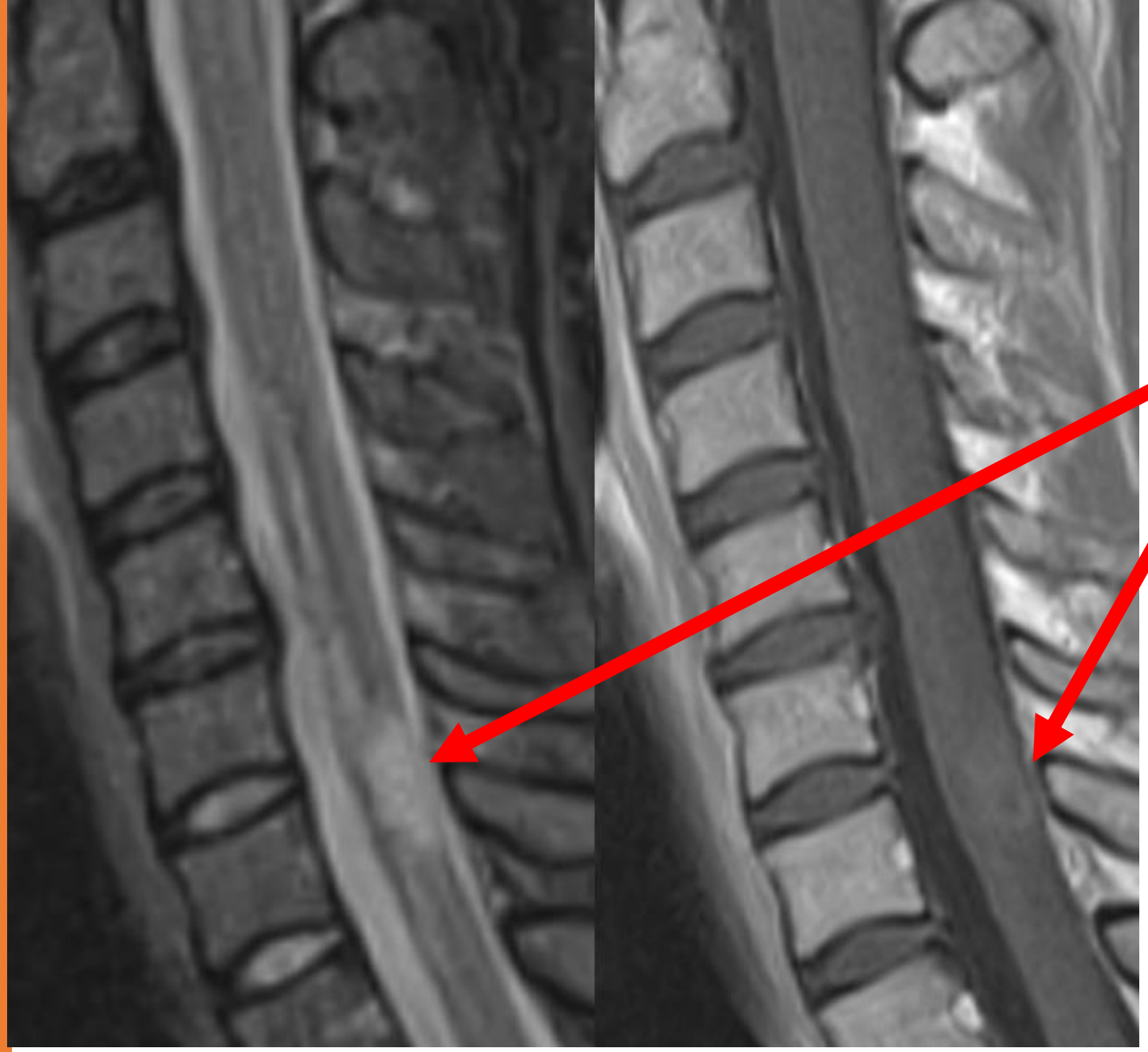
- Brain MRI with and without contrast
- Consider spinal cord MRI with and without contrast



T1 weighted image

Increased signal intensity
in the periventricular regions

emedicine.medscape.com



Similar lesions can occur in the spinal cord

clinical-mri.com

Diagnosis of MS: Laboratory and other diagnostic testing

- Often, history, physical examination and MRI findings are sufficient to diagnose multiple sclerosis.

- Lumbar puncture with CNS analysis if diagnosis remains in question.
  - Oligoclonal IgG bands: seen in 95% of patients with symptomatic MS
  - CSF appears grossly normal
  - CSF cell count
    - Lymphocyte predominant
    - < 5 wbc/mm3 seen in 33% of patients
    - >15 wbc/mm3 in 33% of patients
    - Rarely > 50 wbc/mm3. Consider a diagnosis other than MS

Diagnosis of MS: Laboratory and other diagnostic testing

- Evoked potentials
  - Detects electrical activity in the CNS after stimulation of a sensory organ (ex: eye)
  - Can detect subclinical MS
  - Autoantibody testing

Treating acute exacerbations of MS

(Olek MJ and Howard J, UpToDate 2024)

- Most commonly, patients are hospitalized for intravenous methylprednisolone therapy 1000 mg IV daily for 3 to 5 days. Consider oral glucocorticoid taper .

- Side effects of high-dose steroids: hypertension, hyperglycemia, peptic ulcer disease, psychiatric symptoms.

- If a patient has a severe MS exacerbation and does not respond well to high dose glucocorticoids, consider plasmapheresis.

Chronic Symptomatic Management of Multiple Sclerosis

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Symptomatic Management in MS

- Bladder dysfunction
- Bowel dysfunction
- Cognitive impairment
- Depression
- Gait impairment
- Heat intolerance

Symptomatic Management in MS

- Pain
- Seizures
- Sexual dysfunction
- Sleep
- Spasticity

Disease-Modifying Therapy (DMT) in Multiple Sclerosis

Disease-modifying therapies (DMT) in MS

- DMT are best-studied in relapsing-remitting multiple sclerosis (RRMS).
- DMT are NOT curative, but can decrease MS exacerbations and slow disease progression.
- DMT is typically continued indefinitely.

Disease-modifying Therapies (DMT) in MS

- Interferons
- Other biologic agents
- Immunomodulators
- Monoclonal antibodies

DMT in MS: Interferons--Mechanism of action **unknown**. Alters cell surface receptor interactions

Medication	**Dose**	**Side Effects/Toxicity**	**Cost**
Interferon beta-1a (Avonex)	30 mcg IM weekly	Fever, headache, fatigue,myalgias, depression, GI upset, leukopenia, elevated LFTs. CBC and LFTs every 6 months	Pen for IM use: $9,919.01

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DMT in MS: Interferons--Mechanism of action **unknown**.
Alters cell surface receptor interactions

Medication	**Dose**	**Common Side Effects/Toxicity**	**Cost**
Interferon beta-1b (Beta-seron)	Target 250 mg SQ every other day	Inflammation at injection site Flu-like symptoms CBC and LFTs every 6 months	300-mg dose $835.96

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DMT in MS: Glatiramer acetate: Mixture of four amino acids forming polymers antigenically similar to myelin basic protein which interferes with interactions between T-cells and myelin

Medication	**Dose**	**Common Side Effects/Toxicity**	**Cost**
Glatiramer acetate (Copaxone)	20 mg SQ daily	Injection site reactions Development of IgG antibodies Nausea Rash No monitoring needed	20-mg dose $284.56

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DMT in MS: Immunomodulators-- Sphingosine 1-phosphate receptor modulators: sequesters lymphocytes in lymph Nodes (Olek MJ and Mowry E, UpToDate 2024)

Medication	**Dose**	**Common Side Effects/Toxicity**	**Cost**
Fingolimod (Gilenya)	0.5 mg po daily	Headache Diarrhea Nausea Cough Elevated LFTs Cardiac monitoring for bradycardia after first dose; Eye exams for macular edema CBC for lymphopenia LFTs Yearly skin exam for basal cell carcinoma	0.5-mg dose $350.52

DMT in MS: Immunomodulators: Fumarates—mechanism unknown; neuroprotective, immunomodulator

Medication	**Dose**	**Common Side Effects/Toxicity**	**Cost**
Dimethyl fumarate (Tecfidera)	120 mg po bid x 7 days then increase to 240 mg po bid	Diarrhea Nausea Abdominal pain Flushing Lymphopenia Regularly monitor CBC and LFTs in first six months of therapy; then every six months	120-mg or 240-mg dose $188.90

Olek MJ and Mowry E, UpToDate 2024

DMT in MS: Teriflunomide—active metabolite to leflunomide, disrupts interaction between T-cells and antigen-presenting cells.

Medication	Dose	Common Side Effects/Toxicity	Cost
Teriflunomide (Aubagio)	7 to 14 mg po daily	Alopecia GI distress Respiratory infections Elevated LFTs Lymphopenia Peripheral neuropathy Regular monitoring of CBC, LFTs blood pressure for first six months of therapy; then every six months	7-mg or 14-mg tablet $373.83

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DMT in MS: Monoclonal antibodies—Natalizumab, against alpha-4 subunit of integrin molecules; limits adhesion and migration of leukocytes

Medication	**Dose**	**Common Side Effects/Toxicity**	**Cost**
Natalizumab (Tysabri)	300 mg IV infusion over 1 hour every four weeks	Headache Chest discomfort Hepatoxicity Infusion reactions Anaphylaxis Risk of Progressive Multifocal Leukoencephalopathy (PML) Rigorous, industry—sponsored monitoring; JC virus testing	300-mg dose $656.75

Olek MJ and Mowry E, UpToDate 2024

DMT in MS: Monoclonal antibodies—Alemtuzumab, causes depletion of CD52-expressing T-cells, B-cells, natural killer cells and monocytes

Medication	Dose	Common Side Effects/Toxicity	Cost
Alemtuzumab (Lemtrada or Campath)	12 mg IV daily x 5 consecutive days then 12 months later, 12 mg IV x 3 consecutive days	Infusion reactions/anaphylaxis Infection (ex: herpesvirus; fungal) Thyroiditis ITP Glomerular nephropathy Skin malignancy Rigorous, industry—sponsored monitoring, monthly CBC, creatinine, UA; check TSH every 3 months; yearly skin exam	12-mg dose $28,798.18

Olek MJ and Mowry E, UpToDate 2024

DMT in MS: Monoclonal antibodies—Ocrelizumab, antibody against CD20 to deplete B-cells, which leads to decreased cell-mediated cytotoxicity and decreased complement-mediated cytotoxicity

Medication	**Dose**	**Common Side Effects/Toxicity**	**Cost**
Ocrelizumab (Ocrevus)	600 mg IV every six months	Allergic infusion reactions Infections (ex: herpervirus, hepatitis B reactivation) increased risk of PML and cancer	600-mg dose $4017

Olek MJ and Mowry E, UpToDate 2024

DMT in MS and Risk of Progressive Multifocal Leukoencephalopathy (PML)

DMT associated with risk of PML	Manifestations of PML
• Fingolimod • Dimethylfumarate • Natalizumab • Ocrelizumab	• Altered mental status • Hemiparesis • Monoparesis • Limb ataxia • Gait ataxia • Hemianopia • Diplopia

Koralnik, I, UpToDate 2021

Selecting Initial Disease-Modifying Therapy for Relapsing-Remitting Multiple Sclerosis: must be individualized

Patient characteristics	Reasonable initial DMT
• Highly active disease • High value on efficacy and tolerant to risk of side effects/toxicity	• Natalizumab IV • Ocrelizumab IV
• Less active disease • High value on convenience of self-administered medication	• Oral dimethylfumarate • Oral fingolimod
• Less active disease • Highest value on safety	• Interferon beta-1a SQ • Interferon beta-1b SQ • Oral glatiramer acetate

Olek MJ and Mowry E, UpToDate 2024

Prognosis of MS

- Prognosis of multiple sclerosis is highly variable.
- Patients who have a relapsing-remitting course have a better prognosis (ie. lower risk of irreversible disability) than patients with a progressive course.
- Otherwise, there are NO other reliable prognostic indicators.

Questions?

Thank you!