I've Got What in My Eye?!
Ocular Manifestations of Systemic Disease

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HOA 2020

Disclosure

• None

Spectrum of Eye Care

What will be important to our future partners?
Key Elements for Healthcare Systems

Every day in the United States,
33 to 66 people to lose their eyesight
ED VISITS

In 2010, there were approximately
186,000 Diabetes-related ED visits for eye complications
VISION LOSS

Most Common Systemic Diseases with Ophthalmic Manifestations

• Diabetes Mellitus
• Hypertension
• HSV/HZO
• AIDS
• Sarcoidosis
• Graves Disease/Thyroid Disease
• Rheumatoid Arthritis
• Multiple sclerosis

DIABETES MELLITUS

Epidemiology

• Systemic, microvascular disease affecting (not limited to) the liver, kidneys, and eyes.
  – Type I caused by destruction of the islets of Langerhans in the Pancreas.
  – Type II caused by the body’s developed resistance to insulin.
• It is the most common cause of blindness in the 20-70 year old population.
  – Diabetic retinopathy is prevalent in 30% of the diabetic population.

Diabetes Mellitus

• Damages blood vessel lining and smooth muscle
  – Leading to CM retinopathy and neuropathy
• Who is affected:
  – 9.3% of Americans (almost 30 million people)
  – 28.5% of those older than 40 with diabetes have retinopathy

Diabetic Retinopathy

• Occurs due to a breakdown in the retina’s ability to auto regulate its blood supply properly
  – Hyperglycemia increases retinal blood flow and therefore causes “capillary hypertension.”
• This hypoxic environment causes an up-regulation of the angiogenic factor VEGF
  – VEGF stimulates the growth of new blood vessels to meet the needs of the starving retina.
Risk factors for developing DR
- Duration of DM
- Control of DM will not prevent but delays
  - Fasting BS <126 and A1C <7%
- Hypertension/Hyperlipidaemia
- Renal Disease
- Pregnancy
- Sleep apnea
- Obesity
- Smoking
- Anaemia

ETDRS Classification of Diabetic Retinopathy

<table>
<thead>
<tr>
<th>DR Level</th>
<th>Retinal Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild NPDR</td>
<td>At least one MA and 1 or more of following:</td>
</tr>
<tr>
<td></td>
<td>Retinal hemorrhages</td>
</tr>
<tr>
<td></td>
<td>Hard exudates</td>
</tr>
<tr>
<td></td>
<td>Soft exudates</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>Hemorrhages and MA or soft exudates, VB, and IRMA present</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>Any of the following and no signs of PDR (4-2-1 rule)</td>
</tr>
<tr>
<td></td>
<td>&gt;20 intraretinal hemorrhages in each of 4 quadrants</td>
</tr>
<tr>
<td></td>
<td>Definite venous beading in 2 or more quadrants</td>
</tr>
<tr>
<td></td>
<td>Prominent IRMA in 1 or more quadrants</td>
</tr>
<tr>
<td>Very Severe NPDR</td>
<td>2 or more of lesions of Severe NPDR</td>
</tr>
</tbody>
</table>


Severe NPDR
- Within one year, 52-75% of patients falling into this category will progress to PDR (Aiello 2003).

New Treatments Diabetic Retinopathy
- Proliferative Disease:
  - Pan Retinal Photocoagulation or Focal Laser
  - Ranibizumab (Lucentis) and Afibbercept (Eylea)-anti-VEGF
- RISE/RIDE studies showed a 3 line VA improvement in diabetic eyes treated with anti-VEGF

Diabetic Macular Edema
- DME incidence based on duration and type of diabetes
  - IDDM
    - <8 years rare
    - 10 years 7-10% incidence DME
    - 20 years 25-30% incidence DME
  - NIDDM
    - 10 years 5% incidence DME
    - 20 years 15% incidence DME
  - NIDDM w/ insulin use
    - 10 years 10% incidence DME
    - 20 years 30-35% incidence DME
- DME is also closely associated with degree of DR present
  - Mild NPDR ~ 3% incidence
  - Moderate- Severe NPDR ~40% incidence
  - PDR ~71% incidence

Current Treatment
- New mainstay treatment: Intravitreal Injections
  - Lucentis (FDA)
  - Eylea (recent FDA)
  - Ozurdex (recent FDA)
  - Avastin
  - Triamcinolone, Dexamethasone (Ozurdex), Fluocinolone acetonide
  - Focal laser with intravitreal injection

Hypertension
- Chronic elevated blood pressure
  - Essential vs secondary
  - The following guidelines were published by the Joint National Committee of Prevention, Detection, Evaluation, and Treatment of High Blood Pressure:

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>Stage 1 BP</th>
<th>Stage 2 BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120/80</td>
<td>&lt;120/80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-129/80</td>
<td>120-129/80</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>130-139/85</td>
<td>130-139/85</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>&gt;140/90</td>
<td>&gt;140/90</td>
</tr>
<tr>
<td>Hypertensive Emerg</td>
<td>&gt;160/100</td>
<td>&gt;160/100</td>
</tr>
<tr>
<td>Hypertensive Crisis</td>
<td>&gt;180/110</td>
<td>&gt;180/110</td>
</tr>
</tbody>
</table>
### Risk Factors HTN
- Genetic predisposition
- Excess salt
- Adrenergic tone
- Obesity
- Race
  - Blacks 33.5% vs whites 28.7%

### HTN
- Persistent high BP causes organ damage
  - Affects brain, heart, kidneys, and eyes
- Vascular changes occur with both chronic and acute elevated BP
  - Affect both retina and choroid
  - Early warning signs of organ damage from HTN

### Ocular Manifestations of HTN
- Anterior ischemic optic neuropathy
- Central or branch retinal artery occlusion (CRAO or BRAO)
- Central or branch retinal vein occlusions (CRVO or BRVO)
- Choroidal infarction
- Cranial nerve palsies
- Progression of diabetic retinopathy
- Glaucoma
- Hypertensive retinopathy
- Idiopathic polypoidal choroidal vasculopathy (IPCV)
- Macular edema
- Ocular ischemic syndrome
- Subconjunctival hemorrhage
- Transient visual obscurations

## HTN Retinopathy
- HTN patients have 50-80% chance of developing HTR
  - Patients with signs of HTR are more likely to have high BP

## HTR Classification
- **Keith-Wagener-Barker Hypertensive Retinopathy Classifications**
  - **Stage 1:** Mild retinal vascular changes (generalized arteriolar narrowing).
  - **Stage 2:** Moderate to severe retinal vascular changes (arteriovenous crossing changes).
  - **Stage 3:** Stage 1 and 2 findings, plus cotton-wool spots, retinal hemorrhages and exudates
  - **Stage 4:** Stage 3 findings, plus associated optic nerve head swelling and macular star formation.


## HTR Management
- **Stage 1-3**
  - Observation and management of BP with DFE of ten
- **Malignant HTN ** >200/140
  - Emergency referral for treatment with PCP or ER

## Vein Occlusions
- Arteriosclerosis associated with CRVO and BRVO due to arteries and veins sharing of tissue
- End result is blood stasis and hypoxia: cycle occurs when blood backs up in capillary beds, then leakage, edema, and flame hemorrhages in anterior capillary bed and then inter-retinal hemorrhages in deeper capillary bed
- Aging, HTN, elevated cholesterol, diabetics, increased IOP
- HTN contributes to thrombosis leading to vein occlusion
  - 50% BRVO linked to HTN

## Risk Factors
- Increase risk with aging, HTN, elevated cholesterol, diabetes, increased IOP
- HTN contributes to thrombosis leading to vein occlusion
  - 50% BRVO linked to HTN

## CRVO/BRVO Treatment
- Treat the complications
  - Neovascularization vs macular edema
    - Injections
    - Steroids vs anti-VEGF
    - Laser photocoagulation
    - Surgical therapy
Artery Occlusions
- Occlusion of the bloodflow in the retinal blood vessel
  - Embolism (hollenhorst plaque), thrombus, inflammatory, traumatic
- Central retinal artery occlusion (CRAO) vs branch retinal artery occlusion (BRAO)
- High risk
  - Atherosclerosis
  - Cardiac disease
  - Coagulopathy (sickle cell, oral contraceptive, platelet)
  - Collagen vascular disease

HERPES: HSV/HZO
- Herpes virus
  - Herpes simplex virus type 1 (HSV-1)
  - Herpes simplex virus type 2 (HSV-2)
  - Varicella-zoster virus (VZV/HZV)
  - Cytomegalovirus (CMV)
  - Epstein Barr virus (EBV) (Mons)

Herpes Simplex Virus
- Can be contagious through contact with saliva or an open blister
  - HSV-2 periodically sheds the virus
- Primary vs. recurrent infections
  - More common as a recurrent HSV
- Remain dormant in cell bodies of neurons in the sensory ganglia
  - More than 90% carry the latent virus
- Active phase can lead to destructive inflammatory phase

HSV Ocular Signs and Symptoms
- Symptoms
  - Pain
  - Photophobia
  - Blurred VA
  - Tearing
  - FB sensation
- Signs
  - Recurrent
  - Unilateral
  - Follicles
  - Palpable preauricular lymphadenopathy
  - Eyelid vesicles
  - Epithelial dendrites
  - Decreased K sensitivity
  - K edema
  - KPs
  - Iris stroma / sphincter
  - High IOP
  - Vitritis
  - Retinits
  - Papillitis

Primary Ocular HSV Infection
- Unilateral blepharoconjunctivitis
- Follicular conjunctivitis
- Palpable preauricular lymphadenopathy
- Skin or eyelid vesicles
- Epithelial keratitis
- Stromal keratitis / uveitis are rare

Recurrent Ocular Infection
- Reactivation of virus in latently infected sensory ganglion
- Recurrence 27% at 1 year, 50% at 5 years, 63% at 20 years
  - Increased risk with each occurrence
  - Increased risk with DES and CL use
- Can occur in almost any ocular tissue
  - Blepharoconjunctivitis
  - Epithelial keratitis – lowest risk
  - Stromal keratitis – highest risk
  - Iridocyclitis

Treatment for HSV Epithelial Keratitis
- Dendritic keratitis usually resolves within 3 weeks
- Goal to minimize stromal damage and scarring
  - Consider epithelial debridement
- Topical / Oral antivirals
- Topical steroids??
Diagnosis

- HSV Epithelial Keratitis OS
  - Treatment:
    - Zirgan 5X daily
    - Zirgan 0.15% ganciclovir ophthalmic gel
      - Approved for treatment of acute herpetic keratitis
      - Dosage: One drop 5 times a day until healed, then
        one drop 3 times a day for 7 days
      - Supplied in 5 gm tube

Treatment for HSV Stromal Keratitis

- Topical corticosteroids
  - Prednisolone acetate 1% q2h with taper over 1-2 weeks
  - Difluprednate q.d.

- Topical / oral antiviral
  - Trifluridine q.d.
  - Acyclovir 400 mg 5 times a day
  - Valacyclovir 500 mg q.d.

- Use concurrently until patient off steroids

Herpes and Bell’s Palsy

- HSV or HZV has been shown to cause Bell’s Facial Nerve Palsy
  - Main concern is dry eye secondary to poor lid function

Herpes Zoster Ophthalmicus

- HZO accounts for 10-25% of all cases of shingles
- 90% of U.S. population infected with V2V by adolescence
- 100% of U.S. population by 60 years of age
- 1.5-3.4 cases per 1,000 individuals
HZO: Signs and Symptoms

- Prodromal phase: fatigue, malaise, low-grade fever
- Unilateral rash over the forehead, upper eyelid, and nose
  - 60% of patients have dermatomal pain prior to rash
  - Other symptoms: eye pain, conjunctivitis, tearing, decrease VA, eyelid rash
- Post-herpetic neuralgia: >12 months for 50%

HZO

- Treatment
  - Oral and topical antiviral drugs
  - Topical steroid vs oral steroid
  - Wound care

Vaccines for HZO - Zostivax

- Zostivax is live attenuated herpes zoster (HZ) virus
  - 50% reduction in the incidence of HZ
  - 80% reduction in symptom severity in patients who developed HZ
  - 66.5% reduction in postherpetic neuralgia.

HIV/AIDS

- Human immunodeficiency virus (HIV) is a blood borne retrovirus
  - Acquired immune deficiency syndrome (AIDS) is caused by HIV when profound immune suppression occurs and allows for opportunistic infections, neoplasms, neurological manifestations, possible death

HIV

- After initial exposure self limited acute illness with flu like symptoms
  - Rash, sore throat, vomiting, myalgias, fever, weight loss, fatigue
- Chronic stage the patient may be asymptomatic and last for years
- Final stage is progression to AIDS
  - CD4 T cell count less than 200/ul
  - Viral load reflects activity

HIV/AIDS

- Most frequent ocular complaints
  - Irritation of the conjunctiva
  - Keratoconjunctivitis sicca
  - HIV-related retinal microangiopathy
  - Cycloplege/keratitis
  - Immune recovery uveitis
  - Acute retinal necrosis
  - Progressive outer retinal necrosis
  - Multimorbid corneal disease
  - Syphilis
  - Toxoplasmosis
  - Pneumocystis jiroveci
  - Mycobacterium tuberculosis
  - Neoplasm (Kaposi sarcoma)

HIV/AIDS

- 80% HIV patients will be treated for an HIV associated eye disorder
- Control of immune system using antiretroviral therapy helps to decrease incidence and improve response to treatment of occurrences
- Should undergo regular ocular evaluations
Sarcoidosis

- Systemic inflammatory disease forming granulomas in organs (lungs, lymph nodes, skin, eyes)
- Often young, African American females
- Enlarged lymph nodes
- Shortness of breath
- Fatigue
- Diagnostic Testing
  - Chest X-ray
  - Elevated ACE
  - PPD: TB vs. Sarcoid
  - Biopsy of nodule

Angiotensin Converting Enzyme (ACE)

- Produced by a variety of cells including granulomatous cells
- Serum ACE levels reflect the total amount of granulomatous tissue in the body
- Screen for sarcoidosis
  - 75% sensitive
  - 95% specific
- False positives include:
  - TB
  - Lymphomas
  - Leprosy
- Consider serum lysozyme / calcium assay

Purified Protein Derivative (PPD)

- Skin test to screen for tuberculosis
- Intradermal injection of 0.1ml of soluble antigen from a given TB organism in forearm
  - Positive test – 5 – 15 induration in 2-3 days
  - Specificity increased with chest x-ray
- False positives include prior exposure to TB

Sarcoidosis: Ocular manifestations

- Redness, pain swelling of lids or lacrimal gland
- Painless subcutaneous nodular mass of eyelids
- Ptosis
- Diplopia
- Cicatrizing conjunctival inflammation
- Conjunctival nodules
- Keratoconjunctivitis sicca
- Band keratopathy
- Granulomatous anterior or posterior uveitis
- Corneal
- Retinal peripheral or neovascularization
- Optic nerve disease or glaucoma

Sarcoidosis: Treatment

- NSAIDS
- Steroid
- Methotrexate
- Hydroxychloroquine
- Cyclophosphamide
- Azathioprine
- Aforementioned blood work
- Uveitis topical and possible oral steroids
- Dacryoadenitis treated with systemic steroids
- Consult with PCP

Thyroid Disease

- Causes
  - Hypothyroidism
    - Hashimotos Disease
    - Thyroid removal
    - Pituitary gland
    - Low iodine intake
    - Lithium exposure
  - Hyperthyroidism
    - Autoimmune (Grave’s Disease)
    - Toxic adenomas
    - Subacute thyroiditis
    - Pituitary gland
    - Cancers
- Systemic: Hypo vs. Hyper
  - Hypothyroidism
    - Fatigue, weakness
    - Weight gain (decreased appetite)
    - Cold intolerance
    - Depression
    - Menstrual disturbances
    - Hair loss
    - Dry skin
  - Hyperthyroidism
    - Nervousness
    - Anxiety
    - Increased perspiration
    - Heat intolerance
    - Hyperactivity
    - Palpitations
    - Weight loss

### Ocular Manifestations

- **Anterior segment**
  - Evaporative DES
  - SLK (65% have thyroid dysfunction)*
  - Lid retraction (Dalrymple’s sign)
  - Lid lag
  - Exophthalmos

- **Posterior Segment**
  - Optic nerve hypoplasia
  - Optic nerve swelling/compression
  - Chorioretinal striae

- **Intra-Orbital**
  - EOM restriction (IM SLO)
  - EOM enlargement
  - Optic nerve compression

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### Grave’s Disease

- **Autoimmune Disease**
- **Women > Men (3-10 times)**
- Occurs in 4th-5th decade of life**
- When men are affected, symptoms are worse**
- Ocular manifestation generally appear 2.5 years after onset of disease **
- 25-50% Grave’s dz patients develop ocular manifestations
- Most common in Hyperthyroid, but can occur with hypothyroidism

### Diagnosis/Testing

- **Tonometry (primary gaze and up gaze)**
- **Exophthalmometer**
- **Appearance**
- **Thyroid panel/ Autoimmune markers**
- **Imaging (CT and MRI)**
- **Forced duction/motility**

### Treatment options

- **Self Limiting:** Graves’ disease usually runs a progressive course for 3-5 years and then stabilizes.*
- **Concern is patient comfort and treatment of Dry eye concerns.**
- Lid weights/taping/tarsorrhaphy may be required to decrease exposure

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### Rheumatoid Arthritis

- **Chronic autoimmune disease causing symmetrical and destructive joint inflammation**
- Exact cause unknown
- Middle aged women
- Morning stiffness
- **Diagnostic Testing**
  - Positive Rheumatoid factor
  - Anti-CCP present
  - Elevated CBC
  - Joint X-ray

### Rheumatoid Factor (RF)

- **Differentiates RA from other chronic arthritides**
- Positive values (titers > 1:80) occur in approximately 70% of patients with rheumatoid arthritis
- Positive in only 5% of patients with JRA
- Can be positive in the following
  - Sjogren’s
  - SLE
  - Syphilis
  - Chronic infections
  - Sarcoidosis
  - Liver disease
Rheumatoid Arthritis

• 25% RA patients have ocular manifestations
  – Keratoconjunctivitis sicca - 15-25% patients
  – Sjogren’s frequently accompanies RA
  – Scleritis - 0.87% - Most common extra-articular condition associated with RA
  – Uveitis

• NSAIDs
• Steroids
• Disease Modifying Anti-rheumatic Drugs
  – Methotrexate
  – Sulfasalazine
  – Hydroxychloroquine

Rheumatoid Arthritis Treatment

Recent Clinical Findings for Sjögren’s Diagnostics


MULTIPLE SCLEROSIS

Multiple Sclerosis

• Immune-mediated process directed against the CNS
  – Attacks the myelin and the nerve fibers
  – Damaged myelin forms scar tissue (sclerosis)
  – Damage to myelin sheath or nerve fibers causes distortion or interruption to impulses traveling along involved nerves
  – Triggered by combination of 1 or more environmental factors in genetically susceptible individual

Risk Factors

• Age: can occur at any age, but most common 15-60 YOA
• Women>Men 2:1
• Hx of certain viruses i.e. Epstein-Barr (mono)
• Caucasian>Asian>African>Native American
• Increased risk with Thyroid Dz, Diabetes Type 1, and IBD
• Smokers

Diagnosing MS

• Must meet MS diagnostic McDonald criteria:
  – First evidence of damage in at least 2 separate areas of the CNS including brain, spinal cord, and optic nerves –AND- 2 or more attacks (relapses)
• MRI scan of the brain (T1 and T2) with fluid attenuated inversion recovery sequencing (FLAIR) and gadolinium infusion
• CSF abnormal in 90% of cases
  – Increased IgG

Symptoms of MS

• Vary, depending on the location of affected nerve fibers
  – Numbness or weakness in one or more limbs that typically occurs on one side of your body at a time, or the legs and trunk
  – Partial or complete loss of vision, usually in one eye at a time, often with pain during eye movement
  – Tingling or pain in parts of your body
  – Electrotactile sensations that occur with certain neck movements, especially bending the neck forward
  – Tremor, lack of coordination or unsteadiness while walking
  – Slurred speech
  – Fatigue
  – Depression
  – Changes in bowel and bladder function
Multiple sclerosis

- Immune-mediated process directed against the CNS
  - Attacks the myelin and the nerve fibers
- Visual Field defects
  - Result of demyelination along visual pathway
- Bilateral internuclear ophthalmoplegia (INO)
  - Diplopia
- Brain stem and cerebellum lesions
  - Dystasia (undershoot/overshoot saccades)
    - Nystagmus
  - Cranial nerve palsies: CN6 and CN3
- Optic Neuritis
  - 75% occurrence, initial symptom in 14-25%

Optic Neuritis

- 6.4 per 100,000 in US
  - Unilateral in 70%
  - Most often 30’s, range 20-60 YOA
- Triad
  - 1. Loss of vision
  - 2. Dyschromatopsia
  - 3. Eye pain (worse with movement)
- Optic disc swelling
  (+) APD
- VF defect (central scotoma)
- Orbital MRI will show inflammation of ON

Optic Neuritis

- Prognosis
  - Visual recovery is good 65-80% recover VA of 20/30 or better within a few months
  - Residual abnormalities in contrast sensitivity, CV, VF loss, and photophobia
- Treatment of MS
  - High dose methylprednisolone (ONTT) followed by oral prednisone
  - Interferon-beta treatment
    - Avonex and Rebif
    - Early use with Avonex during first episode may help delay development of definite MS
  - Copaxone
    - Mimic myelin basic protein, early stages
    - Immune modulator that blocks attacks on myelin

Conclusions

- The eyes are affected by what is going on in our body
- Important to work alongside primary care physicians and specialists to monitor and treat systemic diseases
Thank you!

References


