ESSENTIALS IN SYSTEMIC DISEASE

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Financial Disclosure

Speaker has no financial interests in any of the products discussed within this presentation

OPTOMETRIC MEETING

2019

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Dr. Pelino is on the advisory board /committee for Thrombogenics

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The eye is an extension of the brain
The Case of Bilateral Optic Nerve Swelling

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A 59 year-old African-American female presented for a non-urgent eye examination. She complained of painless, bilateral, mildly blurred intermediate vision of gradual onset.

Her systemic history was positive for type 2 diabetes mellitus, hypertension, and hypercholesterolemia.

At that time, she was taking Avandia® (rosiglitazone maleate), Micronase® (glyburide), Zestril® (lisinopril), Carozide® (hydrochlorothiazide), Zocor® (simvastatin) and Aspirin® (acetylsalicylic acid).

The patient did not recall her most recent fasting blood glucose but did know that her glycosylated hemoglobin (hemoglobin A1C) was approximately 11%. Her last eye examination was 1.5 years prior.

Best-corrected distance acuities were 20/40 OD and 20/40 OS.

The visual acuity did not improve with pinhole.

Extra-ocular movements were full. Pupils were normal in size and shape, equally reactive to light, and without afferent defect.

Color vision via Ishihara was normal in each eye.

Confrontation fields were full to finger count in each eye.

Cover testing revealed orthophoria at distance and near.

Slit lamp examination revealed grade 1 nuclear sclerotic cataract in each eye.

Intraocular pressure via applanation measured 14 mmHg in the right eye and 15 mmHg in the left.

Blood pressure was measured at 205/100 (right arm sitting).

Dilated fundus examination revealed signs of severe non-proliferative diabetic retinopathy (NPDR) in each eye, as well as advanced hypertensive retinopathy (HR)

Clinically significant edema (CSME) was present in each macula. Both optic nerve heads appeared edematous. No retinal breaks or detachments were noted in either eye.

The patient was scheduled for a neuro-ophthalmic consultation and visual field testing (the results showed an enlarged blind spot in each eye).

In addition, the patient was referred to a retinal specialist for further evaluation (including fluorescein angiography) and treatment of the CSME.

A same-day appointment was made for the patient to see her primary care physician in order to better control the urgent hypertension and more closely monitor both the diabetes and hypercholesterolemia.
Optic disc edema can result from various etiologies, including cardiovascular and ischemic vascular disease.

The patient in this case study presented with bilateral, hyperemic disc swelling with prominent dilated disc vessels. The disc edema may be to the result of diabetic papillopathy, hypertension, or a combination of both. A neuro-ophthalmic consult and visual field testing were ordered to rule out the possibility of other compressive optic neuropathies.

The plan was to have the patient return for follow-up after stabilization of her retinal condition and assessment and treatment of her urgent hypertension and other systemic issues.

Both the retinopathies (HR and DR) and disc edema will be followed closely for resolution or progression.

Diabetic papillopathy is a term that was initially used in 1971 to describe a unilateral or bilateral (40% of cases) transient optic disc edema in young people with type 1 DM. Telangiectasia and disc hyperemia are usually present. Several researchers have since identified diabetic papillopathy in older patients with type 2 DM.

The papillopathy is associated with minimal reduction of visual function (>20/40 in 75% of cases) that usually recovers within 2-10 months without treatment. The minimal visual function deficit and remission (usually without significant vision loss) help clinicians distinguish the disease from non-arteritic anterior ischemic optic neuropathy (NAION).

Diabetic papillopathy may be due to localized microangiopathy that occurs at the superficial optic disc (such as the radial prepapillary capillaries), whereas NAION occurs at the deep optic disc as a result of macroangiopathy.

NAION is a disease characterized by a sudden, painless, irreversible, non-progressive, significant visual loss. It is initially unilateral, though it may become bilateral. Clinical signs include optic nerve fiber bundle field defects, a relative afferent papillary defect, and optic disc edema that may be sectoral.

The incidence of NAION increases with age and is associated with hypertension, diabetes mellitus, arteriosclerosis, and hypercholesterolemia. Visual field testing will typically reveal a corresponding inferior or superior altitudinal loss. Inferior nasal and cecocentral scotomas may also occur.

NAION results from an occlusion of the short posterior ciliary arteries, causing infarction to the anterior portion of the optic nerve. Inflammation, demyelination, and compression are absent. In NAION, the fellow eye becomes involved approximately 18% of the time. Ocular/periocular pain and transient monocular vision loss are rare in NAION patients. The HLA-A29 gene may be linked to NAION.

In contrast to the arteritic form of AION, NAION is a diagnosis that is supported by normal erythrocyte sedimentation rate and C-reactive protein test results.
Diabetic papillopathy (NAION) may occur in older patients as well as young. It can affect type 2 patients as well as type 1.

Affected eyes may have macular edema or other retinal vascular disease that can adversely affect the visual outcome.

Patients suspected of having diabetic papillopathy (NAION) should be monitored closely and alternative diagnoses should be considered if the disc edema persists beyond several months.

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### Beyond Retinopathy: 15 Key Factors in Diabetes Wellness

#### #1. Hb A1C under 7% ADA, AACE <6.5%
- Can be higher in patients with cardiovascular disease, hypoglycemia, shorter life expectancy and children (7%–8%)
- ACCORD vs. ADVANCE studies

#### #2. Hypertensive patients with diabetes need a BP of 125/80 or better

#### #3. Cholesterol needs to be under control
- LDL <100 mg/dl if no history of cardiovascular disease, Pattern A vs. Pattern B
- LDL <70 mg/dl if pre-existing history of CVD
- HDL >50 mg/dl in women and >40 mg/dl in men
- Triglycerides <150 mg/dl

#### #4. Sleep Apnea needs to be ruled out
- CPAP - reduce nocturnal hypertension, increase oxygen, decrease fasting blood sugar

#### #5. Anemia needs to be ruled out = hemoglobin needs to be above 11
- Procrit (Epoetin alfa) needs to be considered if hemoglobin below 9. Starts early and has a negative impact on cardiovascular morbidity and mortality

### Who is driving the train ????

#### #6. Proteinuria (albuminuria) – Starlings Law (hydrostatic vs. osmotic)
- 30-299 mg = microalbuminuria
- 300 mg or more = albuminuria
- ADA - yearly urinalysis followed by GFR (glomerular filtration rate)
- Start ACE inhibitors or ARB = renoprotective

#### #7. Stop smoking
- Increases proteinuria, blood vessel wall damage, and vasoconstriction

#### #8. Vasculitis (R/O gum disease, leg ulcers, gastritis, urinary tract infections)
- Daily aspirin decreases heart disease in Type 1 and Type 2
- ADA 81-325 mg /day (not studied extensively for patients < 30)
- CRP of 3.0 mg /L or higher can triple your risk of heart disease
- CRP of 0.5 mg /L or less rarely experience heart attacks

#### #9. Vitamin D status
- Measurement of serum 25-hydroxyvitamin D (25(OH)D) is the best test to determine vitamin D status. Levels of 25(OH)D are interpreted as follows:
  - 21-29 ng/mL (52.5-72.5 nmol/L): Vitamin D insufficiency
  - < 20 ng/mL (< 50 nmol/L): Vitamin D deficiency
**#10 Obesity - BMI (body mass index) less than 30 ... better if less than 25**

AACE recommends bariatric surgery to patients with BMI > 40 or equal to 35 kg/m². Surgery is recommended when conditions are present such as pancreatitis, obesity, sleep apnea, hypertension, heart disease, polycystic ovary syndrome.

**#11 Insufficient Sleep**

Leads to a change in gene expression and cellular aging in some in certain tissues and inflammation

**#12 Chronic Stress**

Leads to a change in gene expression and cellular aging in some in certain tissues and inflammation

**#13 Vitamin B12 deficiency in diabetes taking metformin**

Vitamin B12 deficiency is estimated to be present in up to 41% of patients with diabetes taking metformin. The risk for vitamin B12 deficiency increases with patient age and the dose and duration of metformin use.

**#14 Hyperhomocysteine**

Hyperhomocysteinemia has been associated with microalbuminuria and retinopathy in type 1 and type 2 diabetes. In patients with type 2 diabetes, plasma homocysteine concentration has also been shown to be elevated in microvascular disease and death.

**#15 Vaccinations for Adults with Diabetes**

- Hepatitis B - If you are younger than 60 and have never received or completed a series of HepB vaccine. If 60 or older, discuss your need for HepB vaccine with your healthcare provider.

- Influenza - A flu shot is needed every fall for your protection.

- Pneumococcal - Diabetics need to get vaccinated with the pneumococcal polysaccharide vaccine (PPSV23). If you’re 65 or older, you will need to get another dose when you are 65 or older, as long as it’s been at least 5 years since your previous dose.

**Hb A1C = 13 %**

Vitreous hemorrhage in "advanced" proliferative diabetic retinopathy

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**Vitrectomy and endophthalmitis**

- Diabetics need to get a vitrectomy (if adult choroidal neovascularization) and vitrectomy (if adult choroidal neovascularization) and vitrectomy (if adult choroidal neovascularization) and vitrectomy (if adult choroidal neovascularization). After that, you need to follow-up every 6 months.
Diabetes in the United States: ADA June 10 2014

Diabetes 29 million individuals (9.3%)
1.5 million Type 1  28 million Type 2

Type 2  70% diagnosed and 30% undiagnosed 8.1 million

Pre-diabetes = 86 million people
(37% of individuals > 20 years old)

Obesity = BMI (body mass index) > than 30

Visceral vs. Subcutaneous fat
BMI 30 - 35 Type I Obesity
BMI 35 - 40 Type II Obesity
BMI > 40 Extreme Obesity
Visceral vs. Subcutaneous Fat = TOFI

Visceral fat increases risk of diabetes, heart disease, dementia and cancer

Reward Center = Nucleus Accumbens = Dopamine

Downregulation of dopamine receptors in the NA

Tolerance and withdrawal = Addiction
Longevity and obesity:

• Insulin needs to be low
• IGF is low
• mTOR is low
• AMP kinase is high
• Ras is low

An African American male presented emergently with unilateral vision loss in his left eye of one week’s duration. He denied flashes, floaters, or any other visual or ocular symptoms.

The patient’s past ocular history is unremarkable. His medical history was positive for asthma, controlled with a rescue inhaler, and three bouts of fevers within the year. The fever was attributed to exposure to mononucleosis after a blood work up was performed through his family doctor.

No allergies were reported to medications or environment

No family ocular or systemic history noted

Social history was negative for smoking or drinking

Anterior segment examination was unremarkable in the right eye. The left eye exhibited fine inferior keratic precipitates and a grading of 1+ cells in the anterior chamber.

Intraocular pressures were measured with Goldmann applanation tonometry at 15 mmHg in the right eye and 18 mmHg in the left eye.

Dilated fundus examination revealed scattered mid-peripheral to peripheral focal areas of retinal hemorrhages and vascular sheathing in the right eye.

This was also present in the left eye but more pronounced and with an accompanying superior hemiretinal vein occlusion. As a result, there was extensive macular edema in the left eye. A low grade vitreal reaction was also present in the left eye.
The patient was promptly referred to the retina service for evaluation. Fluorescein angiography was performed and interpreted as inferior venous leakage of the right eye and extensive venular leakage with superior HRVO and non-perfusion in the left eye.

The treatment plan initiated was 40mg of oral prednisone daily, topical prednisolone acetate (Pred Forte 1%) one drop every two hours in the left eye, and atropine sulfate 1% (Isopto Atropine™) twice a day in the left eye only.

He was also referred to rheumatology for a systemic work up to determine the underlying etiology.
Two weeks later, the patient returned for re-evaluation reporting very little improvement in vision despite compliance with topical and oral therapy.

When measured, visual acuity did improve to 20/200 in the left eye.

Intraocular pressures remained mildly asymmetric with 13 mmHg in the right eye and 18 mmHg in the left eye.

The anterior chamber reaction in the left eye had markedly improved with no cells in the anterior chamber and clear corneas.

Dilated fundus examination also displayed improvement with only trace vitreous cells in the left eye. Venous sheathing and sclerosis persisted in the right eye but the macular edema in the left eye showed significant improvement.

Neovascularization of the disc had developed and the superior HRVO was still present.

What makes this case so interesting?

The patient was 15 years old

At this stage of the case, there is no definitive diagnosis. However, there are two main differentials considering the patient history, ophthalmic manifestations, and laboratory findings.

Both pediatric sarcoidosis and Churg Strauss Syndrome (CSS) are probable systemic causes that may elicit this clinical picture.

Though they differ vastly as disease processes, they are similar in that they both yield an inflammatory response that produces a retinal vasculitis and resultant vein occlusion.

Retinal vasculitides can arise from one of several multisystem conditions.

Resulting vascular occlusion is a serious complication which can lead to ischemia, neovascularization, or retinal detachment.

Vessel occlusions are frequently encountered in the ophthalmic setting and attributed to thromboembolic disease, often in the elderly.

However, as seen in this case, there are several etiologies depicting a similar clinical presentation.

While it is important for prompt referral and treatment of the retinal sequelae, it is also imperative to consider initiating workup to rule out an even more devastating underlying systemic pathology.

Thanks to Dr. Bisant Labib

Patients with retinal vein occlusion (RVO) were at an increased risk of stroke compared with patients without RVO, according to a study in the Archives of Ophthalmology.1

The study authors concluded the event rates for MI were similar in patients with RV and controls; however, the event rate for CVA in patients with RVO was almost two-fold that observed in controls.

The risk factors for CRAO are the same atherosclerotic risk factors as for stroke and heart disease.

Individuals with CRAO may be at risk of ischemic end organ damage such as a cerebral stroke.

The management of CRAO is not only to restore vision, but at the same time to manage risk factors that may lead to other vascular conditions.

In the USA, historically intracranial hemorrhage (nontraumatic) has been due to uncontrolled arterial hypertension and its eventual sequelae: arteriolosclerosis

- Arteriolosclerosis: hylanized, thickened and calcified arterioles
- Hypertensive hemorrhages typically occur in areas where arteriolosclerosis is most severe:
  - Basal ganglia (60%)
  - Thalamus (10%)
  - Pons (10%)
  - Cerebellum (10%)

Glaucoma: A progressive optic neuropathy

- Glaucoma is an "end stage" clinical presentation of many diseases
- Example: Heart failure is not a disease but a clinical end stage of many causes such as hypertension, coronary artery disease, etc.

Glaucoma:

Ocular Hypertension and Normal tension are not clinical entities. They are meaningless statistical constructs.

Von Graefe concluded that all glaucoma optic nerves were associated with high pressure based on finger tension.

Samples from older European derived populations.

IOP without POAG had a mean of 15. Less than 2% of the general population was expected to have IOP greater than 21 or 22. Uncommon had become abnormal.

Population surveys found a number of patients normal IOP, NTG entered as a clinical entity.
Table showing the percentage of eye with POAG and screening IOP lower than 22 mm Hg

<table>
<thead>
<tr>
<th>Study</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baltimore Eye Study</td>
<td>59%</td>
</tr>
<tr>
<td>Beaver Dam Eye Study</td>
<td>32%</td>
</tr>
<tr>
<td>Melbourne VI Project</td>
<td>39%</td>
</tr>
<tr>
<td>Rotterdam Study</td>
<td>39%</td>
</tr>
</tbody>
</table>

If the prevalence (risk) of glaucoma increases in patients with higher IOP, how can half the patients with POAG have a screening IOP lower than 22 mm Hg?

Because the vast majority of the population has low IOP

Theories of Damage:

- **Mechanical Theory** – distortion of lamina cribrosa backward and compression of axons
- **Vascular Theory** – poor perfusion of blood to the optic nerve = (diastolic BP - IOP) should not be lower than 50 during the day
- **Toxicity Theory** – Glutamate toxicity to the ganglion cells
- **Fluctuation Theory** – differences of IOP throughout the day
- **Neurogenic Theory** – not IOP, susceptibility to the IOP

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Relationship Between Intraocular Pressure and Primary Open Angle Glaucoma Among White and Black Americans

The Baltimore Eye Survey

Alfred Sommer, MD, MHS; James M. Tielsch, PhD; Joanne Katz, MS; et al.

Harry A. Quigley, MD; John D. Gottsch, MD; Jonathan Javitt, MD; Kuldev Singh, MD


- A detailed ocular examination, including perimetry, was conducted on 5308 black and white subjects aged 40 years and older in a population-based prevalence survey in east Baltimore, Md. Roughly half of all subjects with optic nerve damage from primary open angle glaucoma, regardless of race, were unaware that they had the condition. The average intracocular pressure (IOP) among black patients with glaucoma who were receiving treatment was virtually identical to that in those black patients who were not receiving treatment (median IOP, 20 mm Hg); treated eyes of white patients had a lower IOP than those eyes of white patients who were not receiving treatment (mean [±SD] IOP, 18.69 ±3.23 mm Hg vs 24.15±5.23 mm Hg; *P*<.001). The risk of glaucomatous optic nerve damage increased with the height of the screening IOP, particularly at levels of 22 to 29 and 30 mm Hg and above (relative rate compared with IOP of 15 mm Hg or lower, 12.8 and 40.1 mm Hg, respectively). More than half of all glaucomatous eyes had a screening IOP below 21 mm Hg, whether these eyes were receiving treatment or not. The IOP in glaucomatous eyes tended to rise on follow-up, in contrast with non-glaucomatous eyes in which the IOP was as likely to rise as to fall. Results confirmed that IOP is an important factor in glaucoma, but did not support the traditional distinction between “normal” and “elevated” pressure, nor its corollaries, “low-tension” glaucoma and “high-tension” glaucoma.
Glaucoma and intraocular pressure in EPIC-Norfolk Eye Study: cross sectional study
Michelle P Y Chan, research fellow, David C Broadway, professor, Anthony P Khawaja, research fellow, Jennifer L Y Yip, clinical lecturer, David F Garway-Heath, professor, Jennifer M Burr, reader, Robert Luben, head of biomedical informatics, Shabina Hayat, research coordinator, Nichola Dalzell, study coordinator, Kay-Tee Khaw, professor, and Paul J Foster, professor

Objectives
To report the distribution of intraocular pressure (IOP) by age and sex and the prevalence of glaucoma.

Design
Community based cross sectional observational study.

Setting
EPIC-Norfolk cohort in Norwich and the surrounding rural and urban areas.

Participants
8623 participants aged 48-92 recruited from the community who underwent ocular examination to identify glaucoma.

Main outcome measures
Prevalence and characteristics of glaucoma, distribution of IOP, and the sensitivity and specificity of IOP for case finding for glaucoma.

Results
The mean IOP in 8401 participants was 16.3 mm Hg (95% confidence interval 16.2 mm Hg to 16.3 mm Hg; SD 3.6 mm Hg). In 363 participants (4%), glaucoma was present in either eye; 314 (87%) had primary open angle glaucoma. In the remaining participants, glaucoma was suspected in 607 (7%), and 863 (10.0%) had ocular hypertension. Two thirds (242) of those with glaucoma had previously already received the diagnosis.

In 76% of patients with newly diagnosed primary open angle glaucoma (83/107), the mean IOP was under the threshold for ocular hypertension (21 mm Hg). No one IOP threshold provided adequately high sensitivity and specificity for diagnosis of glaucoma.

Conclusions
In this British community, cases of glaucoma, suspected glaucoma, and ocular hypertension represent a large number of potential referrals to the hospital eye service. The use of IOP for detection of those with glaucoma is inaccurate and probably not viable.

LABORATORY EVALUATION

Certainly, in order to rule out certain systemic considerations to help confirm the diagnosis of normal pressure glaucoma, it is reasonable to obtain several laboratory and/or radiologic tests. In general, there have always been two schools of thought which have tempered the clinical judgment of ophthalmologists regarding testing of these patients. There are those practitioners who will obtain almost no tests whatsoever.

Conversely, there are those that will obtain every test imaginable. We would advocate that in general it is reasonable to perform limited testing to detect certain obvious disorders which are either treatable, or require further medical evaluation to assess potential treatment, and therefore should be performed on all patients with normal pressure glaucoma. The following tests should be viewed as the minimal essential testing to be performed, and their rationale are as follows:

A) Complete blood count with differential and platelets. There is no easier test to identify obvious blood dyscrasias, or common anemias, which may impair the delivery of oxygen to the high energy requirement tissues of the retina and optic nerve.

B) Antinuclear antibody panel (ANA). This test is a useful screen for collagen vascular disease, and other autoimmune abnormalities. A hospital generally offers ANA panels of varying complexity and we would advocate that the most complete panel offered, which typically tests for antibodies to extractable nuclear antigens such as Ro/SSA, La and Sm antibodies, are the most useful. Positive findings to the presence of these autoantibodies may signify the identification of the autoimmune subset of patients with normal pressure glaucoma.
VDRL and FTA. One of the great masqueraders of glaucomatous optic neuropathy is indeed luetic disease. In our experience two out of every 100 patients with optic atrophy that have been referred to us for normal pressure glaucoma have tertiary syphilis which requires treatment.

Serum immunofixation for paraproteins. In our experience in a tertiary care setting, approximately 10-15% of patients with normal pressure glaucoma have a monoclonal gammopathy (i.e., paraproteinemia), which is a clonal expansion of B cells which produces excessive serum immunoglobulin. While the majority of monoclonal gammopathies in an older adult population generally represents a benign condition (called “monoclonal gammopathy of undetermined significance”), approximately one-third of these gammopathies will turn out to be caused by lymphoproliferative disorders such as multiple myeloma or other neoplastic conditions. It is recommended, therefore, that the ophthalmologist test for this condition and if a paraproteinemia is found, refer the patient to a hematologist for further workup which may include a bone marrow aspirate. Although paraproteinemias can often be determined by obtaining full serum protein electrophoresis profiles, a much easier and cheaper test is available most laboratories in which immunofixation testing is performed in order to detect a serum monoclonal protein.

Additional laboratory testing which may be useful in selected patients include the following:

SMA12. It is not unreasonable to obtain electrolytes and studies of liver and renal function in patients in whom there is a high index of suspicion of such disease. We have found, however, that routine testing for these values has been rather unproductive in virtually all patients with normal pressure glaucoma.

Complement studies. Testing for C3 and C4 complement has been unproductive in our hands as a assessment of potential collagen vascular disease.

B12 and folate. Those two have likewise been unrevealing. Although they are often obtained when there is a high degree of suspicion of an intrinsic neuropathy affecting central vision, we have not found them to be of value in assessing patients with normal pressure glaucoma.

cryoglobulins. These may be useful in patients in whom there is Raynaud’s phenomenon or evidence of marked peripheral vasospasm, but is otherwise not very helpful.

Radiological studies: There is considerable debate as to whether there is any utility in obtaining a CAT scan or MRI in patients with normal pressure glaucoma.

Obviously, these tests are more useful in patients in whom there is a loss of central vision with preservation of peripheral vision, or in patients in whom chiasmal lesions are suspect. On the other hand, one might argue that it is not unreasonable to leave “no stone unturned”

Gene Mutations in Cutaneous Melanoma

<table>
<thead>
<tr>
<th>Gene</th>
<th>Incidence (%)</th>
<th>Type of melanoma</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRAS</td>
<td>48-50</td>
<td>Cutaneous</td>
<td>Found most frequently in sites where sun damage is intermittent and not chronic</td>
<td>22</td>
</tr>
<tr>
<td>NRAS</td>
<td>15-30</td>
<td>Cutaneous</td>
<td>NRAS mutations are mutually exclusive of BRAF mutations</td>
<td>21, 24</td>
</tr>
<tr>
<td>GNAQ</td>
<td>5-10</td>
<td>Aural and mesosalpinx</td>
<td>Found more frequently in chronic sun damaged skin</td>
<td>35</td>
</tr>
<tr>
<td>GNAQ and</td>
<td>80</td>
<td>Unusual (melanocytic)</td>
<td>Uveal melanomas are very rare</td>
<td>16</td>
</tr>
</tbody>
</table>

Uveal melanoma is the second most common form of melanoma and the most common primary intraocular malignancy.

Up to one-half of patients are at risk for the fatal metastatic disease.
Nevus of Ota have increased amounts of melanin (pigment) and melanin producing cells (melanocytes) in and around their eyes. This includes the intracocular blood vessel layer called the uvea (choroid, ciliary body and iris), on the sclera, and in the eyelids.

Risk Factors of Melanoma

Nevoma

Intrinsic Blood Vessels

To Find Small Ocular Melanoma

- T= thickness
- F= subretinal fluid
- S= symptoms
- O= orange pigment
- M= tumor margin disk
- N= tumor margin touches
- No risk factors (<4%)
- 1 risk factor (36%)
- 3 risk factors (50%)
- 5 risk factors (70%)

DOCUMENTED GROWTH - MEANS EVERYTHING

Using Helpful Hints = Ultrasound hollow, Halo absent

Collaborative Ocular Melanoma Study

- Organized and funded in 1985 to address issues related to the management of choroidal melanoma. > 4000 patients. 65% pts eligible
- Primarily to study the overall survival of patient following treatment

Small melanomas < 2.5 mm in height
Medium melanomas 2.5 – 10.0 mm in height
Large melanomas > 10.0 mm in height

- Secondary outcomes = metastasis-free survival, years of useful vision
It is left in place for 4 to 7 days to provide 8,000 centigray of radiation to the entire tumor. The remainder of the body receives a small amount of radiation, about the equivalent of 1 chest x-ray.

**Treatment Options for Uveal Melanoma**

- Using fluorescence in situ hybridization and molecular assay techniques, several genetic abnormalities in uveal melanoma were found on chromosomes 1, 3, 6, and 8
- Monosomy 3
  - Found in up to 50% of uveal melanomas
  - Imparts a worse prognosis.
  - In small melanoma it provokes the argument for earlier treatment than observation.

Role of Cytogenetics

Gene expression profiling (GEP) divides uveal melanoma into 2 molecular subgroups:
- Class 1 A and B (low risk)
- Class 2 (high risk)

GEP allows oncologists to accurately predict which patients with uveal melanoma will get metastatic disease.

Technology is now available as a routine clinical test (DecisionDX-UM, Castle Biosciences)

**Improving the prognosis for uveal melanoma**

Simulation

- Proton beam radiotherapy
- Local resection
- Enucleation

- Mutations in the G alpha subunits GNAQ and GNA11 are mutually exclusive and represent early or initiating events that constitutively activate the MAPK pathway.

- Mutations in BRCA1-associated protein-1 (BAP1) and splicing factor 3B subunit 1 (SFP3B) also appear to be largely mutually exclusive, and they occur later in tumor progression.

- BAP1 mutations are strongly associated with metastasis, whereas SFP3B mutations are associated with a more favorable outcome. BAP1 mutations can arise in the germ line, leading to a newly described BAP1 familial cancer syndrome.

**Cell-Signaling Advances in Uveal Melanoma**
Types of Choroidal Melanoma

Class 1A tumors account for about 45% of all uveal melanomas,
Class 1B tumors about 15%.
Class 2 about 40%.
The five-year risk of metastasis is less than 5% for Class 1A,
about 15% for Class 1B, and 70-80% for Class 2.
The goal is to be able to offer adjuvant therapy to all Class 2
patients and to selected Class 1B patients in the near future.

Adjuvant Therapy

**Adjuvant:** A substance that helps and enhances the effect of a
drug, treatment, or biologic system.

From the late 16th century: from Latin adjuvant- ‘helping
toward’, from the verb adjuvare, from ad- ‘toward’

The first class of compounds consists of various types of
agents that activate the patient’s immune system to kill
tumor cells.

Such agents include interferon and ipilimumab or Yervoy.

Systemic Workup

Will be set per the Gene Expression Profiling (GEP):

Physical Examination with metabolic panel and CBC

- Liver enzyme studies – does not show much with regards to metastasis
  - AST
  - ALT
  - Alkaline Phosphatase
  - Total / Direct Bilirubin
  - GGT
- Chest radiograph
- Hepatic US (Ultrasound)
- CT chest/abdomen/pelvis at the initial work up
- MRI of brain / liver without contrast (10% of UM patients have
  another cancer elsewhere). MRI more sensitive than CT or PET

Adjuvant Therapy
Breast Metastasis

**Choroidal Metastasis**

Lung Metastasis

**Choroidal Metastasis**

Metastatic Prostate Cancer

**Choroidal Metastasis**

- Ocular metastases are the most common ocular malignancies
- Estimated incidence of 30,000 cases per year
- Choroidal melanoma 2,500 cases per year

**Metastatic Tumors**

- Breast cancer is the most common tumor to metastasize to the eye - followed by lung cancer
- 85% of patients with breast cancer metastases will have a known history of breast cancer
- Breast cancer metastases tend to be bilateral and multiple
- 40% of these patients have a brain metastasis
Metastatic Tumors

- Breast cancer in 2010
  - (< 1%) new cancers in men
  - 192,400 (27%) new cancers in women

- Metastasis from breast cancer occurs in 25% of women at a median of 5 years. 3 years if ocular metastasis

- The most common location is the lung, bone, lymph nodes and liver

Brain Metastases on MRI Images

Thrombus Disorders

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

Coagulation Pathway

Hypercoaguable State / Protein C deficiency / Protein S deficiency / Antithrombin III deficiency

- Autosomal Dominant. Results in venous thromboembolism
- Thromboembolism occurs in early adulthood

Factor V Leiden

- Resistant to normal degradation of activated protein C
- Found in ~ 6% of the Caucasian population
- Rare in African blacks and Asians

Hyperhomocysteinemia

- Homocysteine is a naturally occurring amino acid
- Autosomal recessive disorder causing high levels
- Due to rare enzyme deficiencies, vitamin deficiencies, drugs, illnesses
- Treated with Vitamin B6, B12, and folic acid
- May cause both central retinal artery and brain occlusion
Hypercoaguable State

Prothrombin 20210 gene mutation
- Results in elevated plasma prothrombin
- Increase risk of venous thrombosis
- Found in ~ 4% of the Caucasian population

Antiphospholipid syndrome
- Antibodies to phospholipids activate the coagulation cascade
  - Anticardiolipin antibody
  - Lupus anticoagulant (misnomer)
- Can lead to both artery and vein occlusions
- Prevalence is ~ 7% of the normal population

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
- **Hyperhomocysteinemia** = MI < 40 years old are all screened

Ophthalmic Presentations:
- Central Retinal Artery Occlusion
- Branch Retinal Artery Occlusion
- Central Retinal Vein Occlusion

Hypercoaguable State: Treatment
- Monitor patient closely with Primary Care Physician/Hematologist
- Coumadin, Heparin, Aspirin therapy
- Treat ocular conditions accordingly

Patient D.G.

Systemic history
- Recent weight gain
- Headaches
- Anemia
- Asthma
- Seasonal/environmental allergies
- Surgical history
  - Tonsillectomy with adenectomy 07/2013
- Ear tube insertion 07/2013
- Medications
  - Ibuprofen, Abilify, Prozac, Singular, Albuterol, Vitamin D, Omeprazole, Fe, multi-vitamins
- NKDA

Immediate/same day referral to St. Christopher's Hospital
Patient D.G.

- Discharged 08/08/2013
  - Weight: 144kg = 317 lbs
  - BMI: 51.2 km/m²
    - Obesity = BMI of 30 or greater
  - BP: 102/50
- Acetazolamide
  - 250mg 1 tabs PO BID x 3d, then 2 tab PO BID
- Continue: Albuterol, Vitamin D, Prozac, Ibuprofen, Singulair, multi-vitamins, Omeprazole, miralax
- Weight management course at CHOP
  - Laparoscopic band procedure recommended

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  - NKDA

Treatment of Pseudotumor Cerebri:

Must lose ~ 10% of body weight – # 1 proven tx
Carbonic Anhydrase Inhibitor – Diamox 1000 mg/day

PTC is the most common cause of increased ICP in an optometric practice

PTC: Treatment

- Restoration of visual acuity and resolution of papilledema
- Weight loss 10% reduction in body weight
- Medication
  - Acetazolamide
    - 500mg tablets PO BID
    - Gradually increased up to 500mg QID if tolerated
  - Side effects
    - Topiramate, Furosemide
- Surgical procedures
  - Therapeutic lumbar puncture
  - Optic nerve head sheath fenestration
  - Neurosurgical shunting procedure

Neuroimaging: Impressions

- No acute intracranial abnormality
- No evidence of dural venous sinus/cavernous thrombosis
- Findings suggestive of idiopathic intracranial hypertension

Pseudo Tumor Cerebri (PTC)

- 92% are females
- Rare in males
- Patients may be:
  - Asymptomatic
  - Headache – 90%
  - TVO – transient visual obscurations
  - Diplopia – cranial nerve palsy
  - Pulsatile tinnitus 27% - ringing in right ear

Thanks to Dr.’s Lindsey Perno and Lorraine Lombardi
Cytomegalovirus Retinitis

HIV encephalopathy, Toxoplasmosis, PML

Human Immunodeficiency Virus (HIV)

~ 1 million Americans are living with HIV / AIDS

- CDC estimates that ~ 56,000 people are infected with HIV each year – 2006

- In the United States, about 15,500 people with AIDS died in 2010. HIV disease remains a significant cause of death for certain populations. To date, more than 635,000 individuals with AIDS in the United States have died.

- HIV is largely an urban disease, with most cases occurring in metropolitan areas with 500,000 or more people. The South has the highest number of individuals living with HIV, but when you take population size into account, the Northeast has the highest rate of persons living with new HIV infections.

- Worldwide, there were about 2.5 million new cases of HIV in 2011. About 34.2 million people are living with HIV around the world.

HIV facts:

- > 1.1 million people are living with HIV / AIDS in the United States. 18% do not know that they have the disease

- CDC estimates that about 50,000 people are infected with HIV each year. 47,500 new cases in the United States in 2010

- In the United States, about 15,500 people with AIDS died in 2010. HIV disease remains a significant cause of death for certain populations. To date, more than 635,000 individuals with AIDS in the United States have died.

- HIV is largely an urban disease, with most cases occurring in metropolitan areas with 500,000 or more people. The South has the highest number of individuals living with HIV, but when you take population size into account, the Northeast has the highest rate of persons living with new HIV infections.

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AIDS in Africa has had a short but devastating history.

"It all started as a rumor... Then we found we were dealing with a disease.

Then we realized that it was an epidemic. And, now we have accepted it as a tragedy."

- Chief epidemiologist in Kampala, Uganda

http://www.avert.org/history-aids-africa.htm

Scientists identified a type of chimpanzee in West Africa as the source of HIV infection in humans.

They believe that the chimpanzee version of the immunodeficiency virus (called simian immunodeficiency virus, or SIV) most likely was transmitted to humans and mutated into HIV when humans hunted these chimpanzees for meat and came into contact with their infected blood.

Studies show that HIV may have jumped from apes to humans as far back as the late 1800s. Over decades, the virus slowly spread across Africa and later into other parts of the world.

We know that the virus has existed in the United States since at least the mid- to late 1970s.
Zoonoses is when a microbe jumps from a nonhuman to a human host.

5 Major lineages of Primate Lentiviruses

- Chimpanzees; Gorillas = SIVcpzUS, SIVcpzCAM3, SIVcpzGAB1, SIVcpzANT
- Monkeys; Mandrills = SIVhoest, SIVman, SIVmnd
- African Green Monkeys; Baboons = SIVagmver3
- Sooty Mangabeys = SIV
- Sykes’ monkeys = SIVsyk

Two major serotypes of HIV in Humans

**HIV – 1**
- Group M
- Group N
- Group O
- Group P

**HIV – 2**

**Group M Group N Group O Group P**

Clade A B C D F G H J K (9 clades)

Clade B is the major US strain

Clade B most common in North America
Clade B spread through anal sex

Most common theory of Zoonotic Crossover

- Bushmeat trade which hunted primates for food
- Many SIV strains incorporated
- Social disruption (sex trade)
- Increased transportation methods / roads between forests and cities

Another Theory

Jonas Salk

Hilary Koprowsky

Albert Sabin

Edward Hooper

Vaccine to 1 million people in the Belgium Congo / Rwanda / Burundi

Strains related to human HIV ????

**HIV -1**

Major strains most closely related to SIV strain in chimpanzee subspecies Pan troglodytes troglodytes (common chimpanzee)

**HIV -2**

Major strains most closely related to SIV strain in sooty mangabeys
**Pre-Exposure Prophylaxis**

PrEP stands for Pre-Exposure Prophylaxis. The goal of PrEP is to prevent HIV infection from taking hold if you are exposed to the virus. This is done by taking a pill that contains two HIV medications every day. These are the same medicines used to stop virus growing in people who are already infected.

The medication that was shown to be safe and to help block HIV infection is called "Truvada". Truvada is a combination of two drugs (tenofovir and emtricitabine). These medicines work by blocking important pathways that the HIV virus uses to set up an infection. Truvada as PrEP daily, the presence of the medication in the bloodstream can often stop the HIV virus from establishing itself and spreading in your body.

Some people in clinical trials had early side effects of upset stomach or loss of appetite but these were mild and usually went away within the first month. Some patients also had a mild headache.

**HIV Retinopathy**

**HAART**

HAART = “Highly active anti-retroviral therapy” for HIV / AID patients

HAART = “triple cocktail” started in 1996 inhibits HIV viremia (virus in blood)

HAART = 1 Protease inhibitor and 2 Reverse Transcriptase inhibitors

HAART = Decreased HIV viremia and increases CD4 T lymphocytes

Fusion inhibitor or an integrase inhibitor

**Acquired Immune Deficiency Syndrome (AIDS)**

Course of the Disease

- **Initial Stage** – Influenza like illness ~ 4-12 weeks after infected

- **Chronic Stage** – Latent period ~ 10 years - minor immune dysfunction

- **Final (Crisis) Stage** – Weight loss, fever, skin rashes, opportunistic infections and neoplasms. The virus is replicating within the lymph nodes
THANK YOU.

ANY QUESTIONS?

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