NEURO-OPHTHALMIC DISEASE AND RELATED MEDICATIONS

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Dr. Kelly Malloy does not have any relevant financial relationships with a COPE defined commercial interest to disclose.
Dr. Tracy Offerdahl does not have any relevant financial relationships with a COPE defined commercial interest to disclose.

Dynamic Duos 2018
Dr. Tracy Offerdahl
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Salus University
CASE 1

It's Time For Your Eye Exam
56 year old woman

• Double vision x 1 month

• First, has a migraine like headache on the right side of her head (does not typically get migraines)
  – Tylenol did not help
  – Headache was constant
    • 10 on a 1-10 scale

• Also had watery eyes and sinus congestion
• A few days later, saw her PCP
  – Put her on antibiotic for presumed sinus infection
    • No relief
    • Headache got even worse

• The next day, the vision got blurry so she saw an eye doctor
  • No cause for blur found
• 2 days later, went to Urgent Care
  – Given Flonase and Amoxicillin
    • no relief

• Soon after, developed a bump on medial aspect of right brow
  – It scabbed and then fell off
  – Began oozing
• She then saw an ophthalmologist and was diagnosed with Shingles and elevated IOP OD
  – Was prescribed
    • Valtrex 1 gram TID x 10 days
    • Pred Forte QID OD
    • Combigan BID OD
    • Told to discontinue the antibiotics

• She already had gabapentin for spine pain
  – PCP told her to use this for the shingles related pain as well
    • Using it 2-3 x per day.
• After 3 days, she felt her vision, eye pain and headache were worsening
  – Returned to ophthalmologist
    • Told IOP was improved
    • No changes to treatment plan made

• 2-3 weeks later, she returned to the ophthalmologist
  • Switched her from Combigan to Cosopt due to cost
  • Tapered the Pred Forte from QID to BID OD

• They noted an abduction deficit, for which they referred her to a neuro-ophthalmologist
  • Instead, she presented to the ER service at TEI
• She now reports horizontal diplopia
  – Worse at distance and in right gaze
  – Closes an eye when driving
  – Sees better when she turns her head to the right
• Occasional pain in right eye
• Skin above OD is sensitive to the touch
• Last night felt “pins and needles” on right forehead
• She denies any other neurologic symptoms
Systemic History

- Hypertension
- Hypercholesterolemia
- Arthritis
- Sickle cell trait
- Kidney stones
EXAM RESULTS

• VA: OD 20/20 OS 20/20
• Color: OD 14/14, OS 14/14
• (-) RAPD, (+) LND OD
• CF: Full OU
• Exophthalmometry: OD 17 OS 17
• Palpebral Apertures; OD 8 mm OS 8mm
• **IOP**: OD 10 mmHg, OS 14 mmHg

• **SLE**: OD inferior injection, clear cornea
  – Features of tonic pupil OD
    • Stromal streaming, stromal spread, sector paralysis

• **DFE**: optic discs with distinct margins and no pallor OU
  – Cupping: OD .45/.5  OS .4/.45
## Ocular Motility

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<th>25 eso</th>
<th>8 eso</th>
<th>1 eso</th>
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<tr>
<td>6 eso</td>
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DIFFERENTIAL DIAGNOSIS

Abduction Deficit

CN VI Palsy
DIFFERENTIAL DIAGNOSIS

Abduction Deficit

- Orbit
  - Neuro-muscular Junction
    - Weakness of LR
      - Myasthenia Gravis
    - Thyroid Infiltration of MR
      - Sub-arachnoid Hemorrhage
    - Orbital Mass
  - Increased Intracranial Pressure
    - Syphilis
    - Lyme
    - Other Bacterial or Viral
      - Herpes Zoster
    - Other

- Sub-arachnoid space
  - Infections
    - Lyme
    - Other Bacterial or Viral
      - Herpes Zoster
    - Other

- Clivus
  - Inflammations
    - Autoimmune Process
    - Inflammatory Conditions
      - Sarcoid
      - GCA
      - Other

- Cavernous Sinus
  - Superior Orbital Fissure

- Brain (Pons)
  - CN VI in pons
    - NOT NUCLEUS
      - Ipsilateral CN VII
      - Contralateral Weakness
      - Contralateral Numbness
Neurologic Exam

- Cranial Nerve Testing
  - Abnormal right abduction
  - No other abnormalities
- Motor Testing
  - Normal, symmetric strength
- Sensory Testing
  - Normal sensation
- Coordination Testing
  - No ataxia
- Reflex Testing
  - Normal reflexes
DIFFERENTIAL DIAGNOSIS

Abduction Deficit

- Neuro-muscular Junction
  - Myasthenia Gravis
  - Sub-arachnoid space
  - Clivus
  - Cavernous Sinus
- CN VI Palsy
- Superior Orbital Fissure
- Vasculopathic

Sub-arachnoid Hemorrhage

- Increased Intracranial Pressure
- Infections
  - Syphilis
  - Lyme
  - Other Bacterial or Viral
    - Herpes Zoster
    - Sarcoid
    - GCA
    - Other
- Inflammations
  - Autoimmune Process
    - Other
DIFFERENTIAL DIAGNOSIS

Abduction Deficit

- Neuro-muscular Junction
  - Myasthenia Gravis
  - Sub-arachnoid space
  - Clivus

- CN VI Palsy
  - Cavernous Sinus
  - Superior Orbital Fissure
  - Vascularopathic

Sub-arachnoid Hemorrhage

- Increased Intracranial Pressure
  - Syphilis
  - Lyme

- Infections
  - Other Bacterial or Viral
    - Herpes Zoster
  - Sarcoid
    - GCA
  - Other
MANAGEMENT PLAN

• Fresnel Prism
  – 8pd BO over OD

• Work-Up (likely related to Herpes Zoster, but must rule out other treatable causes)
  – Labs
    • CBC, platelet count, ESR, CRP, Lyme titer, ANA, RPR, FTA-ABS, ANA, ACE, BUN, and creatinine
  – MRI
    • Brain and orbits with and without contrast
REMARKABLE RESULTS

ESR 27

CRP 5.74
MRI Result

• The original MRI report was unremarkable.
• We saw enhancement in the inferior temporal R orbit.

• We discussed this with the radiologist.
  – Linear enhancement noted along the right inferior lateral margins of the right orbital apex which extended back to the cavernous sinus.
  – Could represent an inflammatory process, possibly of CN VI itself.
  – Possibly from re-activation of the zoster virus, or another inflammatory process.
• Put patient back on Valtrex 1 gram TID for 3 weeks.

• Abduction deficit resolved
• Episcleritis resolved
HERPES ZOSTER
Herpes – Basic Facts and Figures

• Very common cause of human viral disease...right behind the flu and the common cold!

– 5 herpes viruses are known to infect the eye
  • Herpes simplex 1
  • Herpes simplex 2 } No longer an “above the waist” vs “below the waist”
  • *Varicella zoster*

• Epstein Barr
• Cytomegalovirus
**Herpes zoster**

- *Virus* of the varicella (chicken pox) family
- Harbored in trigeminal ganglion

- Travels along branches of the trigeminal nerve
- By axoplasmic flow

- Can spread to other cranial nerves
Herpes Zoster Ophthalmicus

- V1 affected (nasociliary branch)
  - Conjunctivitis
  - Keratitis
  - Episcleritis
  - Scleritis
  - Uveitis
  - Secondary Glaucoma
  - Cataract
  - Retinal Necrosis
Neuro-Ophthalmic Manifestations of Herpes Zoster

• Abnormal Ocular Motilities
  – Cranial Nerve Palsies
    • CN III
    • CN IV
    • CN VI

The CN palsies usually appear 2-4 weeks after initial rash
Theories why CN Palsies occur in HZ

- Direct effect of virus on neural tissue
- CNS immune response to virus
- Occlusive vasculitis induced by virus
- VZV activates another latent neuropathic virus in brain

With abduction deficit, could also be orbital myositis

Herpes Zoster with associated pupil changes or CN palsies warrants immediate neuro-imaging
HERPES ZOSTER TREATMENT
Oral Anti-Viral Agents

• Antiviral therapy most effective when started within 72 hrs of rash onset
  – Generally ALWAYS true when using an anti-viral!
Oral Anti-Virals

- 3rd generation, go into every cell but only activate in viral infected cells
  - (1st generation=mutogenic)
    * Gangiclovir
    * Valgangiclovir

- The oral agents HAVE been reclassified in the new federal pregnancy and lactation guidelines.
  - Helpful when evaluating patients!
MEDICATION FOCUS

ANTI-VIRAL
ZO VIRAX
Zovirax (acyclovir)

• Good for simplex and zoster
• Available in 200, 400 and 800 mg, IV
• Dosage: 800 mg/5 times/day (4 grams daily)
  • Poor GI absorption
• Maintenance dose: 200-400 mg bid
• Caution if impaired renal function
  • Excreted by kidneys
• Category B
MEDICATION FOCUS

ANTI-VIRAL

VALTREX
Valtrex (valacyclovir)

- Pro-drug of acyclovir
- Available in 500 and 1000 mg
- GI upset
- HSV-1, HSV-2, VZV
- Dosage: 1g tid x 1 week (3 grams daily)
- Caution if impaired renal function
- Category B
MEDICATION FOCUS

ANTI-VIRAL

FAMVIR
Famvir (famciclovir)

- Available in 125, 250 and 500 mg
- Dosage: Zoster 500 mg tid
  Recurrent Simplex 125-250 mg bid
- Caution if impaired renal function
- Category B
Off-Label

• Valtrex and Famvir used for the eye
  – Off label indication
  – Only approved for genital herpes

  – Medical literature tells us DOSE!
    • Insurance many time tells us WHICH AGENT!
MEDICATION FOCUS

ANTI-VIRAL TOPICALS
Topical Anti-Viral Options

• Is there any place for topical agents here?

• **Viroptic (trifluridine solution)**
  – One drop every 2 hours while awake (up to 9 drops per day)
  – 21 days of treatment
  – ADRs are more severe on the eye

• **Zirgan (ganciclovir ophthalmic gel) 0.15%**
  – One drop five times per day until the corneal ulcer heals; Then one drop three times per day for seven days

  – Get to know your local pharmacist...these products are EXPENSIVE!
MEDICATION FOCUS

GABAPENTIN
Anti-Seizure Medications

• Gabapentin (Neurontin)
  – LABELED for post-herpetic neuralgia (PHN)
  – Dosing: 1,800 – 3,600mg in 2-3 divided doses
    • Treatment for up to 1 year!

<table>
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<th>Daily Dose</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Days 3-6</th>
<th>Days 7-10</th>
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<td>300mg</td>
<td>600mg</td>
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<td>1,200mg</td>
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*Gralise (gabapentin) [prescribing information]. Newark, CA: Depomed Inc; September 2015
Gabapentin (Neurontin)

• Things to consider...
  – Addiction potential?
    • Gabapentin (Neurontin) versus Pregabalin (Lyrica)
    • Pearl: 3 states have made this a CIV drug

  – COMPLETELY renally cleared

  – Side Effects:
    • Sedation
    • Confusion
    • Weight gain
    • Alteration of seizure threshold
MEDICATION FOCUS

HERPES ZOSTER VACCINE
Vaccines...

• Zostavax – SQ, live vaccine; 60 years and older
  – “the only game in town...”
    • 50-ish% effective; 1 dose
    • Efficacy wanes after 4-5 years

• Shingrix – has replaced Zostavax
  – We are moving in the right direction!
  – Recommended for 50 years and older
    • 90+% effective?; 2 doses; IM; recombinant vaccine
    • Efficacy *seems* solid up to 7-8 years
Shingrix

- Recombinant vaccine with adjuvant for added immunogenicity
- VERY difficult to get right now
- Post-shingles:
  - Wait until acute episode and symptoms are resolved
- Post-Zostavax patient:
  - Wait 8 weeks after Zostavax vaccine before giving Shingrix
CASE 2

It’s Time For Your Eye Exam
52 year old man

- Referred for diplopia x 6 days
  - Horizontal
  - Relief with closing either eye
  - Worse at distance and in right gaze
  - Wearing a patch to function

He also reports a headache (8/10)
  - located in occipital region
  - extra strength Excedrin q 4 hrs for relief
• 1 day after noticing the diplopia
  – Went to the ER
    • Had unenhanced MRI of brain and MRA of head (normal)
  – Saw an eye doctor
    • No cause for diplopia found
    • Ordered ESR and CRP (both normal)
  – Saw a neurologist
    • Noted subtle abduction deficit
    • Ordered more testing, but not yet completed
Tests Ordered by Neurology

Treatment

1. Diplopia
Start Eye Patch Miscellaneous, as directed, patch R eye, 1, Refills 0
Start Aspirin Tablet, 81 MG, 1 tablet, Orally, Once a day, 30 day(s), 30
LAB: COMPREHENSIVE METABOLIC PANEL W/EGFR
LAB: ACETYLCHOLINE RECEPTOR BINDING ANTIBODY
LAB: ACETYLCHOLINE RECEPTOR MODULATING ANTIBODY
LAB: C-REACTIVE PROTEIN
LAB: HEMOGLOBIN A1c
LAB: CBC (INCLUDES DIFF/PLT)
LAB: SED RATE BY MODIFIED WESTERGREN
LAB: T4, FREE
LAB: TSH
LAB: LIPID PANEL WITH REFLEX TO DIRECT LDL
LAB: ACETYLCHOLINE RECEPTOR BLOCKING ANTIBODY
• Other health issues lately

  – 3 weeks ago, sudden chest pains
    • Went to ER, all tests on heart were normal
    • Stress test ordered, but not yet done

  – Excruciating back pains
    • Muscle relaxers
    • Pain patches
    • Spinal manipulation with chiropractor

  – Numbness in fingers on left hand
    • Told of pinched nerve

    • Difficulty sleeping, chills, feels feverish

    • Swelling / itching around eyes (PCP Rx’d Medrol dose pack)

Denies any trauma, new rashes, or recent insect bites.
• Before the past few weeks, he had not seen a doctor in years

• Recent labs showed elevated cholesterol (248) and LDL (157), HbgA1c was 5.5%.
EXAM RESULTS

• VA 20/20 OD 20/25 OS
• Color (Ishihara): 2/14 OD, 2/14 OS
  – History of congenital color blindness
• PERRLA (-) RAPD
• CF: full OU
• Exophthalmometry: 17 OD 17 OS
• Apertures: 9mm OD 9mm OS
OCULAR MOTILITY IMAGES
Ocular Motility

85-90

100

100

100

100

100

2 eso

16 eso

10 eso

ortho

12 eso
• Palpebral aperture  9mm OD  9mm OS
• Pre-fatigue 8mm OD  9mm OS
• Post-fatigue 5mm OD  8mm OS
• Pre-Ice 6mm OD  9mm OS
• Post-Ice 6mm OD  9mm OS

• Lid Crease 8mm OD  7mm OS

• Levator Function 19mm OD  19mm OS

• + weakness of right orbicularis oculi
Ocular Health Assessment

• SLE: NS I OU
• IOP: 13mmHg OD  14 mm Hg OS
• DFE: .2/.2 cupping OU
  – Distinct margins OU
  – No neuroretinal rim pallor OU
DIFFERENTIAL DIAGNOSIS

Abduction Deficit

CN VI Palsy
• Plan: ** = previously ordered by neurologist
  – Order labs
    • CBC with platelets **
    • ESR and CRP **
    • Lyme
    • ANA with reflex titer
    • RPR and FTA-ABS
    • ACE
    • TSH**, T3, T4, thyroperoxidase antibody, thyroglobulin antibody
    • Acetylcholine receptor antibodies (binding, blocking, and modulating) **

• Follow-up in one month, or sooner PRN
Shortly after his visit with us

- Patient developed right sided facial droop.
- Went to his PCP; dx with Bell’s palsy
  - Treated with oral prednisone and Valtrex
DIFFERENTIAL DIAGNOSIS

- Bell's Palsy (Idiopathic)
- Multiple Sclerosis
- Stroke
- Sarcoid
- Lyme Disease
- Ramsay Hunt Syndrome (VZV)
- Middle Ear Infection
- Trauma
DIFFERENTIAL DIAGNOSIS

MRI was normal a few weeks ago
• Neurologist ordered another brain MRI with contrast

  – Small foci of signal abnormality within the white matter, possibly due to ischemia, gliosis or a demyelinating process

  – Complete opacification of the right maxillary sinus
DDX BRAIN WHITE MATTER CHANGES

- Multiple Sclerosis
- Small Vessel Ischemic Disease
- Migraines
- Lyme Disease
- Hypertension
• It can be difficult to distinguish between MS and Lyme disease clinically

• They both can have white matter changes

• Both can have CSF pleocytosis (+ WBC in CSF)

• Oligoclonal Bands
  – Can be present in both Lyme and MS

• Myelin Basic Protein (best differentiator)
  – Present in MS but not in Lyme

**DOES THIS PT NEED A LUMBAR PUNCTURE?**
LAB RESULTS

- These are the remarkable results

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<th>Index</th>
<th>Interpretation</th>
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Caution must be used in supporting a diagnosis of B. burgdorferi infection when sera are Western blot IgM positive and Western blot IgG negative after the initial 4 week period from onset. Because the likelihood of a false-positive test result is high for these individuals, a positive IgM test alone is not recommended for use in determining active disease in persons with illness of longer than one month duration.

As per CDC criteria, a Lyme disease IgG Immunoblot must show reactivity to at least 5 of 10 specific borrelial proteins to be considered positive; similarly, a positive Lyme disease IgM immunoblot requires reactivity to 2 of 3 specific borrelial proteins.
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<th>Antibody</th>
<th>Molecular Weight</th>
<th>Reactivity</th>
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Two-Tiered Testing for Lyme Disease

First Test
- Enzyme Immunoassay (EIA)
  OR
- Immunofluorescence Assay (IFA)

Positive or Equivocal Result

Negative Result

Consider alternative diagnosis
OR
If patient with signs/symptoms consistent with Lyme disease for ≤ 30 days, consider obtaining a convalescent serum

Second Test
- Signs or symptoms ≤ 30 days
  - IgM and IgG Western Blot
- Signs or symptoms > 30 days
  - IgG Western Blot ONLY
LYME DISEASE
Lyme Disease

- Lyme disease is caused by the bacterium *Borrelia burgdorferi*
- Transmitted to humans through the bite of infected blacklegged ticks.
- Typical symptoms include
  - Fever
  - Headache
  - Fatigue
  - skin rash called erythema migrans
If left untreated, infection can spread to
  - joints
  - heart
  - nervous system

Most cases of Lyme disease can be treated successfully with a few weeks of antibiotics. The ticks that transmit Lyme disease can occasionally transmit other tick-borne diseases as well.
Lyme Disease

- Early Signs and Symptoms (3 to 30 days after tick bite)
  - Fever
  - Chills
  - Headache
  - Fatigue
  - muscle and joint aches
  - swollen lymph nodes
Lyme Disease

• Early Signs and Symptoms (3 to 30 days after tick bite)

• Erythema Migrans (EM) rash:
  – Occurs in approximately 70 to 80 % of infected persons
  – Begins at site of tick bite after a delay of 3 to 30 days (average is about 7 days)
  – Expands gradually reaching up to 12 inches or more (30 cm)
  – May feel warm to the touch but is rarely itchy or painful
  – Sometimes clears as it enlarges, resulting in a target or “bull's-eye” appearance
  – May appear on any area of the body
Lyme Disease

• **Later Signs and Symptoms** *(days to months after tick bite)*
  – Severe headaches and neck stiffness
  – Additional EM rashes on other areas of the body
  – Arthritis with severe joint pain and swelling, particularly the knees and other large joints.
  – Facial palsy
  – Intermittent pain in tendons, muscles, joints, and bones
Lyme Disease

• **Later Signs and Symptoms** *(days to months after tick bite)*
  – Heart palpitations or an irregular heart beat
  – Episodes of dizziness or shortness of breath
  – Inflammation of the brain and spinal cord
  – Nerve pain
  – Shooting pains, numbness, or tingling in hands / feet
  – Problems with short-term memory
Ophthalmic / Neuro-op Features of Lyme

• Cranial Neuropathies
  – III
  – IV
  – VI
  – VII (most common)
    • Unilateral or bilateral
Mechanisms of Motility Issues in Lyme

• Cranial Nerve III, IV, VI palsies
  – Local inflammation in the subarachnoid space (meningitis)
  – Mononeuritis multiplex with vasculitis
  – Direct invasion of the nerve by spirochetes
  – Increased intracranial pressure (CN VI)
  – Immunologic pathogenesis
Ophthalmic / Neuro-op Features of Lyme

- Follicular Conjunctivitis
- Keratitis
- Intraocular Inflammation
  - Uveitis
  - Vitritis
  - Neuroretinitis
  - Choroiditis
- Orbital Inflammation
  - Myositis
- Pupil Abnormalities
  - Argyll Robertson Pupils
  - Tonic Pupils
  - Horner Syndrome
Ophthalmic / Neuro-op Features of Lyme

• Optic Nerve Dysfunction
  – Papilledema
    • From meningitis and meningoencephalitis
    • Can be confused with IIH
      – Differentiate with abnormal CSF analysis
        » Features of meningitis
          • Elevated protein
          • Lymphocytosis
  – Optic Atrophy (from papilledema and meningitis)
  – ? Optic Neuritis
BACK TO THE PATIENT

DX: CN VI & CN VII from Lyme

• Referred to Infectious Disease Specialist
• Treated with Doxycycline
  – Shortly after, all of his symptoms resolved, and he felt back to normal

Why Doxycycline?
What Route of Administration? Does it Matter?
How Long is Treatment Needed?
MEDICATION FOCUS

ANTIBIOTICS
DOXYCYCLINE
Doxycycline

• Tetracycline anti-microbial
  – Protein synthesis inhibitor (30S and 50S ribosomal subunits)
    • Mechanism matters: also impacts rapidly-dividing mammalian cells
  – The best tolerated of the tetracycline group
  – Now indicated for the treatment of Lyme in kids 8 and up!
    • NE United States is ENDEMIC for Lyme
Doxycycline

Side Effects:

• Skin photosensitivity
• GI discomfort – take with FOOD
• Skin discoloration/rash

Why not given to children under age 8?

• chelation – to bone, teeth
  – Chelation: binding to cationic substances
• CONTRAINDIATED in pregnancy, breastfeeding, and in children under 8 years old!
The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America

Gary P. Wormser,1 Raymond J. Dattwyler,2 Eugene D. Shapiro,3,4 John J. Halperin,3,5 Allen C. Steere,6 Mark S. Klempner,7 Peter J. Krause,3 Johann S. Bakken,2,11 Franc Srle,12 Gerard Stanek,13 Linda Bockenstedt,1
Durland Fish,6 J. Stephen Dumler,12 and Robert B. Nadelman1

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Evidence-based guidelines for the management of patients with Lyme disease, human granulocytic anaplasmosis (formerly known as human granulocytic ehrlichiosis), and babesiosis were prepared by an expert panel of the Infectious Diseases Society of America. These updated guidelines replace the previous treatment guidelines published in 2000 (Clin Infect Dis 2000; 31[Suppl 1]:1-14). The guidelines are intended for use by health care providers who care for patients who either have these infections or may be at risk for them. For each of these *Ixodes* tickborne infections, information is provided about prevention, epidemiology, clinical manifestations, diagnosis, and treatment. Tables list the doses and durations of antimicrobial therapy recommended for treatment and prevention of Lyme disease and provide a partial list of therapies to be avoided. A definition of post–Lyme disease syndrome is proposed.
<table>
<thead>
<tr>
<th>Category, grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength of recommendation</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Strongly in favor</td>
</tr>
<tr>
<td>B</td>
<td>Moderately in favor</td>
</tr>
<tr>
<td>C</td>
<td>Optional</td>
</tr>
<tr>
<td>D</td>
<td>Moderately against</td>
</tr>
<tr>
<td>E</td>
<td>Strongly against</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Evidence from ≥1 properly randomized, controlled trial</td>
</tr>
<tr>
<td>II</td>
<td>Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from &gt;1 center); from multiple time series studies; or from dramatic results from uncontrolled experiments</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees</td>
</tr>
</tbody>
</table>

**NOTE.** Categories reflect the strength of each recommendation for or against use and the quality of the evidence.
Doxycycline

**Prophylaxis:** recommended ONLY if:
1. Tick identified as adult or nymphal *Ixodes scapularis*
2. Estimated attachment to skin ≥ 36 hours.
3. Prophylaxis able to be started within 72 hours of tick removal.
4. Local rate of Lyme is ≥ 20%.
5. Doxycycline is not contraindicated.

**Adults:** 200mg po x 1 dose

**Children** (≥ 8) 4mg/kg po x 1 dose
**Left to Right:** ticks transmit *Borrelia burgdorferi*, which CAUSES Lyme Dz

*I. Scapularis* larva, nymph, adult male, adult female tick
Doxycyline

**Early Treatment:**
- Adults: 100mg po bid x 14 days (10-21 days)
- Children: 4mg/kg/day po in ÷ bid x 14 days (max 100mg per dose)

**Alternatives:**
- Oral: Amoxicillin, Cefuroxime axetil
- IV: Ceftriaxone

**Misc:** azithromycin, clarithromycin, erythromycin, cefotaxime, penicillin G (none of these are considered PREFERRED treatments)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage for adults</th>
<th>Dosage for children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred oral regimens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>500 mg 3 times per day(^a)</td>
<td>50 mg/kg per day in 3 divided doses (maximum, 500 mg per dose)(^a)</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg twice per day(^b)</td>
<td>Not recommended for children aged &lt;8 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For children aged ≥8 years, 4 mg/kg per day in 2 divided doses (maximum, 100 mg per dose)</td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
<td>500 mg twice per day</td>
<td>30 mg/kg per day in 2 divided doses (maximum, 500 mg per dose)</td>
</tr>
<tr>
<td><strong>Alternative oral regimens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selected macrolides(^c)</td>
<td>For recommended dosing regimens, see footnote (d) in table 3</td>
<td>For recommended dosing regimens, see footnote in table 3</td>
</tr>
<tr>
<td><strong>Preferred parenteral regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2 g intravenously once per day</td>
<td>50–75 mg/kg intravenously per day in a single dose (maximum, 2 g)</td>
</tr>
<tr>
<td><strong>Alternative parenteral regimens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>2 g intravenously every 8 h(^d)</td>
<td>150–200 mg/kg per day intravenously in 3–4 divided doses (maximum, 6 g per day)(^d)</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>18–24 million U per day intravenously, divided every 4 h(^d)</td>
<td>200,000–400,000 U/kg per day divided every 4 h(^d) (not to exceed 18–24 million U per day)</td>
</tr>
</tbody>
</table>
Table 3. Recommended therapy for patients with Lyme disease.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Treatment</th>
<th>Duration, days (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tick bite in the United States</td>
<td>Doxycycline, 200 mg in a single dose(^{a,b}), (4 mg/kg in children ≥ 8 years of age) and/or observation</td>
<td>...</td>
</tr>
<tr>
<td>Erythema migrans</td>
<td>Oral regimen(^{c,d})</td>
<td>14 (14–21)(^e)</td>
</tr>
<tr>
<td>Early neurologic disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis or radiculopathy</td>
<td>Parenteral regimen(^{c,f})</td>
<td>14 (10–28)</td>
</tr>
<tr>
<td>Cranial nerve palsy(^{a,g})</td>
<td>Oral regimen(^{c})</td>
<td>14 (14–21)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>Oral regimen(^{a,c,h}) or parenteral regimen(^{a,c,h})</td>
<td>14 (14–21)</td>
</tr>
<tr>
<td>Borrelial lymphocytoma</td>
<td>Oral regimen(^{c,d})</td>
<td>14 (14–21)</td>
</tr>
<tr>
<td>Late disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis without neurologic disease</td>
<td>Oral regimen(^{c})</td>
<td>28</td>
</tr>
<tr>
<td>Recurrent arthritis after oral regimen</td>
<td>Oral regimen(^{a,c}) or parenteral regimen(^{a,c})</td>
<td>28</td>
</tr>
<tr>
<td>Anti-biotic refractory arthritis(^i)</td>
<td>Symptomatic therapy(^i)</td>
<td>...</td>
</tr>
<tr>
<td>Central or peripheral nervous system disease</td>
<td>Parenteral regimen(^{c})</td>
<td>14 (14–28)</td>
</tr>
<tr>
<td>Acrodermatitis chronica atrophicans</td>
<td>Oral regimen(^{c})</td>
<td>21 (14–28)</td>
</tr>
<tr>
<td>Post–Lyme disease syndrome</td>
<td>Consider and evaluate other potential causes of symptoms; if none is found, then administer symptomatic therapy(^a)</td>
<td>...</td>
</tr>
</tbody>
</table>
MEDICATION FOCUS

OTHER PREFERRED ANTIBIOTICS
AMOXICILLIN
CEFUROXIME AXETIL
Amoxicillin and Cefuroxime Axetil

• Both are beta-lactam antimicrobials = better tolerated than doxycycline

• Amoxicillin is an extended-spectrum penicillin

• Cefuroxime axetil is a 2\textsuperscript{nd} gen cephalosporin
  – Generally recommended for patients UNABLE to take or tolerate doxycycline, as they are considered to be less effective
Amoxicillin and Cefuroxime Axetil

- Both are beta-lactam antimicrobials = better tolerated than doxycycline
- Penicillin allergy?
  - True allergy?
    - Statistics? Staggering...
  - Cephalosporin considerations
    - Cross-reaction is 3-10%
      - In a true, Type-I hypersensitivity reaction
MEDICATION FOCUS

PREFERRED PARENTERAL ANTIBIOTIC
CEFTRIAXONE
Ceftriaxone

- IV 3\textsuperscript{rd} generation cephalosporin
- Indicated for patients with neurologic symptoms, or those hospitalized with other Lyme manifestations
  - Potentially in patients who have post-treatment Lyme Disease Syndrome
    - Controversial subject...

- Why do we not see any 1\textsuperscript{st} generation cephalosporins like cephalexin (Keflex)?
Debate about PTLDS
(Post-Treatment Lyme Disease Syndrome)

• Is there any benefit to long-term antibiotic treatment?
• This has caused a lot of controversy
• Data from animals and humans
  – Conclusions that we see...
Lyme Treatment (extended)

• Studies do not advocate long term antibiotic treatment
• Benefit does not outweigh the risk

There is a possibility of Post-Lyme Disease Syndrome, but consider a co-infection with another tick-borne illness, which may need to be treated differently
Other Tick-Borne Diseases

- Babesiosis
- Ehrlichiosis
- Rocky Mountain Spotted Fever
- Relapsing Fever
- Stair/Masters’ Disease
- Tularemia
- Bartonella
- Q Fever
- Tick Paralysis
- Tick Borne Encephalitis
- Colorado Tick Fever
Patient Was Treated With Steroids Before He Was Diagnosed With Lyme Disease

• What about being on steroids when you have an infection??
MEDICATION FOCUS

STEROIDS

MEDROL DOSE PACK (GIVEN FOR SWELLING OF EYES)

ORAL PREDNISONE (GIVEN FOR FACIAL PALSY)
Medrol Dose Pack (Methylprednisolone)

- Given for swelling of the eyes
- Convenient for patient
  - 6 day “automatic taper”
- Sometimes it is not HIGH enough of a dose or LONG enough of a treatment duration

- 4mg methylprednisolone = 5mg prednisone

MDP equivalent:

Day 1: 30mg; Day 2: 25mg; Day 3: 20mg; Day 4: 15mg; Day 5: 10mg; Day 6: 5mg
Millipred Dose Pack (Prednisolone)

- 5mg prednisone/prednisolone = 4mg methylprednisolone

- An alternative to a Medrol dose pack
  - COST/AWP: Medrol = $30
  Millipred = $400
Prednisone

- Used for facial palsy (**this case shows need to r/o Lyme 1st**)
- More potent steroid when compared to methylprednisolone.

- Prednisone is MORE likely to cause fluid retention in the periphery due to a higher mineralocorticoid potency
  - ie. Prednisone has more salt and water retaining potential
CASE 3

It's Time For Your Eye Exam
58 Year Old Woman

• Referred by OD

• 1 month ago, episode of vision loss while driving
  – First, saw dark spots OU
  – Then, highway and cars were wavy
  – Next, things went double
  – Finally, vision went completely black OU
    • Lasted 10-15 seconds
• For 1 week prior to the episode of transient vision loss, she had R temporal and frontal HA – 7/10 in severity
  – Pain was worse when she touched her skin
  – No left-sided pain

• History of sinus infections
  – She thought this was sinusitis
Went to Urgent Care

• Told could be vertigo
  – Rx’d anti-vertigo meds
• Did not find any sinusitis
• Told her to see her OD and neurologist
  – She had previously seen a neurologist for HA
Went to OD the Next Day

• Found large hyperopic shift OS
• Questioned mild optic disc edema OS

• Sent the patient immediately to ED to r/o GCA (good job!)
Work-Up Done at Hospital

CRP
- 1.6 (normal range <0.8)

ESR
- >130 (normal range 0-30)  [Began IV Methylprednisolone x 3d]

MRI / MRA
- No infarct, mass, abnormal enhancement
- No significant stenosis of carotids or vertebrals in head or neck

Temporal Artery Biopsy (Left Side)
- Negative for GCA
• Discharged while awaiting results of biopsy
  – on 80mg oral Prednisone

• 1 week later, called / told of negative biopsy results
  – Told to begin taper of steroids
  – Was completely off steroids by 2 weeks later
  – Was told to follow-up with rheumatology, but she has not yet done so

  – Symptoms returned, OD sent pt to us

• Has been off steroids x 2 weeks at the time of visit to us
• She does not have a PCP...so has not seen a doctor
While on the steroids

- Headache resolved
- No eye problems
- Did have nausea and GI issues
Now that off the steroids, symptoms returned

- Headaches
- Jaw gets tired when chewing
- Scalp tenderness
- Hip Pain

- Does not have the symptoms during the exam, but they occur intermittently
Repeat Labs
(1 day prior to final steroid dose – prior to seeing us)

- **CRP**
  - 30.5 (normal range up to 4.9)

- **ESR**
  - 27 (normal range 0-40)

- **Platelets**
  - 409
Now What?

• If it’s not GCA...
  – What caused the extremely high initial ESR?
  – Why is the CRP elevated now?
  – What else could it be?
  – Do we still need to be concerned since she is not having any current visual complaints?
DDX FOR ELEVATED INFLAMMATORY MARKERS

- Giant Cell Arteritis
- Autoimmune Disease
- Other Vasculitis
- Other Systemic Inflammation
- Cancer

High Inflammatory Markers
SOCIAL HISTORY

• Smoker - ½ pack/day for 30 years
• Social alcohol use
Systemic History

- s/p gastric bypass
- Hypertension
- s/p thyroidectomy (Grave’s disease at age 18)
- Hypercholesterolemia
- s/p tonsillectomy
- s/p cholecystectomy
- (-) DM, cancer

Sees a cardiologist q 2 years since her father died of aortic aneurysm
Current Medications

- Metalozone
- Pataday Ophth soln
- Prednisolone acetate 1% ophth soln
- Prevacid
- Synthroid
- Triamterene / HCTZ
- Aspirin 81 mg
Exam Results - Afferent

• BCVA OD 20/20  OS 20/20
  – Anisometropia (more hyperopic OS)
• Color: OD 14/14, OS 14/14
• PERRLA (-) RAPD
• CF: Full to FC and red targets OU
Fixation Target: Central
Fixation Losses: 3/14
False POS/Errors: 20 X
False NEG/Errors: 16 X
Test Duration: 05:30
Fovex: 35 dB

Visual Acuity:
Strategy: SITA-Standard
Time: 10:54 AM
RX: +3.75 DS DC X
Age: 56

Fixation Target: Central
Fixation Losses: 1/15
False POS/Errors: 6 X
False NEG/Errors: 3 X
Test Duration: 06:05
Fovex: 34 dB

Visual Acuity:
Strategy: SITA-Standard
Time: 10:46 AM
RX: +3.75 DS DC X
Age: 56

*** Excessive High False Positives ***
GHT Within Normal Limits
VFI 98%
MD = -0.13 dB
PSD 1.71 dB

Total Deviation
Pattern Deviation

The Eye Institute
1200 West Godfrey Avenue
Philadelphia, PA 19141
Unit 4

© 2010 Carl Zeiss Meditec
HFA ii 750-11008-5.0/5.0
Exam Results - Efferent

- Exophthalmometry: OD 27  OS 27
- Palpebral apertures: OD 8   OS 8
- No nystagmus
- Worth 4-dot: fusion at all distances
Exam Results – Ocular Health

- **IOP**: OD 16 mmHg, OS 16 mm Hg
- **SLE**: 1+ conjunctival injection, (-) cells/flare
- **DFE**: 
  - ONH slightly elevated, but with no edema
  - C/D: OD .4/.45   OS.35/.35
  - Macula clear
  - No hemes or exudates
  - Periphery clear
Her Eye Exam is Normal

• Do we need to even be concerned about this?
• Should we just send her to rheumatology?
  – First appointment is in 1 month...

COULD THIS STILL BE GCA?
  – Symptoms of GCA
  – Significantly elevated ESR on day of TVL
  – Significantly elevated CRP on last day of steroid taper
  – Has had elevated platelets
  – Father died of aortic aneurysm
CGA and aortic aneurysm

- GCA patients have increased risk of aortic aneurysm
  - 17.3 times more likely to develop a thoracic (TAA) aneurysm.
  - 2.4 times more likely to develop an abdominal aneurysm (AAA).

- GCA patients often have no acute symptoms of the aneurysm
  - mean time to detection is > 1 year after GCA diagnosis.

- The blood pressure of patients needs to be aggressively treated

- 50% of GCA patients with TAA will die secondary to the aneurysm.

- Prompt treatment of the aneurysm with corticosteroids or possibly surgical repair is important for improved prognosis.
CGA and aortic aneurysm

• The initial evaluation of GCA should include
  – baseline and annual abdominal ultrasound
  – chest radiography (or more sensitive CT / MRI)
  – transthoracic echocardiography

• Patients with GCA need long term cardiology follow-up
  – catastrophic aortic complications can occur years after the typical GCA symptoms resolve
  – even in the setting of a normalized ESR and C-reactive protein.
Our Plan

Recently had a mammogram and a colonscopy

Rheumatology Consult
STAT Labs
(1 day after visit with us)

- CRP: 10.1 (normal range up to 4.9)
- ESR: 59 (normal range 0-40)
- Platelets: 510 (normal range up to 400)
• Patient resumed use of oral steroids (40mg)
• Saw a PCP
• Started to feel better shortly after re-starting steroids
• Symptoms resolved
Repeat Labs
(1 week later after resuming steroids)

- CRP
  - 0.7 (normal range up to 4.9)

- ESR
  - 22 (normal range 0-40)

- Platelets
  - 488
While waiting for Rheumatology Appt

• We ordered a second GSTA Biopsy of the right side
  – All of her pain has been on the right side
  – She never had any pain on the left side

Was the initial biopsy negative because the side with the highest yield was not tested?
3-7 mm segment

**GSTA BIOPSY**
GSTA Biopsy

• Patient called and told us she was told by vascular surgery that the biopsy was negative for GCA

• We called and got the pathology report
  • There were no giant cells or specific signs of inflammation
  • Reported to be negative for GCA
  • Note was made of fragmentation of the internal elastic lamina!
• Discussion with Pathology

• Rheumatology Consult
  – Agreed that this was GCA
  – But, started a very slow TAPER of Prednisone
  – Will taper down to 15mg over 6 weeks
    • Patient concerned because mild symptoms are returning
    • GI issues
    • Moon face
  – Rheumatology started her on Actemra.
GCA
Giant Cell Arteritis

- May be associated with poly-myalgia rheumatica (PMR)
  - Autoimmune pathophysiology
- More common in women
- More common in caucasians
- Presentation:
  - Headache; tender temporal artery
  - Visual defects (sudden, monocular vision loss)
  - Labs: increased ESR and CRP
GCA
TREATMENT
MEDICATION FOCUS

STEROIDS IN GCA
Steroids

• Patients are typically on HIGH doses of prednisone
  – Ex. 60-80mg prednisone daily
• Benefits:
  – Immediate symptomatic improvement
  – Decreases risk of blindness
  – So helpful, that patients have a very difficult time tapering the steroids
    • NEED TO TAPER SLOWLY
IV Steroids

• Some patients require admission for management of symptoms
• Methylprednisolone 1 gram x 1-3 days
  – Helps manage symptoms of acute vision loss and helps protect unaffected eye
MEDICATION FOCUS

ACTEMRA
Actemra (Tocilizumab)

• Mechanism of action:
  – Interleukin-6 inhibitor
  – Typically used in rheumatoid arthritis

• Approved May, 2017 for GCA

• SQ administration – given weekly
GiACTA Trial

• Compared to prednisone + placebo, patients taking Actemra had a significant improvement in sustaining remission
  – Evaluated weeks 12-52
  – Remission: absence of symptoms; normalization of labs
  – Patients on Actemra used much lower doses of prednisone
Actemra (Tocilizumab)

• Side Effects:
  – Infection
  – Reactivation of latent disease (TB, hepatitis)
  – Increase in LFTs
  – Increase in LDL cholesterol
MEDICATION FOCUS

SPECIALIZED PRO-RESOLVING MEDIATORS
Fish Oil

• Three types:
  • Ethyl Ester: DHA and EPA
    – Cheaper to make
    – RX products fit here
    – More likely to give “fishy” burps and aftertaste
  • Triglyceride: DHA and EPA
    – Purified product = better absorption
    – “you get what you pay for…”
    – Less likely to cause fishy side effects
Fish Oil

• Specialized Pro-Resolving Mediators
  – 18-HEPE (18-hydroxyeicosapentaenoic acid)
  – 17-HDHA (17-hydroxydocosahexaenoic acid)

– These typically are produced during the resolution phase of an acute inflammatory response

• As we age, or have disease, etc., the ability to produce these is DIMINISHED
Specialized Pro-Resolving Mediators (SPM)

α-linolenic acid

- Essential fatty acids
  - Must be acquired through diet

EPA

- Conditionally essential fatty acids support:
  - Cell membrane integrity
  - Brain and eye health
  - Healthy triglycerides levels
  - Heart health

DHA

- Inefficient multi-step conversion
- Multi-step process, and production affected by certain health conditions

SPMs

- Unique role in supporting the resolution of the immune response and inflammation – necessary for healthy aging and active living
  - Neutrophil activity is curtailed
  - Macrophages remove dead neutrophils, bacteria and debris
  - Tissue is remodeled
  - Return to homeostasis (cells’ previous normal conditions)

Inefficient Conversion to meet needs in the face of inflammation, particularly in an already compromised host

Fish Oil

• Benefits: decrease in inflammation; cardiac protection; good for cognitive function

• Side Effects:
  – Fishy aftertaste
  – Increased bleeding time
  – reflux
CASE 4

It's Time For Your Eye Exam
30 Year-Old Woman

• Presents emergently
  – Hard to focus x 1-2 weeks

  – Then, about 4 days ago, she noticed vertical diplopia, which has been constant since that time
    • If she covers either eye, she sees better

  – A few days ago, one eyelid may have been droopy
• She thought her symptoms may have been related to her history of sinus issues
  – She went to see her ENT

• Due to the visual symptoms, the ENT sent her to the ER
  – They did labs and a CT scan and did see some chronic sinusitis, but did not find a reason for her visual complaints.
  – They gave her an “IV for an ocular migraine”

• The hospital sent her to an oculoplastics specialist
  – They did not find an orbital cause, and sent her to another eye specialist

• Instead of doing that, she presented to us...
• She feels some pressure in her head, that feels like when she has sinus issues
  • Feels better when she lies down
• She denies any problems swallowing or breathing, or any weakness
• She unintentionally lost 10 lbs over a few months
  • Current weight is 215
• She does note some problems with balance
  • History of vertigo 9 years ago
• No other neurologic symptoms
MEDICATIONS

- Montelukast sodium
- Flovent
- Zyrtec
- Culterelle
EXAM RESULTS

• VA: OD 20/20  OS 20/20
• Color: 14/14 OD and OS
• CF: full OU
• PERRLA (-) RAPD
• SLE, IOP normal
• DFE: CD .5/5 OD , .55/55 OS, no edema or pallor OU
• BP: 122/95
DDX FOR VERTICAL OCULAR MISALIGNMENT

- Myasthenia Gravis
- Orbital Mass
- Thyroid Eye Disease
- Skew Deviation
- CN IV Palsy
- CN III Palsy
MOTILITY VIDEO
Ocular Motility

Right head tilt: 4 RH
Left head tilt: 4 RH

Asymmetric endgaze nystagmus
• What test will help us make a diagnosis?
Double Maddox Rod Testing
10-15 incyclotorsion OD, 10-15 excyclotorsion OS
SKEW DEVIATION
BRAINSTEM MOTILITY DISORDER

Skew Deviation

Multiple Sclerosis

Younger

Stroke

Older
MANAGEMENT

• Fresnel prism
  – 2pd BD OD

WORK-UP

Get MRI of brain with and without contrast
  - looking for lesion in brainstem (MLF), as well as for any white matter changes to suggest MS
• MRI report
  – 3 enhancing lesions in the brain parenchyma
  – 1 enhancing lesion in the right inferior anterior cerebellum
  – 1 enhancing lesion in the left periatrial white matter, at the junction of the left pons and brachium pontis
  – Enhancing lesion in the periventricular region

• Reported differentials include:
  – demyelinating disease
  – Lyme disease
  – vasculitis
ADDITIONAL WORK-UP

• LAB TESTING
  – CBC with differential and platelet count
  – ESR
  – CRP
  – Lyme titer
  – ANA with reflex titer
  – RPR, FTA-ABS
  – vitamin B 12
  – vitamin D(25 hydroxy)
  – NMO IgG Ab
Initial Lab Report

• NMO-IgG, ANA, and RPR still pending

• Remarkable for
  – low vitamin D at 22
  – elevated CRP at 18.8
  – elevated platelet count at 412
ADDITIONAL LAB TESTING

- RPR: Negative
- ANA: Negative
- NMO-IgG: Negative
• The Vitamin D level was low. Is that related to MS?

• We know from the ONTT, that patients with optic neuritis associated with MS benefit from IV steroids, but what about patients with a presentation affecting the efferent visual system?
  
• Should they get IV steroids?

• Do we set her up for the next available neurology appt?

• Or, do we arrange for her to get IV steroids ASAP?
• Once infectious process was ruled out, we spoke with neurology and sent the patient to ED to initiate IV steroid treatment and further work-up regarding likely MS

• Vision / diplopia improved shortly after getting IV steroids

• MRI of spine and Lumbar Puncture confirmed diagnosis of MS
MULTIPLE SCLEROSIS
Multiple Sclerosis

• MS is a chronic, autoimmune, disease
• Affects CNS – brain and spine
• Types of MS
  – Relapsing-Remitting
  – Primary Progressive
  – Secondary Progressive
  – Progressive Relapsing
  – Body attacks nerve fibers and myelin sheathing
  – Alters electrical messages to the brain
Multiple sclerosis: Vitamin D deficiency may predict onset

By Ana Sendola | Published Thursday 14 September 2017

A new, large-scale study in Finnish women suggests that vitamin D deficiency can significantly raise the risk of multiple sclerosis, which makes it a reliable predictive marker for the disease. By contrast, correcting this deficiency may reduce the risk.

It is not currently known what causes multiple sclerosis (MS), a debilitating neurological disease that is estimated to affect 400,000 people in the United States.

However, it is known that women are at much higher risk of developing the disease than men. And new research in a large sample of women has found a risk factor: low vitamin D levels.

The new study was published in the journal Neurology, and the first author of the paper is Dr. Kassandre Munger, of the Harvard T.H.

25-Hydroxyvitamin D deficiency and risk of MS among women in the Finnish Maternity Cohort

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Methods: We conducted a prospective nested case-control study among women in the Finnish Maternity Cohort (FMC). The FMC had 1.8 million stored serum samples taken during the pregnancies of over 800,000 women at the time of this study. Through linkages with hospital and prescription registries, we identified 1,092 women with MS diagnosed between 1983 and 2009 with at least 1 serum sample collected prior to date of MS diagnosis; ≥2 serum samples were available for 511 cases. Cases were matched to up to 3 controls (n = 2,123) on date of birth (±2 years) and area of residence. 25-Hydroxyvitamin D (25[OH]D) levels were measured using a chemiluminescence assay. We used conditional logistic regression adjusted for year of sample collection, gravidity, and parity to estimate relative risks (RRs) and 95% confidence intervals (CIs).

Results: A 50 nmol/L increase in 25(OH)D was associated with a 39% reduced risk of MS (RR 0.61, 95% CI 0.44–0.85), p = 0.003. Women with 25(OH)D levels <30 nmol/L had a 43% higher MS risk (RR 1.43, 95% CI 1.02–1.99, p = 0.04) as compared to women with levels ≥50 nmol/L. In women with ≥2 samples, MS risk was 2-fold higher in women with 25(OH)D <30 nmol/L as compared to women with 25(OH)D ≥50 nmol/L (RR 2.02, 95% CI 1.18–3.45, p = 0.01).

Conclusions: These results directly support vitamin D deficiency as a risk factor for MS and strengthen the rationale for broad public health interventions to improve vitamin D levels.
MULTIPLE SCLEROSIS TREATMENT
MEDICATION FOCUS

VITAMIN D
Vitamin D

- Fat-soluble vitamin
- The gut requires vitamin D in order to absorb calcium!
- The medical community “missed the boat” for many years on the importance of vitamin D.
- Quandry...
  - Vitamin D2 versus D3
    - D2 = inactive
    - D3 = active
Vitamin D

• TREATMENT is managed with INACTIVE vitamin D2
  – Vitamin D2
    • 50,000 IU weekly for 6-8 weeks

  – Vitamin D3
    • Dietary supplement versus RX
    • 5,000 – 10,000 IU daily for LIFE?
MEDICATION FOCUS

STEROIDS
IV METHYLPREDNISOLONE
Why use steroids in MS?

• Used in MS patients experiencing a relapse
  – new or returning neurological symptoms that have evolved over at least 24-48 hours

  – Goal of steroids is to accelerate recovery and gain prompt control of the disease

  – May shorten the duration and severity of the relapse
MEDICATION FOCUS

MS TREATMENT
ORALS
PO Agents

• Tecfidera (dimethyl fumarate)
  – 1\textsuperscript{st} line therapy

• Gilenya (fingolimod)
  – No longer 1\textsuperscript{st} line
  – Fingolimod associated macular edema (FAME)

• Aubagio (teriflunomide)
  – 1\textsuperscript{st} line therapy

• Leflunomide (Arava)
  – Pro-drug; used in RA 2\textsuperscript{nd} or 3\textsuperscript{rd} line
Fingolimod-Associated Macular Edema

• In the MS cohort it appears as though
  – diabetes
  – prior uveitis
  – presence of a pre-existing epiretinal membrane
  – other evidence of vitreoretinal traction
  constitute the greatest risk for the development of macular edema, although diabetes was explicitly an exclusion criterion in the original MS clinical trials.

• The rate of macular edema was officially reported at 0.2% at the approved dose of 0.5 mg/ day.

• Highest risk during the first year. Resolves with discontinuation of the medication.
Fingolimod-Associated Macular Edema

• The American Academy of Ophthalmology has recommended a complete ophthalmologic exam (ophthalmoscopy with evaluation for macular edema / OCT)
  – at baseline
  – 3-4 months after medicine initiation
  – repeat evaluation 6 months later
  – then annually thereafter
Avoidance of live virus vaccinations (i.e. varicella zoster virus (VZV), influenza, etc.) is recommended while on fingolimod.

All patients treated with fingolimod must have either been previously infected with, or immunized against, VZV and demonstrate maintained immunity (via assessment of their anti-VZV serological status) before initiating the drug.

If a patient requires steroids while on therapy (to treat an exacerbation, for example) many clinicians will prophylactically treat with valacyclovir given reported cases of herpes virus reactivation or systemic infection.
MEDICATION FOCUS

MS TREATMENTS
INJECTABLES
Non-IV Injectables

• Betaseron/Extavia (interferon beta-1b) - SQ
  – 1st line

• Avonex/Rebif (interferon beta-1a) – IM/SQ
  – 1st line

• Zinbryta (daclizumab) – SQ
  – Considered after failure on 2+ MS meds

• Glatopa (glatiramer) – SQ
  – 1st line
MEDICATION FOCUS

MS TREATMENT
INFUSIONS
Infusions

• Lemtrada (alemtuzumab)
  – Considered after failure on 2+ MS meds

• Tysabri (natalizumab)
  – Considered after failure on 2+ MS meds

• Ocrevus (ocrelizumab)
  – Considered after failure on 2+ MS meds
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