The Eye is an extension of the brain
- The anatomy of the eye is structured to serve the functions of the “retina”
- The primary reason for dilation is to detect systemic disease

Essentials in Systemic Disease
Carlo J. Pelino, OD
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DISCLOSURE STATEMENT
Dr. Pizzimenti is CEO of Optometryboardcertified.com
Dr. Pizzimenti has received honoraria from Alcon, Reichert,
Zeavision, and Carl Zeiss Meditec
Dr. Pelino has received honoraria from Carl Zeiss Meditec

Please silence all mobile devices
At the conclusion of this course, please properly dispose of your trash as you leave this room
Classification of Blood Pressure (Adults 18 and older)

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic Blood Pressure</th>
<th>Diastolic Blood Pressure</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 120 mm Hg</td>
<td>&lt; 80 mm Hg</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139 mm Hg</td>
<td>80-89 mm Hg</td>
</tr>
<tr>
<td>Hypertension (Stage 1)</td>
<td>140-159 mm Hg</td>
<td>90-99 mm Hg</td>
</tr>
<tr>
<td>Hypertension (Stage 2)</td>
<td>&gt; 160 mm Hg</td>
<td>100 mm Hg</td>
</tr>
</tbody>
</table>

Source: U.S. Department of Health Services; NIH no. 03-5231 May 2003

Grading of Hypertensive Retinopathy

- Grade 1: Retinal vessels narrowed
- Grade 2: Nicking of retinal vessels
- Grade 3: CWS, Hemes, Lipid exudates
- Grade 4: Grade 3 + Optic disc swelling

*Grades 3 and 4 = increase risk of cerebral, heart and kidney problems*
54 year old
+ Diabetes
+ HTN
+ Cholesterol
Grade 4 Hypertensive Retinopathy
Malignant Hypertension:
- Defined as Blood Pressure > 210/130

Ocular Presentation: May present with the following
- Disc Edema
- Arterio-venous crossing changes
- Nerve fiber layer infarcts (cotton wool spots)
- Macular edema
- Hard exudates
- Flame-shaped hemorrhages
- Choroidal ischemia (usually seen in young patients)
Malignant Hypertension: Systemic Presentation

- Patient may be asymptomatic.
- Patient may have encephalopathy, headaches, vomiting or coma.

Treatment of Malignant Hypertension:

- Blood pressure measurement.
- Immediate referral to emergency room or primary care doctor for slow lowering of the blood pressure.
- Visual field testing.
- MRI to rule out space occupying lesion.
- MRV to rule out venous sinus thrombosis.
- Lumbar puncture if necessary.

Keith et al. found that ~ 80% of patients with Grade 4 Hypertensive Retinopathy (malignant hypertension) died within 1 year.

Also, over a 3 year period, there was a 95% mortality for those with malignant hypertension.

HLA B15 has been associated with malignant arterial hypertension.

Hypertension: ~ 70 million Americans

- Malignant
- Essential
- Secondary HTN (Pheochromocytoma, renal artery stenosis, etc.)

Essential Hypertension: defined as a blood pressure > 140/90

- During young adulthood/early middle age: HTN is more common in males
- Elderly patients: HTN is more common in women
- A family history of HTN usually exists in essential HTN
- Essential HTN is usually controlled with one or two medications
- Blood pressure does not progress to higher levels over a short period of time
- Work Up = BUN/Cr, Lipid Profile, Glucose, CBC, EKG, “Metabolic Panel”

Secondary Hypertension:

- Drugs/Toxins
- Renal Disease: Glomerulonephritis, Diabetes, Chronic nephritis
- Vascular: Coarctation of the aorta
- Neurologic: Increased Intracranial Pressure, G-B syndrome
- Endocrine: Phaeochromocytoma, Hypo-Hyperthyroidism
- Pregnancy
- Stress: Postoperative, Burns, Alcohol withdrawal

Always question the malignant hypertensive patient

**Hypertensive encephalopathy**
- Syncope
- Seizures
- Focal weakness
- Paresthesias
- Speech problems

**Hypertensive Cardiac involvement**
- Chest pain
- Palpitations
- Cough
- Dyspnea

**Hypertensive renal problems**
- Change in renal volume
- Hematuria, abdominal pain

Epiretinal Membrane formation

Hypertensive Choroidopathy
Essential Hypertension - Long standing

Arteriosclerosis Grade 2-3

Retinal Arterial Macroaneurysm

Retinal Arterial Macroaneurysm
Central Retinal Vein Occlusion  
Branch Retinal Vein Occlusion  

“Non - Ischemic” Central Retinal Vein Occlusion  

Valsalva Retinopathy  

Valsalva Retinopathy  
- Rupture of the superficial retinal capillaries  
- Occurs when there is a rise in the intrathoracic or intra-abdominal pressure  
- There is then a rise in the intraocular venous pressure  
- Increased pressure is generated by forceful exhalation against a closed glottis  
- Etiology may be from strenuous coughing, sneezing, vomiting, straining or lifting
13

Day #1
BP 162 / 98
RAS
35 yo AA male

1 Week
BP 135 / 90
RAS

4 Weeks
BP 140/90
RAS

Valsalva Retinopathy

Treatment:
• Usually observation – Most hemorrhages clear spontaneously and have an excellent prognosis
• Vitrectomy
• Nd:YAG laser – disruption to the internal limiting membrane used to disperse the dense hemorrhage into the inferior vitreous

Important Note:
• Toxic damage to the retina if contact with hemoglobin and iron for a long period of time

Systemic Evaluation:
• A work up should include testing for high blood pressure, coagulopathy, and blood dyscrasias especially if positive for a family history
Hypercoaguable State:
- It is a risk factor for artery and venous occlusions
- Has an association with coronary artery disease
- Has an association with cerebral vascular accidents (CVA)
- Hypercoaguable state is associated with peripheral vascular disease

Primary State:
- Protein C deficiency
- Protein S deficiency
- Antithrombin III
- Factor V Leiden
- Hyperhomocysteinemia
- Prothrombin 20210 mutation
- Antiphospholipid syndrome (Lupus anticoagulant / Anti-cardiolipin antibody)
- CBC, differential, Platelet count and PT / PTT

Secondary State:
- Pregnancy
- Malignancy
- Congestive Heart Failure
- Immobility

Hypercoaguable State: Important Note
- Factor V Leiden is the most common hereditary blood coagulation disorder in the United States ~10%
- Prothrombin 20210 mutation is the second most common inherited clotting abnormality in the United States

Ophthalmic Presentations:
- Central Retinal Artery Occlusion
- Branch Retinal Artery Occlusion
- Central Retinal Vein Occlusion
"BRAO" in a 42-yr-old female
Birth-control medication
Hypercoaguable State: Treatment

- Monitor patient closely with Primary Care Physician
- Coumadin, Heparin, Aspirin therapy
- Treat ocular conditions accordingly

Dot and Blot hemes in mid-peripheral retina
Hypoperfusion Retinopathy / Ocular Ischemic Syndrome:

- Usually unilateral but may be bilateral in 20% of cases
- Males > Females by a 2 to 1 ratio
- Dot and blot hemis / microaneurysms found only in the mid-peripheral retina = Hypoperfusion Retinopathy
- When the above is associated with neovascularization of the Disc, Retina, Iris or Angle = Ocular Ischemic Syndrome
Pathogenesis: Ocular Ischemic Syndrome:
- Atheromatous ulceration and stenosis at the bifurcation of the common carotid artery (90% occlusion has to be present)

Symptoms: Ocular Ischemic Syndrome
- Ocular and periorbital pain in 40% of cases = “Ocular Angina”
- Prolonged recovery of vision following exposure to bright light - known as “Light Induced Amaurosis”
- Amaurosis Fugax (Transient Monocular Blindness) in 5% of cases
- Transient Ischemic Attacks (TIA)
- Vision Loss (90%) – Short Posterior Ciliary Arterial hypoperfusion
**Symptoms: Ocular Ischemic Syndrome**

Ocular and periorbital pain in 40% of cases = “Ocular Angina”

- Ischemia to the ophthalmic division of Cranial Nerve 5
- Anterior-segment inflammation
- Elevated intraocular pressure (IOP) from neovascular glaucoma

**Ocular Signs: Ocular Ischemic Syndrome**

- Dilated but not tortuous retinal veins
- Retinal Hemorrhages in mid-peripheral retina (80%) of patients
- Cotton Wool Spots (5%)
- Neovascularization of the Disc (35%)
- Neovascularization of the Retina (8%)
- Rubeosis iridis (65%)
- Uveitis – mild anterior (20%)
- Emboli (retinal)
- Lower IOP – initially
Ocular Ischemic Syndrome

Cholesterol Plaques

55 yo AA male OD

55 yo AA male "BRAO" OD

55 yo AA male OS
**Occipital Lobe Infarct**

**Work Up**:
- Carotid artery evaluation (Carotid - Duplex Scanning) - ICA, ECA, CC
- Color Trans-cranial doppler (TCD) - ocular arteries
- Possible MRA (Magnetic Resonance Angiography)
- Computed Tomography (CT) angiography
- Cardiology work up (Echocardiogram) - Transesophageal / Transthoracic
- HTN, DM, Lipid Panel, ESR, C-reactive protein

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**Ocular Ischemic Syndrome**

**Treatment**:
- Consider carotid surgery if warranted (Endarterectomy)
  - European Carotid Surgery Trial (ECST)
  - North American Symptomatic Carotid End. Trial (NASCET)
- Therapeutic approach - Aspirin (325 mg QD or BID), Plavix
- Control modifiable vascular risk factors - HTN, DM, dyslipidemia
- Stop smoking
- Panretinal photocoagulation (PRP) if neovascularization

**Important Note**:
- Leading cause of death = Ischemic heart disease
- Second leading cause of death = Stroke
The Prevalence of Diabetic Retinopathy

- Hispanic population tends to have the highest prevalence rates of DR
- African Americans tend to have highest rates of vision threatening DR
- No prominent difference between genders were seen in the prevalence of diabetic retinopathy
- The prevalence of diabetic retinopathy is in older age groups

The Prevalence of Diabetic Retinopathy

Diabetes

Classification of Diabetic Retinopathy

- “Non-Proliferative”
  - Mild
  - Moderate
  - Severe (4-2-1 rule)
  - Very Severe
- “Proliferative”
  - Early
  - High risk

Other Ocular Complications:
- Clinically Significant Macular Edema
- Diabetic Papillopathy
- Cranial Nerve Palsy 3,4,6
- Cataract formation

“Severe” Non-Proliferative Diabetic Retinopathy
Diabetes

“Proliferative” Diabetic Retinopathy

Fibrous Proliferation – “Proliferative” Diabetic Retinopathy

Diabetes

“CSME” – Clinically Significant Macular Edema

4-2-1 Rule

- **Severe NPDR**
- At least one of:
  - intraretinal hemorrhages in four quadrants
  - venous beading in two quadrants
  - intraretinal microvascular abnormalities in 1 quadrant

**Standard photographs available at:**
eyephoto.ophth.wisc.edu/ResearchAreas/Diabetes/Diab5
detail
Intraretinal hemorrhages in four quadrants

Venous Beading and Intraretinal Microvascular Anomalies (IRMA)

DIABETIC MACULAR EDEMA

CSME Defined
- CSME, as defined by the ETDRS, exists with any of the following findings:
  - Retinal thickening within 500 mm of the center of the fovea
  - Hard exudates within 500 mm of the center of the fovea with adjacent retinal thickening
  - At least 1 disc area of retinal thickening, any part of which is within 1 disc diameter of the center of the fovea
Diabetic Macular Edema

Management Guidelines: DME
- More recently, laser out-performed intravitreal Kenalog.
- Laser + Lucentis out-performed laser alone.

Diabetes

Some important systemic effects of diabetes that affect retinopathy and increase the risk of "Heart Attack":

1. Proteinuria
   - First sign of renal disease
   - As nephropathy increases...the glomerular filtration rate falls
   - American Diabetes Association (ADA) recommends yearly urinalysis
   - Random Spot Urine or 24 hour collection
     Normal <30
     Microalbuminuria 30 mg – 299 mg
     Albuminuria > 300 mg

2. Anemia
   - Gets more severe as renal disease worsens
   - Kidney production of "Erythropoietin" decrease, which means that less reaches the bone marrow and less red blood cells are made
   - Measured by Hematocrit (HCT) and hemoglobin levels in a CBC
     If hemoglobin levels are less than 11g/dl = anemia
     Anemia may actually be making the retinopathy worse!!!

Treat the patient with "Procrit" if patient is not on dialysis...also give iron...
**Diabetes**

1. Hyperlipidemia
   - Cholesterol and triglyceride healthy levels should be < 200 mg/dl
   - PCP should consider Lipitor if cholesterol high

2. Hypertension
   - Target blood pressure for diabetics with nephropathy is 130/80
   - ACE inhibitors should be given if blood pressure is high
   - ACE inhibitors are both renal-protective and anti-proteinuric
   - Hypertension in diabetics is labile and only effectively measured at home

3. Hyperglycemia
   - Induces vasoconstriction = kidney (glomerular) damage
   - The Hemoglobin A1C should be as close to 7% as possible

**Obstructive Sleep Apnea**

- Progressive relaxation of upper airway musculature in deeper stages of sleep
- Nocturnal Hypertension

**Capillary Leakage & Selective Reabsorption**

- WBC’s adhere to and accumulate within the renal vasculature
- ICAM
- Further breakdown of the blood-renal barrier
- Release of VEGF
- Vascular Endothelial Growth Factor
• Elevated morning BP by 20 - 30 mmHg
• Elevated, resistant BP throughout the day
• Relationship: Congestive Heart Failure, Nocturnal MI / CVA, Nephropathy

DM + Smoking = Blindness

#7. Smoking
• Severely worsens microangiopathy

• Smoking is a risk factor for proteinuria and increased blood pressure
• Nicotine increases blood platelet viscosity which can increase retinopathy
• Smoking also causes arterial wall damage and constriction
Moderate Non-Proliferative Diabetic Retinopathy
ACCORD study

- Patients with tightly controlled blood glucose (HbA1C < 6%) had a 22% higher risk of death vs. those patients with less HbA1C control (7-8%)
- The study was halted

ADVANCE study

- Had different results. Risk reduction by 10% in micro and macrovascular events.

DPP (Diabetic Prevention Program) - Prediabetes

- Lifestyle intervention group vs. med group (metformin) vs. placebo
- Lifestyle group showed the most decrease in diabetes risk

Take Home:

- Diabetic Retinopathy is exacerbated by many concomitant conditions
- Control of the systemic aspects of the disease improves the systemic and ocular health
- Understand how Diabetic Retinopathy relates to the overall systemic health

Cholesterol / Triglycerides

- Cholesterol < 200 mg/dl
- 50% have high cholesterol levels
- In younger people may lead to MI or cardiovascular disease

Triglycerides > 2,500 mg/dl

- Arcus Senilis
- Arcus Juvenilis
- Arcus = “Bow like
- Hyperlipoproteinemia in younger pts.

"Lipemia Retinalis"
The Association of Corneal Arcus with Coronary Heart Disease and Cardiovascular Disease Mortality in the Lipid Research Clinics Mortality Follow-up Study (Am J Public Health 1990; 80:1200-1204)

Prospective study of White men (n = 3,930) and women non-hormone users (n = 2139) followed for an average of 8.4 years.

Results:
• Corneal Arcus was strongly associated with CHD and CVD mortality only in hyperlipidemic men ages 30-49 years.
• Among 30-49 year old males, corneal arcus was a prognostic factor for CHD independent of hyperlipidemia.

Aspirin Use in Diabetes
• Aspirin use in diabetic patients is **not associated** with an increased risk of hemorrhage or progression of retinopathy or macular edema.***
• Aspirin use may actually slow the progression of diabetic retinopathy.**
• Aspirin Therapy (81-325 mg/day): ADA recommendations
  - Family History of coronary heart disease
  - Cigarette smoking
  - Hypertension
  - Obesity
  - Albuminuria
  - Elevated lipid levels
  - Age > 30 years

Management:
• Nutrition Therapy = lifestyle change
• Exercise = lifestyle change
• Drug Therapy: Statins (aka HMG-CoA reductase inhibitors)

Hyperlipidemia
• Type 2 diabetics have elevated triglyceride levels
• Type 2 diabetics have decreased high-density lipoprotein (HDL) levels
• Increases cardiovascular mortality risk = Coronary Artery Disease
29 year old AA female. Dry eye complaints

Cotton Wool Spots OU

HIV Retinopathy – CD4 count 110
Pt. not on HAART
36 year old male. Diabetes history

- CD4 Count – Measure of T-cell count (600 – 1500 cell / m$^3$)
- CD4 / CD 8 Ratio (Normal is 2.0)
- Viral Load - # of HIV 1-RNA molecules / ml blood (10,000 low / 100,000 high)

Cytomegalo-virus (CMV)

CD 4 Count and Ocular Management of the HIV Patient

<table>
<thead>
<tr>
<th>CD4 Count</th>
<th>Frequency of Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 250 cell / mm3</td>
<td>1 year</td>
</tr>
<tr>
<td>150 cell / mm3</td>
<td>6 months</td>
</tr>
<tr>
<td>50 -150 cell / mm3</td>
<td>3 months</td>
</tr>
<tr>
<td>&lt; 50 cell / mm3</td>
<td>1 month</td>
</tr>
</tbody>
</table>

Acquired Immune Deficiency Syndrome (AIDS)

Course of the Disease

- Initial Stage – Influenza like illness ~ 4-12 weeks after becoming infected
- Chronic Stage – Latent period ~ 10 years with minor immune dysfunction
- Final (Crisis) Stage – Weight loss, fever, skin rashes, opportunistic infections, and neoplasms
Five drugs currently available to people with CMV disease:

- **Foscarnet (Foscavir®)**: Through an IV line
- **Ganciclovir (Cytovene®)**: Through an IV line followed by capsules
- **Cidofovir (Vistide®)**: Through an IV line
- **Valganciclovir (Valcyte®)**: Tablets that must be swallowed.
- **Ganciclovir implants (Vitrascert®)**: Surgically implanted directly into the eye.
- **Fomiviren (Vitravene®)**: A shot directly into the eye.

Lupus Retinopathy

Sheathing of Blood Vessels
Three forms of lupus are known:
- Systemic lupus erythematosus
- Cutaneous lupus
- Drug-induced lupus

A multisystem autoimmune disorder that commonly affects women of childbearing age (women >> men)

Common findings include malar rash, arthritis, oral ulcers, renal disease, hematological, seizures and psychosis, pulmonary and GI

“Roth Spot”
Systemic Lupus Erythematosus

- Lupus is more common in the African American, Asian and native American populations
- Approximately 15% of patients with Lupus will have retinal disease
- Retinopathy can be associated with central nervous system complications such as cerebritis

Clinical Retinal Features
- Cotton Wool Spots
- Retinal Hemorrhages
- Vaso-occlusive disease
- Frosted branch periphlebitis

Laboratory Testing in Systemic Lupus Erythematosus

- Complete Blood Count (CBC)
- Platelet count
- Erythrocyte Sedimentation Rate (ESR) - Westergren
- C-Reactive Protein (CRP)
- Antinuclear antibody (ANA) – screening test
- Anti-ds DNA (ordered when ANA is positive)
- Urinalysis
- Complement (C3 and C4) serum levels

**Necrotizing Scleritis**

Scleral thinning and scleromalacia perforans

**Feature**

<table>
<thead>
<tr>
<th>Episcleritis</th>
<th>Scleritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>37</td>
</tr>
<tr>
<td>Age</td>
<td>45</td>
</tr>
<tr>
<td>Gender</td>
<td>30% men</td>
</tr>
<tr>
<td></td>
<td>70% women</td>
</tr>
<tr>
<td>Race</td>
<td>white 84%</td>
</tr>
<tr>
<td>Bilateral</td>
<td>49%</td>
</tr>
<tr>
<td>Systemic disease</td>
<td>RA</td>
</tr>
</tbody>
</table>

“Metastatic” Choroidal Tumor
Choroidal Metastasis

Lung cancer - #1 cause of death in males
Breast cancer - #1 cause of death in females
Prostate cancer - most common cancer in men
  (More common and more aggressive in African Americans)
Colon cancer - 3rd most common in men, 2nd most common in women
Melanoma - skin most common site of cancer development
  (Males = trunk)  (Females = extremities)
Ovarian cancer - disease of postmenopausal women
Pancreatic cancer - usually >65 years old, wt. loss, jaundice, anorexia
Uterine cancer - disease of postmenopausal women
  (abnormal vaginal discharge or bleeding)
Metastatic Tumors

- Choroidal metastasis is the most common ocular tumor
- Most metastases found in the choroid are from the breast and lung
- Only ~65% of patients with a choroidal metastasis have been diagnosed with a form of systemic cancer

Ocular Presentation:
- Dome-shaped lesion yellow to orange in color
- Most often in the posterior pole but can be in iris and ciliary body
- They may be solitary or multifocal
- Bilateral in ~30% of cases

Treatment:
- Observation, external beam radiation, radioactive plaque therapy
- The goal of treatment is to save the patient's vision for the remainder of life
Angioid Streaks:

- Alteration/break of the Retinal Pigment Epithelium (RPE), Bruch’s membrane, and Choriocapillaris
- Patient is usually asymptomatic
- Approximately 90% have associated systemic disease
- Decreased vision is secondary to choroidal neovascularization membrane (CNVM) or a streak through the fovea

Etiology:

- Pseudoxanthoma elasticum (85%)
- Idiopathic
- Ehlers-Danlos syndrome
- Paget’s Disease
- Sickle Cell Anemia
- Lead Poisoning
- Mitral Valve Prolapse

Fundus Appearance:

- Bilateral gray – red – brown linear bands radiating in a spoke wheel pattern from the optic nerve
- May have a “peau d’orange” fundus temporal to the macula
- May have peripheral round lesions called “salmon spots”
- Possibility of Optic nerve head drusen

Differential Diagnosis:

- Myopia (lacquer cracks)
- Choroidal Rupture

Affected Systems:

- Cardiovascular
- HTN
- Angina Pectoris
- Mitral Valve Prolapse
- Skin
- Gastrointestinal
**Initial Presentation**

**3 weeks later**

- Choroidal Ruture

**Treatment:**

- Angioid Streaks
  - Focal laser if (CNVM) is present
  - Management of any underlying systemic disease

**Follow up:**

- Twice a year with a dilated fundus examination
- Amsler Grid testing (~3 x week)

---

**The End !!!**

Any Questions ????

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