Eye in Systemic Disease: Manifestations, Workup, Medical and Nutritional Management

Common Systemic Diseases with Ocular Findings
1. Diabetes mellitus
2. Hypertension
3. Atherosclerosis
4. AIDS
5. Grave’s Disease → TED
6. Sarcoidosis
7. Systemic lupus erythematosus
8. Arthritis
9. Sickle cell disease
10. Multiple sclerosis
11. Cancer
Complementary Medicine/CAM vs. Alternative Medicine

10 Most Common CAM Therapies Among Adults - 2007

Good Websites for additional information on complementary medicine:

- University of Maryland Medical Center
- National Center for Complementary and Alternative Medicine
- Natural Standard
- Natural Medicines
Diabetes mellitus
◆ Prevalence - 26 million in the United States
à 8.3% of the population
79 million à pre-diabetes
Diabetes mellitus

- Mortality
- Diabetes listed as underlying cause on 79,535 death certificates
- Contributed to a total of >252,00 deaths in 2015

*(National Diabetes Fact Sheet)*

Diabetes mellitus

- Complications
  - Heart disease and stroke → 2X/4X
  - High blood pressure
  - Kidney disease
    - Leading cause of kidney failure
  - Neuropathy
  - Amputation
  - Blindness - leading cause new cases blindness
    adults 20–74 yo

CSDME
Diabetes mellitus

Labs
- Fasting Plasma Glucose (FPG)
  - >126 mg/dL suggests DM
  - 100-125 mg/dL pre-diabetes
- Causal Plasma Glucose
  - >200 mg/dL with symptoms \(\rightarrow\) DM
- 2-hr oral glucose tolerance test (OGTT)
  - >200 mg/dL \(\rightarrow\) DM
  - 140-199 mg/dL pre-diabetes
- Glycosylated hemoglobin: A1C
  - >6.5 \(\rightarrow\) DM
  - >6.0 but <6.5 \(\rightarrow\) pre-diabetes
**Diabetes mellitus**

**Medication Classes for Type-2 DM**

- Biguanides: Suppress glucose production/improve insulin sensitivity
- Sulfonylureas/Meglitinides: Increases pancreatic secretion of insulin
- Thiazolidinediones: Increases sensitivity to insulin
- Alpha-glucosidase inhibitors: Reduce GI carbohydrate absorption
- Insulin: Moves glucose from bloodstream into cells

**ACP Clinical Practice Guidelines Type-2 DM**

- Glucophage = Metformin

**AIC Wins**

(Ann Intern Med. 7 February 2012)
Metformin – Anticancer Effects

Can Diet Reverse DM?

Diabetes mellitus

Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triglycerides

FAMILY PRACTICE

DIABETES UPDATE

OCTOBER 2013, ISSUE 1

Can Diet Reverse DM?
Diabetes mellitus

Dietary Supplements

◆ Chromium picolinate
  → increases insulin-responsive glucose transport (GLUT4)
  → enhances tyrosine phosphorylation insulin receptor
  → dosage → 200-1000 mcg daily in divided doses

◆ Magnesium
  → why are we deficient?
  → increases insulin sensitivity and secretion
  → forms of magnesium
  → dosage → 360 mg daily

◆ Botanicals
  → Cinnamon
    ■ decreases insulin resistance
    ■ true cinnamon (Ceylon) vs common cinnamon (Cassia)
    ■ 0.0004% coumarin vs 0.5% coumarin
  → American ginseng
    ■ increased β-cell stimulation → increased insulin synthesis
    ■ increase the activity of a glucose transporter protein, reduce glycogenolysis, increased metabolism
  → Bitter melon
    ■ increases insulin sensitivity
    ■ activates AMPK, regulates glucose uptake (AMP-activated Protein Kinase)
Hypertension (HTN)

Prevalence - 76.4 million ≥20 yo USA (approximately 30% of adults)
- increasing incidence in children

Mortality – increases risk for heart disease and stroke → first and third leading causes of death USA

Complications
→ Heart attack or stroke
→ Heart failure
→ Kidney failure
→ Aneurysm
→ Dementia
→ Ocular
Hypertension

- Ocular
  - Chronic hypertensive vascular changes
  - Acute hypertensive retinal changes
  - Acute hypertensive choroidopathy
  - Acute hypertensive optic neuropathy
  - Staging systems for hypertensive retinopathy

Hypertension

Why do BP on both arms?

Association of a difference in systolic blood pressure between arms with vascular disease and mortality: a systematic review and meta-analysis

Systolic differences of at least 15 mm Hg are associated with an increased risk of peripheral vascular disease and a weaker but significant association with cerebrovascular disease and mortality.
Dietary Supplements

- **Folic acid**
  - co-factor for nitric oxide synthase
  - dosage: 1000 ug daily in females, males possible cancer risk with high dose

- **Vitamin D**
  - inverse relationship between plasma 25-hydroxy D and HTN risk
  - dosage: studies mixed, dosage for HTN not established

- **Vitamin C**
  - high dosages can reduce BP by about 5 mmHg
  - reacts w O2 to generate hydrogen peroxide → increases electrical signal to relax vascular muscles
  - dosage: 500 mg daily

- **Magnesium**
  - involved in activation of calcium activated potassium channels → regulates vascular tone
  - dosage: 360 mg daily

- **Cocoa**
  - increases production of nitric oxide (NO)
  - dosage: 3 oz. dark chocolate

- **Omega-3 fatty acids**
  - best source from cold water fish
  - increases production of nitric oxide (NO)
  - dosage: as high as 3 grams in studies, bleeding of concern at that level
Grave’s Disease

- Prevalence - 13 million in United States (~50% dx’d)
  most common cause of hyperthyroidism USA

- Complications – while we focus on the ocular aspect
  there are several significant systemic complications
  - Cardiac problems including heart failure
  - Thyroid crisis/storm - rapid heartbeat, fever, and
    worsening of all sx’s → fatal if not tx’ed

Treatment

- Anti-thyroid drugs → blocks the binding of iodine
  - Methimazole
  - Propylthiouracil (PTU) → liver issues

- Radioactive iodine-131 (RAI)
  - slow working over months
  - increases risk of TED (15-20%) both short-term and
    long-term
  - hypothyroidism incidence rate up to 80%

- Thyroidectomy
  - young patients and pregnant patients
  - suspicious nodules or cancer, large goiter, concurrent TED

Thyroid Eye Disease:
Optic Neuropathy Treatment

- STAT Treatment!
  → Vision loss can be severe (NLP)
- Prednisone 100 mg po/dy immediately
  → If improved surgery may not be needed

- Radiation tx
  → If not at fibrotic stage and without sig. visual loss

- Posterior orbital decompression
  → Must be done prior to muscle surg.
Orbital Decompression

- Remove medial wall: orbital contents can prolapse into ethmoidal & maxillary cavity
- Decompress: floor, medial wall, roof, lateral wall
- Most common: Two wall → medial wall, medial aspect of floor, transconjunctival approach

Controversy over $^{131}$ I Tx

- $^{131}$ I aggravates TED (15%) NEJM 1998, 338; 73
- Releases thyroid antigens
- Adding corticosteroids decreases incidence of TED
- Remember → smoking increases TED

A study by Bastidas et al., approximately 15% of patients treated with $^{131}$ I only developed or had worsening of TED. In contrast, none of the patients treated with both $^{131}$ I and prednisone had progressive TED, and both therapies showed improvement. Only 8% of patients treated with prednisone had worsening of TED.

Dietary Supplements

- Selenium → for mild TED
  - dosage → 100 mcg twice daily (as sodium selenite)

Selenium and the Course of Mild Graves' Orbitopathy

(Crossland, M.D., Georgiou, Ashley, M.D., Giacomini, E. Williams, M.D., Kondoleon, M.D., York, Howard, M.D.,*)

(Bartov, B., Tassos, J., Bliss, W., Yelling, J., Geer, A., Gliksman, W.,*)

(Novak, M.D., Novak, E., DeWald, M.D., Hooft, M.D.,*)

(Wilhelmi, M.D., Wilhelmi, F.,*)

(NEJM Sept 2011)
Additional treatments

◆ acupuncture
◆ meditation
◆ mind/body therapies
◆ reduce excess dietary iodine (cow’s milk $\rightarrow \text{I}^{131}$, bread, seafood, iodized table salt, etc.), and management of celiac disease if present.

SICKLE CELL DISEASE

◆ group of hereditary (autosomal recessive) hemolytic anemias seen almost exclusively in blacks
◆ characterized by the genetically determined presence of an abnormal type of hemoglobin in the RBC’s:
  → hemoglobin S (valine sub. for glutamic acid)
  → hemoglobin C (lysine sub. for glutamic acid)
  → thalassemia (decrease rate synthesis of the $\alpha$ or $\beta$ hemoglobin polypeptide chain)

SICKLE CELL DISEASE

◆ Systemic Clinical
  → acute painful episodes last hrs to days and are concentrated in bones and chest (SS)
  → repeated vasoocclusion episodes damages the heart, liver, bone, spleen, and kidneys (SS)
  → sickle cell trait (AS) are usually hematologically normal and only have acute painful episodes with vigorous exertion or at high altitudes – BUT CAN BE INFLUENCED BY OVERALL HEALTH
  → Hemoglobin F levels if increased are associated with more benign clinical course
SICKLE CELL DISEASE

**TYPES:**
- **AS (sickle-cell trait)**
  - mildest form and requires severe hypoxia to produce sickling
- **SS (sickle-cell disease or anemia)**
  - causes severe systemic complications and severe hemolytic anemia
  - mild and often asymptomatic ocular findings - **WHY?**
- **SC (sickle-cell C disease) and S-thal (thalassemia)**
  - mild systemic anemia
  - severe ocular complications

>8-10% American blacks have some form of hemoglobinopathy:
- AS...80%
- S-thal...10%
- SS...4%
- SC...1% to 2%

---

SICKLE CELL DISEASE

**Ocular findings**

**Ant. Segment**
- comma or “S” shaped capillary segments in the bulbar conj.
- focal iris atrophy
- anterior segment ischemia/necrosis

---

SICKLE CELL DISEASE

**Non-proliferative retinopathy:**
*(follow pt at this disease stage)*
- venous tortuosity
- black sunburst
- localized pigmented lesions in fundus periphery secondary to old intraretinal or subretinal hem.
- represent reactive RPE hyperplasia
- salmon-patches
- peripheral intraretinal hemorrhages
- when resolved can leave small retinoschisis cavity containing shining crystals or as a black sunburst
- angioid streaks
SICKLE CELL DISEASE

◆ Proliferative sickle retinopathy: (follow until Stage 3)
◆ occurs in retinal periphery at junction of perfused (posterior) and non-perfused (peripheral) retina
◆ STAGES:
  Stage 1 → peripheral arteriolar occlusion
  Stage 2 → peripheral arteriovenous anastomoses
  Stage 3 → proliferative lesions have a "seafan" configuration, with feeding arterioles, draining venules
  Stage 4 → hemorrhage from neovascularization
  Stage 5 → rheumatogenous or tractional RD
SICKLE CELL DISEASE

Laboratory evaluation

→ Sickledex: in-office screening for sickle cell detects the presence of Hemoglobin S
→ Serum electrophoresis is required to confirm the diagnosis and determine which type of disease is present
→ Peripheral blood smear
→ DNA analysis
→ Family pedigree

Management/Treatment

→ Supportive - avoid situations that precipitate sickling episodes: low O2, infections, cold exposure, physical exertion, acidosis, and dehydration
→ PO hydroxyurea with acute/recurrent pain crises (increases hemoglobin F levels)

Ocular

→ Avoid CAI’s (Acetazolamide) in glaucoma patients due to resultant acidosis
→ Prophylactic tx has not been shown to be effective in preventing neovas.
→ Monitor until stage II - scatter laser tx (i.e. PRP) for neo
→ Standard vitrectomy/RD surg. (↑ risk ant. seg. ischemia)
→ What about anti-VEGF’s?
**SICKLE CELL DISEASE**

*Dietary Supplements*

- **Folic acid**
  - Involved in erythropoiesis to reduce the degree of anemia
  - Dosage: 1 mg daily

- **Magnesium**
  - Reduces erythrocyte dehydration with possible reduction of acute pain episodes
  - Dosage: 540 mg daily (final dosage still to be established)

- **L-arginine**
  - Works as a vasodilator by increasing NO levels, typically low in patients with SS
  - Dosage: 2 g to 8 g daily in divide dose (final dosage still to be established)

- **Omega-3 fatty acids**
  - Increases fluidity of RBC membranes
  - Dosage: 1 gram daily (final dosage still to be established)

- **Zinc**
  - Increases the oxygen-carrying capacity of RBC, reduces cell damage
  - Dosage: 220 mg three times daily

---

**Multiple sclerosis (MS)**

- Prevalence - 350,000 in United States
  - Varies by location increasing the farther from the equator in either hemisphere
Multiple sclerosis (MS)

**Clinical Patterns**

- Progressive regarding multiple sclerosis
- Decline often under weight loss
- Uncontrollable attacks

- Secondary progressive multiple sclerosis
- More gradual decline in mobility
-也會 develop cognitive impairments

- Primary progressive multiple sclerosis
- Mobility loss over a period of months

- Reliable regarding multiple sclerosis
- And other neurological disorders

Multiple sclerosis (MS)

**Complications**

- Fatigue
- Loss of mobility (spasticity)
- Bowel and urinary dysfunction
- Cognitive issues/depression
- Paralysis (typically in the legs)
- Ocular – INO/BINO, palsies, ON, uveitis, CNS field loss

Suspect MS  =>  What to order on MRI

MRI of brain and orbits with and without contrast, axial, coronal, with fat sat
Mid sagittal and axial FLAIR* sequences

- T2 weighted images indicate prior lesions
- T1 images indicates active lesions...and "black holes"
- FLAIR removes free fluid (i.e. ventricles) from T2 scan
- Gadolinium plaques which are less than 6 weeks of age
**Magnetic Resonance Imaging (MRI)**

**FLAIR**
- Fluid-attenuated inversion recovery
- Combines T2-weighting and suppression of non-tissue bound H$_2$O (i.e. free H$_2$O)
- Improves imaging of hyperintense lesions that border CSF-filled space

---

**Dawson fingers**

**Flair**

**T2**

**Gadolinium**

**T1**

---

**Axial**
OCT
→ NFL loss even in the absence of clinically evident optic neuritis with the degree of NFL loss correlated with the duration of the disease
→ Macula thickness also sig. effected

Predictors of developing MS:

LONS (Longitudinal Optic Neuritis Study)
→ **Initial MRI with signal abnormalities**  [BEST PREDICTOR]
→ optic neuritis in fellow eye
→ vague, nonspecific neurologic symptoms
→ pain on eye movement
→ female
→ Caucasian
→ <30 yo at presentation
15 year follow up for ONTT…
good news/bad news

**Vision recovery EXCELLENT:**
> 92% 20/40

**Risk of MS was 65%+**, one or more lesions observed on MRI

**25%** in patients with the absence of lesions!

---

**Multiple sclerosis (MS)**

**Dietary Supplements**

- **Omega-3 and/or omega-6 fatty acids**
  - studies have been mixed on results

- **B12 and magnesium**
  - may help with motor function loss

- **Vitamin D**
  - preventive in action, at high dosages can reduce number relapses
  - dosage → 1000-2000 IU daily, study to reduce relapses used 14,000 IU daily
  - Brazil → doctor using 40,000+ IU daily
◆ N-acetylglucosamine (GlcNAc)
  ✷ inhibited the growth and function of abnormal T-cells in mouse model similar to what is seen in the autoimmune dysfunctions of MS patients
  ✷ dosage ➔ still to be established

◆ Reduce saturated-fat in diet
  ✷ reducing saturated-fat decreased sx’s of MS
  ✷ incidence of MS lower in populations that have limited saturated-fat diets

Dr. Terry Wahls - www.terrywahls.com

Cabin Time
albert@nova.edu