Case Presentations: Neuro-ophthalmology and Systemic Disease

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Neuro-ophthalmic Disease

• Relatively “new” compared to other subspecialties
  • Ancient Egyptians performed cataract surgery
  • Ancient Greeks developed salves for infections
  • Limited knowledge regarding eye movement and perception
    • 1820’s: believed globe moved around a fixed point at posterior surface
    • 1880’s: believed cerebral cortex had little, if any, role in perception
  • 1918: Sir Gordon Holmes mapped retina on the visual cortex
  • 1927: Harry Moss Traquair describes our visual field as "an island of vision or hill of vision surrounded by a sea of blindness"
  • 1947: Dr. Frank Walsh published textbook on neuro-ophthalmology
Diplopia

- *Diplous* (Greek for double) + *ops* (Greek for eye)
- Often the first manifestation of many systemic disorders, especially muscular or neurologic disease
- Incidence in United States is unknown
- Eye hospital in London, UK reported the incidence of diplopia as the chief complaint in 1.4% of the presenting cases
- Polyopia: the perception of more than 2 images
  - Often a monocular phenomenon due to refractive aberrations
  - Cerebral polyopia due to extrastriate visual cortex lesions

Sudden Vision Loss

- Incidence unknown due to variable presentations
- The most common cause of painless sudden visual loss is ischemia
- Other etiologies include infection, inflammation, trauma, compression
- Functional visual loss: decreased visual acuity or loss of visual field with no underlying physiologic or organic etiology
  - Accounts for up to 5% of referrals to eye care providers
  - 79% are female and 21% are male

Myasthenia Gravis

- Autoimmune disease
- Antibodies block acetylcholine receptors at neuromuscular junction
- Ocular involvement with myasthenia gravis
  - 70% initially present with ocular signs
  - 90% of all show ocular signs
- Ocular signs:
  - 10% ptosis only
  - 90% ptosis and extraocular muscle weakness
Ocular Myasthenia Gravis

• 50 to 80% progress to general myasthenia gravis
• 10 to 20% have spontaneous remission
• Younger patients = better prognosis
Work Up

• Tensilon test
  • Watch false positives!
• Electromyography
• Blood work
  • Ach antibodies
  • Thyroid panel
  • ANA
  • DM
• Mediastinal imaging
  • 70% have thymic hyperplasia
  • 5 to 20% have thyoma
Clinical Tests

• Sleep Test
  • Complete ocular examination and external photographs
  • Patient then rests in darkened room and encouraged to sleep
  • After 30 minutes patient is awakened and immediately photographed
  • Measure palpebral fissures, ocular alignment and motility
  • Improvement lasts two to five minutes

• Ice Test
  • Lower temperature reduces action of acetylcholinesterase
  • Measure palpebral fissures
  • The patient is instructed to close eyes for two minutes, then palpebral fissures are assessed again
  • Ice pack applied to closed eye(s) for two minutes, then the size of the palpebral fissure is immediately assessed
  • Test is positive if the size of the fissure is greater after cooling than after rest
  • MG patients usually exhibit 2 mm or more increase
  • 90% sensitive and 100% specific for MG
Treatment

• Pharmacologic:
  • Anti-acetylcholinesterase agents
  • Immunosuppressive agents
• Thymectomy
• Plasmapheresis
Pituitary Adenoma

- Pituitary adenomas are benign, slow growing tumors
- Comprise 10-15% of all intracranial tumors
- Classified as micro < 1 cm or macro > 1 cm
- Secretory vs. nonsecretory
- Nonsecretory more likely to have visual effects, in addition to causing hypopituitarism. Also may compress other nearby neurologic structures.
- Secretory are functioning tumors, symptoms depend on hormone secreted
Pituitary Adenoma

- Pituitary gland anterior lobe secretes 6 hormones:
  - thyroid-stimulating hormone (TSH)
  - adrenocorticotropic hormone (ACTH)
  - follicle-stimulating hormone (FSH)
  - leuteinizing hormone (LH)
  - growth hormone (GH)
  - prolactin (PRL)
- Posterior pituitary gland secretes vasopressin and oxytocin
- Most tumors arise from anterior lobe increasing in size creating both systemic & visual effects (due to impingement on anterior notch of chiasm)
- Tumor growth asymmetric, therefore visual field loss asymmetric
Giant Cell Arteritis

- Most common primary vasculitis in adults
  - Incidence in people over 50 is about 18 per 100,000 per year
  - Incidence increases with age and peaks in 8th decade of life
  - Highest prevalence in northern latitudes (Northern European descent)
  - Women 2 to 6 times more commonly affected than men

- Symptoms
  - Headache (most common)
  - Jaw claudication
  - Scalp tenderness
  - Vision loss (30 to 60% of patients)
  - Polymyalgia rheumatica present in 40%

Giant Cell Arteritis

- Arteritic anterior ischemic optic neuropathy (AION)
  - Due to occlusion of the short posterior ciliary arteries
  - May also result from vasculitic ischemia of the choroid, the posterior optic nerve, or retina.

- 54% have initial visual acuity of finger counting or worse
- 50% of untreated individuals develop bilateral involvement days to weeks after presentation
- 44% report preceding episodes of transient vision loss
- 21.2% have visual complaints alone

2. Birkhead NC, Wagener HP, Schick RM. Treatment of temporal arteritis with adrenal corticosteroids: results in 55 cases in which lesion was proven at biopsy. JAMA. 1958;163:821–827.
Giant Cell Arteritis: Work Up and Diagnosis

• Suspect based on:
  • Patient history
  • Medical History
  • Clinical Examination

• Order lab work:
  • Complete blood cell count with differential
  • Erythrocyte sedimentation rate (ESR)
  • C-reactive protein (CRP)

• Order temporal artery biopsy
  • Diagnostic with 100% specificity
  • Relatively low sensitivity (15 to 40% false negative rate)

ESR and CRP

- In study looking at 119 patients with biopsy proven GCA:
  - ESR had a sensitivity of 86%
  - Elevated CRP had a sensitivity of 97.5%
  - Sensitivity of the ESR and CRP together was 99%
  - 1 of the 119 patients (0.8%) had normal ESR and normal CRP
  - 2 patients (1.7%) had elevated ESR and a normal CRP

Giant Cell Arteritis: Treatment

- Glucocorticosteroids are mainstay of treatment
- Initiated immediately and aggressively to suppress inflammation and preventing visual loss and ischemic stroke
- Route of administration debated (IV induction vs. PO only)
- Prednisone dosage varies widely in literature from 20 to 100 mg / day
  - Most patients respond to 40 to 60 mg / day
- Taper over 1 to 2 years

Giant Cell Arteritis: Treatment

- Over 50% have at least one relapse during taper
  - “smoldering” disease with persistent elevation of interleukin-6 levels
  - CRP and ESR can be within normal limits!
- Follow patients closely for at least one year after discontinuation of prednisone

Corticosteroids: Side Effects

• 58% of patients with GCA have at least 1 serious side effect
  • Acute myocardial infarction
  • Brain ischemia
  • Hypertensive crisis
  • Psychosis
  • Hyperosmolar decompensation of diabetes
  • Bone fractures
  • Impaired wound healing

• Are there any other options?

Methotrexate

• Disease-modifying antirheumatic drug (DMARD)
• Chemotherapeutic Effect: competitively inhibits dihydrofolate reductase → inhibits synthesis of DNA, RNA and proteins
• Immunosuppressive Effect:
  • Inhibits enzymes involved in purine metabolism → accumulation of adenosine
  • Inhibits T cell activation
  • Suppresses intercellular adhesion molecule expression of T cells
  • Down regulates B cells
  • Increases CD95 sensitivity of activated T cells
  • Inhibits methyltransferase activity → deactivation of enzymes involved in immune system function
  • Inhibits binding of interleukin 1-beta to cell surface receptors
Methotrexate and Giant Cell Arteritis

• Up until recently, was most studied steroid-sparing agent
• 3 randomized placebo controlled trials compared methotrexate with placebo as adjunctive therapy with corticosteroids
  • Study methods criticized and contradictory results
  • 2 studies found no significant decrease in cumulative steroid dose or in relapse rate at 1 year among patients treated with corticosteroids and methotrexate compared with those treated with corticosteroids and placebo
  1,2
• 1 study reported a significant decrease in cumulative steroid dose and relapse rate at 2 years among patients treated with adjuvant methotrexate compared with placebo

Other Steroid-Sparing Options...

• **Infliximab:** monoclonal anti-TNF-α antibody  
  • Theorized that there is abundance of the cytokine tumor necrosis factor-α (TNF-α) within giant cells, macrophages, and T cells  
  • No significant benefit, trials discontinued

• **Azathioprine:** immunosuppressant (transplants)  
  • Small benefit over placebo after treatment for 1 year  
  • High dropout rate (hepatotoxicity and carcinogenesis)

• **Cyclosporin A:** immunosuppressant  
  • No efficacy date provided by study  
  • Poorly tolerated with high rate of premature termination

IL-6 and Giant Cell Arteritis

• IL-6 is produced by macrophages (and other cells) within blood vessel wall of temporal arteries
• IL-6 is upregulated within inflamed arteries and in peripheral circulation
• Serum IL-6 levels mirror disease activity and decline with effective glucocorticoid therapy
• Pharmacologic inhibition of IL-6 system can ameliorate vascular inflammation
Tocilizumab (Actemra®)

• Humanized interleukin-6 receptor antagonist
• Interleukin-6 triggers synthesis of acute phase proteins, promotes the transition from acute-to-chronic inflammation and facilitates the development of specific immunity
  • Modulates activation, proliferation and differentiation of different T-cell subsets including CD8, Th17 and regulatory T cells
  • Stimulates terminal differentiation of B cells
  • Enhances the survival of plasma cells
  • Induces ‘proinflammatory’ phenotype in monocytes, endothelial cells and stromal cells
• FDA approved for adult patients with moderately to severely active rheumatoid arthritis who have used one or more disease modifying antirheumatic drugs without adequate relief
• May 2017: FDA approved for treatment of giant cell arteritis
Tocilizumab for Patients With Giant Cell Arteritis

- A Phase II, Randomized, Double-blind, Placebo Controlled Study of Tocilizumab in Patients with Giant Cell Arteritis
- Compared tocilizumab (8mg/kg every 4 weeks x 52 weeks) + prednisolone to placebo + prednisone
- 85% of subjects given tocilizumab vs. 40% given placebo reached complete remission by week 12
- Relapse-free survival was achieved in 85% in the tocilizumab group vs. 20% in the placebo group by week 52
- Cumulative prednisolone dose of 43 mg/kg in the tocilizumab group vs. 110 mg/kg in the placebo group after 52 weeks
- IL-6 blockade is first treatment confirmed to be effective in GCA since cortisone was invented in 1948

Standardized Prednisone-Taper Protocols: GiACTA

**Daily Prednisone Dosage**
- Week 1: 60 mg
- Week 2: 50 mg
- Week 3: 40 mg
- Week 4: 35 mg
- Week 5: 30 mg
- Week 6: 25 mg
- Week 7: 20 mg
- Week 8: 15 mg
- Weeks 9-10: 12.5 mg
- Week 11: 10 mg

**Daily Prednisone Dosage**
- Week 12: 9 mg
- Week 13: 8 mg
- Week 14: 7 mg
- Weeks 15-16: 6 mg
- Weeks 17-18: 5 mg
- Weeks 19-20: 4 mg
- Weeks 21-22: 3 mg
- Weeks 23-24: 2 mg
- Weeks 25-26: 1 mg
- Weeks 27-52: placebo
Study of RoActemra/Actemra (Tocilizumab) in Patients With Giant Cell Arteritis (GiACTA)

• Phase III, double blind, randomized, controlled trial
• 251 patients from 76 sites across 14 countries
• Results show tocilizumab + six month steroid regimen more effectively sustained remission through one year compared to a six or 12-month steroid only regimen
• October 4, 2016: The US Food and Drug and Administration granted Breakthrough Therapy Designation status for treatment of multiple autoimmune disease
• May 22, 2017: FDA approval announced

Foster Kennedy Syndrome

- First described in 1911 by neurologist Robert Foster Kennedy
- Described compression of one optic nerve by a sub-frontal meningioma or olfactory groove tumor which results in compressive optic neuropathy (optic nerve head pallor) and increased intracranial pressure causing contralateral optic nerve head edema

Pseudo-Foster Kennedy Syndrome

- Diagnosis of exclusion!
- Sequential anterior ischemic optic neuropathies most common
- R/O giant cell arteritis
  - Check complete blood count with differential, erythrocyte sedimentation rate and C-reactive protein
- Modify vascular risk factors
- No other interventions have found to be effective
Cilioretinal Artery Occlusion

• The cilioretinal artery was first described by Müller in 1856
• Congenital anomaly
• Belongs to posterior ciliary artery system, so it usually arises from the peripapillary choroid or directly from one of the short posterior ciliary arteries
• Found in 49.5% of all patients or in 32% of eyes, bilateral in 14.6%
• Cilioretinal Artery Occlusion is a distinct clinical entity because it does no arise from central retinal artery
  • Non-arteritic cilioretinal artery occlusion alone
  • Arteritic cilioretinal artery occlusion associated with giant cell arteritis
  • Non-arteritic cilioretinal artery occlusion associated with CRVO or HRVO

Acute Retinal Arterial Ischemia: An Emergency Often Ignored

- Retinal arterial ischemia is a form of anterior circulation ischemic stroke caused by decreased blood flow in the ophthalmic branches of the internal carotid artery.
- Transient ischemic attack (TIA), including amaurosis fugax, is well known to be a prodromal syndrome of ischemic stroke.
- Among patients with TIA 10% to 15% have stroke within 90 days, with approximately half occurring within 48 hours.
- Patients with TIA who survive the initial high-risk period have a 10-year stroke risk of 19%, and a combined 10-year stroke, myocardial infarction or vascular death risk of 43% (4% per year).

Transient Ischemic Attack

- American Heart Association and National Stroke Association recommend all patients with presumed retinal ischemia (whether transient or permanent) undergo urgent brain imaging and etiologic testing similar to patients with cerebral ischemia.

- Patients with abnormal diffusion-weighted MRI are diagnosed as having an acute stroke regardless of initial clinical presentation, and are admitted to the hospital and managed accordingly.

- Patients with normal MRI results are evaluated within 24 hours in a dedicated TIA clinic, an emergency department observation unit, or a stroke center.

- This is not routinely performed for patients with retinal ischemia in the United States!
  - Most are never sent to Emergency Room or a stroke neurologist for immediate evaluation.
  - Most health professionals and public consider retinal TIAs benign with low risk of subsequent stroke.
  - Time to treatment for retinal TIA: 48.5 days vs. for cerebral TIA: 15.2 days.
Co-occurrence of Acute Retinal Artery Occlusion and Acute Ischemic Stroke

• Studied 33 consecutive patients with acute RAO who underwent diffusion weighted MRI within 7 days of the onset of symptoms
• Acute ischemic stroke detected in 24.2% of subjects with RAO
  • 37.5% of these had no neurologic signs or symptoms
  • Most infarction patterns were small, multiple and scattered
  • All had identifiable causes

Abducens Nerve Palsy

• Complicated:
  • Brainstem
  • Subarachnoid
  • Middle cranial fossa
  • Cavernous sinus
  • Orbital

• Isolated:
  • Pediatrics
  • Young adults
  • > 50 years old
Tolosa-Hunt Syndrome

- Painful ophthalmoplegia caused by nonspecific inflammation of the cavernous sinus or superior orbital fissure
- Diagnosis of exclusion
- Corticosteroids are the treatment of choice, usually providing significant pain relief within 24-72 hours of therapy initiation
Orbital Pseudotumor

- Second most common inflammatory process of orbit (5-10% of orbital processes)
  - Orbital pseudotumor
    - Female:male ration 1:1
    - Mean age 45
    - 97% unilateral (except pediatrics)
  - Idiopathic orbital myositis
    - Female:male ratio 2:1
    - Mean age 37
    - 50% bilateral

- Signs include diplopia, proptosis, conjunctival injection, chemosis, periorbital edema, ptosis
- Cardinal sign is worsening pain with eye movement
- Visual function usually normal in orbital myositis
- Visual function may be decreased due to compressive optic neuropathy
Orbital Pseudotumor

• Pathogenesis unknown; however, likely immunologic
• Orbital myositis has been associated with systemic lupus erythematosus, rheumatoid arthritis and Crohn’s disease
• May spontaneously resolve after 3 to 6 weeks
• Treatment recommended to relieve pain, diplopia, limit muscle fibrosis and prevent recurrences
• Dramatic improvement after 3 days of systemic steroids
Migraine Headaches

• Common cause of neuro-ophthalmic complaints
• Visual symptom most common
• Symptoms may also include photophobia, pupillary dilation and ophthalmoplegia
Optic Nerve Sheath Meningioma

- Benign
- 20% of all orbital meningiomas, 30% of all optic nerve neoplasms
- Arise from arachnoid cap cells of the optic nerve sheath
- May be direct extension from intracranial meningioma
- Mean age at presentation: 40 years old
- 25% of all ONSM found in children, worse prognosis
- Three times more common in women
- Increased risk in patient with neurofibromatosis type II
- Treatment: observation vs. radiation therapy
- Surgical intervention not recommended
Sarcoidosis

• Abnormal collection of inflammatory cells (granulomas)
• 5-10% of those with sarcoidosis develop central nervous system involvement
  • Of those, 50-70% have abnormalities of cranial nerves
  • CN VII most commonly affected, has best prognosis
• 1% of those will have neurosarcoidosis alone without involvement of any other organs
• Seizures present in 15% of cases
• 10% mortality
Optic Neuritis: Signs and Symptoms

• Acute vision loss (20/20 to NLP)
• Pain on eye movement (92.2%)
• Dyschromatopsia
• Uthoff’s sign
• Afferent pupillary defect
• Visual field defect
• Mild optic nerve swelling
• Mild vitritis
• Pulfrich Phenomenon (altered depth perception)
Typical Optic Neuritis

- 77% female
- Average age 32 years (18-46)
- Pain on eye movements in 92.2%
- MRI: Periventricular abnormalities in 59% vs. 35% when no clinical signs of multiple sclerosis
- Visual field defects:
  - 48% diffuse loss
  - 20% altitudinal, arcuate or nasal step
  - 8% central or centrocecal
  - 16% other
Atypical Optic Neuritis

- Outside 18 to 46 year span
- Painless
- Bilateral
- Continues to worsen beyond 14 days of onset
- Presence of other causative condition
  - Connective tissue disease
  - Infections
  - Infiltrative
- Evidence of retinitis, vitritis or uveitis
Optic Neuritis: Differentials

- Viral infection
- Intra-ocular inflammation
- Malignant hypertension
- Diabetic papillitis
- Sarcoid
- Syphilis
- Tuberculosis
- Collagen Vascular Disease
Optic Neuritis: Management

- No effective treatment of idiopathic optic neuritis
- If periventricular abnormalities on MRI
  - IV Methylprednisone 1gram QD in divided doses for 72 hours
  - Then prednisone 1mg/kg/day PO with taper over 11 days
- Check glucose, PPD and chest x-ray first
Treatment Options

• Immunomodulators for chronic therapy reduce number and severity of relapses
  • Interferon beta (IFNβ)
  • Glatiramer acetate (GA)
  • Natalizumab

• Fingolimod (Gilenya)
  • First FDA approved oral immunomodulating agent
  • Sequesters lymphocytes
  • Fingolimod Associated Macular Edema
Optic Neuritis: Prognosis

• Good
• 70% recover to 20/20
• Typical optic neuritis:
  • 95% recover to 20/40 or better within 1 year
  • Complete recovery usually within 8 weeks
• Permanent subtle color deficits common
Doxycycline Induced Intracranial Hypertension

- Increased intracranial pressure associated with drugs including tetracycline, minocycline and doxycycline
- Proposed mechanism: Drug affects cyclic adenosine monophosphate at the arachnoid granulations which interferes with the energy dependent absorption
- Time to develop intracranial hypertension is unknown
  - In largest review of intracranial hypertension induced by minocycline, time of onset ranged from 2 weeks to 1 year
- Raised intracranial pressure persists for 2 to 5 weeks after discontinuing tetracycline

Intracranial Hypertension: Signs and Symptoms

• Asymptomatic
• Headaches (99%)
• Transient vision loss
• Diplopia
• Tinnitus
• Nausea
• Normal to decreased visual acuity, color vision and contrast sensitivity
• Papilledema
• No spontaneous venous pulsation
• Visual field defects
Medication Induced Intracranial Hypertension

• Vitamin A toxicity
• Tetracycline
• Oral contraceptives
• Nalidixic acid
• Lithium
• Steroid use / withdrawal
Oral Contraceptives

• Pseudotumor cerebri
  • Exact mechanism unknown
  • Some case-control studies show no association\textsuperscript{1,2}
  • Why predominantly in obese women of childbearing age?
    • Female sex hormones + endocrinologically active adipose tissue lead to the syndrome in genetically predisposed individuals\textsuperscript{3}
    • Retinoic acid (which has been linked to pseudotumor cerebri) influenced by both estrogen and adipose tissue.\textsuperscript{3}

• Sinus venous thrombosis

Acute Disseminated Encephalomyelitis (ADEM)

• Inflammatory demyelinating condition
• Closely resembles multiple sclerosis (MS)
  • Multiple sclerosis:
    • Usually a chronic relapsing and remitting disease of young adults
    • Abnormalities of findings on cerebrospinal fluid immunoglobulin studies
  • ADEM:
    • Monophasic disease, often in pre-pubertal children.
    • Usually occurs after a febrile illness or immunization
    • Usually affects many systems of the body
    • Varied degrees of encephalopathy
• Continuum with MS and others?
Thank You!

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