How to and When to: Laboratory and Imaging Studies

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• I have received honorarium and/or serve on the advisory or speakers bureau of:
  • Allergan
  • Alcon
  • Heidelberg
  • Review of Optometry
  • CE in Italy
  There are no conflicts of interests in this presentation

Goals of the Presentation
• One Goal, and One Goal Only:
  • To give you one nugget of information that you can take home and actually use in your practice, maybe two.
    • Use that information to make you a better clinician

Course Outline
• Lab Studies for Anterior Segment Disease
  • Uveal tract

• Lab studies for Posterior Segment Disease
  • Retinal vascular
    • Arterial
    • Venular
  • Optic Nerve

Course Outline
• Review of indications for imaging

• Recommended imaging techniques
Why order Lab Testing?
- Objective measurement
- Helpful in DDx
- Dx confirmation
- Screening for unsuspected illness
- Monitor compliance to therapy
- Monitor response to condition/treatment
- Medico-legal justification of Tx

Can I Order Lab/Image Test?
- Yes, most states allow ODs to order;
- Diagnostic Laboratory test for eye related conditions
- Radiological Imaging test for eye related conditions

What Are My Options?
- Hospital
- In-office
- Reference Laboratory
- Imaging Center
  - Hospital based
  - Private imaging center

Why Order Testing???
Clinical Confirmation
confirmatory diagnosis
Adjunct to Thorough Examination
covering the bases
Co-Management vs. Direct Involvement
refer vs. orchestrate
Typical Laboratory Tests

- Complete Blood Count (CBC)
- Blood Chemistry/Profiles
- Urine Analysis
- Serology

Profile Examples

- Autoimmune Profile
  - Anti-ANA antibodies, ANA, Complement C3
- Lipid Profile (VAP Cholesterol)
  - Cholesterol, HDL, LDL, Triglycerides
- Thyroid Function Profile
  - Free Thyroxin index (FTI), T4, T3 Uptake, Thyroid Stimulating Hormone (TSH)

Imaging Tests Available

- Plain Film X-Ray
- Computed Tomography (CT)
- CT Angiography (CTA)
- Magnetic Resonance Imaging (MRI)
- Magnetic Resonance Angiography (MRA)
- Magnetic resonance Venography (MRV)
- Carotid Doppler Ultrasonography
- Temporal Artery Ultrasonography

Anterior Segment Indications for Laboratory Studies

- Typically for the evaluation of patients with chronic, recalcitrant and/or bilateral ocular inflammation
- Uveitis
- Episcleritis
- Graves Disease

Uveitis

- BEFORE ordering lab tests or referring the patient out for secondary treatment:
  - Make sure the uveitis is being properly treated topically
  - Aggressive topical management:
    - Cycloplegia (atropine) BID-QID
    - Pred Forte (Dexamethasone) Q1-2H

Anterior Segment Inflammation

- Episcleritis
  - Often induced by exogenous sources
  - OSD, DES, environment, chronic allergies
  - Eliminate the etiology
  - ?? 20% of cases have underlying etiology
- Uveitis
  - Often induced by extraneous sources
  - ?? % systemic etiology
  - Infection—Zoster, bartonella
  - Autoimmune—rheumatoid, sarcoid, ankylosing spondylitis
  - Inflammatory—IB, Crohns
Ant Seg Inflammation

- Autoimmune Diseases
  - 20-50 yo
  - Underlying inflammation suspected
    - In early stages of (unknown) disease, many patients will test negative
    - >2/3 of patient will initially not be lab+
  - The chronicity of the ant seg inflammation is what threatens vision

Ant Seg Autoimmune Dz

- These present a diagnostic challenge in clinic
- Thorough history is critical
- Rheum consult?
- Negative finding = idiopathic

Anterior Seg Inflammation

- Sarcoïdosis
  - Inflammatory disease systemwide
  - ‘granulomatous’ uveitis
  - Pulmonary infiltration/granuloma
  - Elevated ESR and ACE
    - ACE is produced by endothelial cells and monocytes
    - ACE is elevated in 60-90% of active sarcoidosis
    - ACE can also be elevated in Histo/Toxo/TB

Rheumatoid--Autoimmune

- ANA (anti nuclear antibodies)
  - Immune system attacking cell nuclei
  - When elevated, may indicate several autoimmune disorders
  - When low, less likely to have lupus (SLE)

- HLA-B27
  - A genetic marker elevated in diseases that are seronegative spondyloarthropathies
  - Ankylosing Spondylitis
  - Psoriatic Arthritis

- Compliment System
  - Various proteins involved in mediating inflammation
  - When low, inflammation generally symptomatic
Don’t forget Syphilis

• The great mimicker

• An infection associated with disseminated inflammation

Take Home Lab Pearls-Anterior

• For all uveitis patients:
  • CBC with Diff
  • ESR
  • CRP
  • RF
  • ANA
  • FTA-Abs
  • VDRL or RPR

Take Home Lab Pearls-Anterior

• If Sarcoid or TB suspected, add:
  • ACE
  • CXR
• If younger and suspected AS or Reiter’s, add:
  • HLA B27
  • PA and LAT lumbar plain films
• Infectious? Add:
  • Lyme?? (ELISA then Western Blot), toxo titers as warranted by history

Posterior Segment Indications

• Retinal inflammatory/infectious
  • Retinology handled

• Retinal Vascular
  • Hemorrhage
  • Arterial
  • Venular
  • Optic Nerve

Retinal Hemorrhage

• Associated with a variety of etiologies
  • Diabetes, HTN, atherosclerosis, Valsalva, infection, trauma, red cell etiologies, white cell etiologies etc etc etc

Complete Blood Count (CBC)

• WBC w/ Differential
• RBC Count
• Hematocrit
• Hemoglobin
• RBC Indices (MCV, MCH, MCHC)
• Peripheral Blood Smear
• Red Cell Distribution
• Reticulocyte Count
• Platelet Count

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<th>Complete blood count (CBC)</th>
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<td>RBC (×10^6/µL)</td>
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<td>MCH (pg)</td>
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<tr>
<td>MCHC (%)</td>
<td>35.8</td>
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<tr>
<td>Platelets (×10^3/µL)</td>
<td>228</td>
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</tbody>
</table>
CBC

• 70-80% of hematological diseases can be diagnosed by simple CBC

• Do you run labs on all retinal heme patients???

Atherosclerosis Risk in Communities
Study ARIC

• Initiated by the National Heart Blood and Lung Institute
• Investigate factors that are involved with the development of atherosclerosis and the incidence of CHD, stroke and other cardiovascular diseases
• Measure cardiovascular disease rates in communities over time
• 15,792 initial participants

ARIC Stroke and Retinopathy

• Wong et al
• 1684 participants
• One arm of study compared MR findings with retinopathy in the context of STROKE
• Retinopathy included:
  • microaneurysms, retinal hemorrhages, soft exudates, hard exudates, macular edema and optic disc swelling

ARIC Prelim Results

• The overall incidence of stroke was found to be related to:
  • 1: MR findings of white matter lesions
  • 2: presence of “retinopathy”

ARIC Does Retinopathy relate to MR Lesions

• Findings:
  • No retinopathy:
    • 9.9% have MR lesions
    • 1 out of 10
  • With retinopathy:
    • 22.9% have MR lesions
    • 1 out of 4 !!!

What about both together in a patient???

Atherosclerosis Risk in Communities

• Findings:
  • 5-year cumulative incidence of stroke:
    • (-) white matter lesions and (-) retinopathy: 1.4%
    • (+) white matter lesions and (-) retinopathy: 20.0%

• The study suggests that healthy people with white matter lesions detected by MRI may benefit from a retinal examination to assess their risk of stroke.
Retinal Arterial Indications

- Emboli

What About Cholesterol

- We know we have a problem in the USA
- Modify my habits?????
- Just give me Lipitor

Lipoproteins

- 5 categories
  - HDL (high density lipoproteins)
  - LDL (low density lipoproteins)
  - Chylomicrons
  - VLDL (very low density lipoproteins)
  - IDL (intermediate density lipoproteins)

Low Density Lipoprotein

- One type of lipoprotein that transports cholesterol and triglycerides from liver to peripheral tissues
- Serum is water-based; LDL's allow fats and cholesterol to circulate
- LDL particles vary in size and density
  - Subtype A
    - Larger, less dense
  - Subtype B
    - Smaller, more dense

LDL Subtypes A and B

- Subtype B is more likely to penetrate vascular endothelium
  - More highly associated with risk of CAD
- Normal vascular endothelial gaps are about 26nm
Measurements of LDL

- Measurement of LDL is widely available and relatively inexpensive
- Not very well correlated with development of atherosclerosis
- Measurement of sub types of LDL are more correlated with cardiovascular disease

Accurately Assessing Risk

- 85% of lipid panels are same basic testing available for years 1970's
- Estimates LDL-C levels
- Recent data:
  - 1.3M US adults
  - Calculated LDL vs measured LDL
  - Friedewald is lower than direct LDL in high risk patients
    - Risk UNDERESTIMATED by 25-60%

Friedewald Estimated vs Directly Measured LDL-C and Treatment Implications. J. Amer. College Cardiology. 62.8 732-739 August 2013 Martin, Blaha et al.

Vertical Auto Profile

- Directly measures LDL
- Friedewald Formula not accurate when triglycerides are elevated
- LDL Pattern B
- LDL Pattern A

Take Home Pearls

- Standard LDL calculations don’t mirror the RISK of atherosclerosis
- New substrates: apoB, apoA1, and stratification of LDL types are being looked at as 
  predictors of AS
- AS includes a whole host of ophthalmic conditions

When does ASCVD Begin?

- PDAYS Study
  - Pathobiological Determinants of Atherosclerosis in Youth Study
  - Lesions in the intimal lining of ALL the aortas and 50% of the Right Coronary Arteries are present by age 9
Homocysteine (AminoAcid)

- Elevated plasma levels of homocysteine is an established risk factor for ASCVD, Cerebrovascular disease, peripheral vascular occlusive disease
- Hcy levels are lower in premenopausal women than in men and post menopausal women
  - May be related to the increased incidence of ASCVD in postmenopausal women

Homocysteine and the Eye

- Include Hcy levels in work up of patients with:
  - ASCVD
  - emboli
  - TIA, TVB
  - retinal vascular disease,
  - neuro visual field defects,
  - vascular diplopia

Retinal Vein Occlusions

- Did the thrombus form because a thick walled artery compressed a thin walled venule?
  - Then ASCVD is the underlying problem
- What if there is no evidence of ASCVD causing a compressive etiology?
  - Clotting moves up the differential list

Retinal Vein Occlusions: Etiology???

- What is the underlying problem?
  - THROMBUS
- Our goal, clinically, is to determine HOW that thrombus formed
Clotting Considerations in RVO

• In the absence of clinical findings of ASCVD (no dyslipidemia, no diabetes, no HTN...)

• What can the patient clot more readily?

Antiphospholipid Syndrome APS

• AKA: antiphospholipid antibody syndrome

• Autoimmune where by antibodies (anticardiolipin antibodies) are produced that ultimately increase coagulability

• Arterial and venular thrombus formation

• 'younger' individuals

• History of multiple miscarriages

Factor V Leiden

• Genetically inherited autosomal dominant

• Anticoagulant protein C cannot inactivate Factor V...coagulation

• Primarily venular thrombus formation

• Consideration in young patients <45 and Caucasians of European descent

Labs for Coagulability

• CBC

• Anticardiolipin Antibodies

• ELISA

• Factor Leiden V

• Lab to determine

Retinal Vascular Labs: Summary

• Considerations of which labs is predicated upon patient specific findings.....ALWAYS!

• CBC as baseline

• ASCVD etiology???

• Lipids, stratified

• Diabetes, HTN, obesity, smoking???

• Homocysteine

• CRP

• Extraneous coagulation

• Antiphospholipid antibodies

• Factor V Leiden

Optic Nerve Indications

• NAION

• AAION
57 y/o Hispanic Woman

• c/o acute loss of vision OS
• BCVA:
  • 20/20 OD
  • 20/200 OS
Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)

• 2nd most common optic neuropathy
• Age > 50
• Caucasian predilection (based-on cup size)
• Rapid onset painless vision loss (+/- acuity)
• Afferent pupillary defect

Risk Factors for NAION

• Hypertension: 34-47%
  • Only significant for young, age-matched NAION patients
• Diabetes: 10-24%
  • Statistically significant for all ages of NAION
• Homocysteine (?)
• MI (?)
• Smoking (?)
• Stroke (?)
• CRP (?)
• Thrombophilic factors (lipoprotein (a), factor V Leiden) (?)
• Iatrogenic factors (PDE-5 inhibitors) (?)

Arnold AC. J Neurol Ophthalmol 2003
Pianta et al. Ophthalmology 2009

Optic Disc - Acute

• Disc edema with mild-modest hemorrhage
  • Coexistent or preceding vision loss
• Prelaminar capillary telangiectasis
• Juxtapapillary arteriolar attenuation & sheathing
• Small cup in same/fellow eye (“disc at risk”)

Optic Disc - Chronic

• Rapid optic atrophy
  • < one month

F/U x 6 months

• BVA:
  • 20/20 OD
  • 20/80 OS
Visual Recovery with NAION (IONDT results)

- Optic nerve sheath decompression
  - Improved: 32.6%
  - Worsened: 23.9%
- Followed
  - Improved: 42.7%
  - Worsened: 12.4%

IONDT Research Group JAMA 1995

Clinical Kernels: NAION

- Older age than optic neuritis
- Vasculopathic risk factors (notably diabetes)
- No pain!
- Some disc hemorrhage
- Altitudinal field / ganglion cell complex loss
- Approximately 40% spontaneous visual improvement (dyschromatopsia not as pronounced as in ON)
- PDE-5 inhibitors (?)

Arteritic AION/ GCA

- GCA is an arterial vascular disease
  - It affects arteries of medium size
    - Temporal artery as well as other distributions of the external carotid
- 2-10% of GCA patients develop a CRAO either at onset of other symptoms or at a later date
GCA/AION

- Sudden onset of vision loss
- Fatigue, malaise, claudication, neck pain, facial pain
- + APO
- Disc swelling/hemorrhage
- Older than NAION

- Vision loss is severe, and other eye is at risk
- STAT Labs:
  - CBC w/ Diff
  - ESR
  - CRP

C Reactive Protein levels:
- are a marker of vascular inflammation
- if elevated, are a risk factor for cardiovascular disease
- if elevated, are more sensitive in determining AION than ESR

Ischemic Optic Neuropathy

- Hayreh et al, AJO March 1997
  - ascertained reliability, sensitivity and specificity of signs, symptoms and diagnostic tests for early diagnosis of GCA
  - Findings most strongly suggestive of GCA:
    1: jaw claudication
    2: C-reactive protein > 2.45mg/dl
    3: neck pain
    4: ESR > 47mm/hr

- Hayreh et al, AJO March 1997
  - Sensitivity of CRP: 100%
  - Sensitivity of ESR: 90%
  - ESR + CRP gave best specificity (97%)
Clinical Kernel: Arteritic-AION

- AKA: Giant Cell Arteritis
- Elevated CRP and ESR
- Patients need to be medicated with oral steroids (60-80 mg/day)
- Definitive diagnosis is via temporal artery biopsy
  - Biopsy must be made within 2-3 days of starting PO steroids
  - Temporal artery ultrasonography

Case

- 82 y/o new patient referred for evaluation of vision loss OD
- Difficult historian...onset of symptoms vague
- Recent cessation of HTN and cholesterol meds secondary to lethargy 'not feeling well'
- CF OD
- + APD OD

Case

- ESR = 18
- CRP = 0.45
- BP in office 198/106

Case Not GCA!

Case Management

- HTN and Lipid control...D/C ASA
Case Management

Retinal Vascular/ON Summary

- Atherosclerosis remains a significant etiology for many retinal vasculopathies
- Venular Problem?
  - AS, clotting etiologies...history and demographics
- Non Glaucomatous Optic Neuropathies
  - Sudden vision loss, APD
  - History and demographics.

IMAGING

Part 2

Plain Film X-Ray

- Electromagnetic Radiation
- Exposure Film
- Advantages: Fast, Widely Available, Inexpensive
- Disadvantages: Limited Value, Radiation to the Eye and Body
- Indications: Fractures, Chest/Sinus Films, Foreign Body Localization
- Ordering: Series Requested, Tentative Dx, Views Requested

Plain Film X-Ray

- Fairly limited use in primary eye care
- Typically CXR and Lumbar PA and Lateral Views
  - Sarcoidosis
  - Reiter’s
  - HLA-B27
  - Ankylosing Spondylitis

Computed Tomography

- Many advantages:
  - Readily accessible
  - Inexpensive
  - Good overall views
- Disadvantage:
  - Electromagnetic radiation
  - Does not image soft tissue well
Computed Tomography

- What it images well:
  - Bone
  - Air
  - Fresh hemorrhage

Computed Tomography (CT)

- Same Physics as Plain Film
- Computer Integrated & Image Formation
- Soft Tissue Differentiation
- Contrast Enhancement Usually Recommended
- Indications: Orbital Fx, Foreign Body, Intracranial Acute Hemorrhage (sub Arachnoid), Sinus
- Ordering: Same as Plain Film, w/ or w/o Contrast

CT - Orbital Trauma

(Subjective)

- 52 YOWF c/o Face vs. Ground in Bike Accident. She Denies Reduced VA or Diplopia. Her Cheek is Tender and c/o Retro-Orbital Pain when Sneezing.
- POHx: Unremarkable
- PMHx: Unremarkable
- Meds: None
- NKDA

CT - Orbital Trauma

Discussion

CT Angiography

- Same physics as conventional CT
- Electromagnetic radiation
- More software intensive than conventional CT
- Contrast material usually employed
- Quickly becoming as useful as conventional angiography
  - Sharp images
  - Low morbidity and mortality
CT Angiography

- Clinical Uses:
  - Pulmonary emboli
  - Venous thrombosis
  - Aortic aneurysms and dissections
  - Carotid stenosis
  - Cerebral aneurysms
  - Cerebral tumor vascular supply
  - Coronary artery visualization

- Contraindications/Complications
  - Contrast dye (iodine) related
  - Pregnancy
  - Extravasation at injection site

- Limitations:
  - Unable to visualize small vessels
  - Patient movement blurs images
  - Significant stenosis difficult to visualize

CTA: Carotid Arteries

- Digital Subtraction Angiography is considered the gold standard (Carotid DSA)
  - Risks associated with procedure
- CTA of Carotids
  - Slightly underestimates degree of stenosis
  - Less invasive, less risk
- CTA vs DSA:
  - Highly correlated

Carotid Artery Disease

- Ordering Protocol
  - Carotid Dopplers
    - Non-invasive
    - "Screener" for presence of likely disease
    - Quantifiable stenosis
  - CTA
    - Mildly invasive
    - Surgical Guidance
Magnetic Resonance Imaging (MRI)

- Atomic Orientation and Signal Production by Alternating High Levels of Magnetic Fields
- Superior for Soft Tissue Differentiation
- Gadolinium Contrast
- Special Techniques for Orbits (Fat Suppression/Surface Coils)
- Some Limitations
- Ordering: Indicate Area of Question w/ or w/o Contrast, r/o Diagnosis, Special Techniques

MRI-EOM Deficit Subjective

- Sunday page by local urgent care MD
- Has a 22 year old white female with complaints of “eyes not working together”
- MD says vision good, pupils look OK, but her eyes are doing something he has never seen before
- Sounds like decompensated phoria; OK to see patient Monday AM

EOM Pattern

MRI and Multiple Sclerosis

- Case just seen MRI needed to confirm clinical suspicion of pontine lesion
- How do we typically see patients in whom we suspect that MS may be at hand?

OK, ON and they’re in you chair

- A 28 year old presents to you with classic findings of optic neuritis (+ APD, reduced acuity, decreased color vision, cecocentral scotoma). Do you image her with an MRI?
  - 1: Yes
  - 2: No

Obvious Next Question

- Why image a patient with classic findings of optic neuritis?
  - Incorrect answer:
    - To see if they have MS
  - Correct answer:
    - To assess their risk of developing MS
MRI and Optic Neuritis

Magnetic Resonance Angiography (MRA)
- Non-Invasive Angiogram
- Avoids Potential Complications of IV Angiogram
- Paramagnetic Contrast not Needed
- Generates 3-Dimensional Multi-Plane Scans
- Can Detect Aneurysms as Small as 3-4 mm
- Indications: TIA, OIS, CN Palsies, A-V Mal.

MRA - CN III Palsy (Subjective)
- 50 YOWM c/o Int. Horiz. Diplopia X 2 d. Pt. has Difficulty Verbalizing Specifics.
- POHx: Unremarkable
- PMHx: GI Ulcer
- FMHx: DM, HTN, CVA, Colon Ca
- Meds: Prilosec
- NKDA

MRA - CN III Palsy (Objective)
- BVA: 20/25 OD, 20/25 OS
- Neuro: P 8mm/6mm Rd, APD; CF FTFC, EOM Down & Out Deviation OD w/ 3 mm Ptosis
- SLE: Unremarkable
- TA: 16/14 mmHg
- DFE: Unremarkable
- BP: 185/95 LAS

MRA - CN III Palsy Discussion
MR Venography MRV

- Useful in evaluating the dural venous sinuses
- Cerebral Venous Sinus imaging

Dural Venous Sinuses

- An important component to evaluate for the patient with papilledema
  - The manifest disc swelling is a result of thrombosis in a dural venous sinus, preventing venous drainage from the head
  - Resultant increase in ICP

Magnetic Resonance Venography

MRV Clinical Utilization

- Papilledema
- Normal MRI
  - No space occupying mass
  - No shift/displacement of cerebral tissue
- Normal LP opening pressures*
  - *sometimes
  - Post partum
- Cerebral Venous Sinus Thrombosis

Cerebral Venous Thrombosis CVT

- Clinical picture resembles pseudotumor
  - Headache
  - Disc edema
- Cavernous sinus thrombosis
  - Cavernous sinus syndrome
- Considerations:
  - Hypercoaguable syndromes (anticardiolipin Ab's, Factor Leiden 5 allele, etc.), trauma, pregnancy, dehydration, altitude sickness...
  - Mortality due to transtentorial herniation
Questions???

Thank You!