Tackle Toxicity
Drug-Induced Retinal Complications

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Course Description
This course presents the latest information, screening protocols, diagnostic modalities, and management of medications, such as plaquenil, tamoxifen, interferons, and other drugs inducing vision threatening retinal complications.

Goal
To provide the newest information on plaquenil, tamoxifen, interferons, and other drug-induced retinal/macula complications.

Learning Objectives
At the conclusion of this course, attendees will be able to:

1. Discuss current drug information on Plaquenil, tamoxifen, interferon, and other drugs causing maculopathy.
2. Use of diagnostic imaging modalities for detection and monitoring of ocular findings, including fundus autofluorescence (FAF), SD-OCT, and OCT angiography.
3. Describe the latest in the management of these conditions.

Abstract
Systemic medications have the potential to induce adverse vision-threatening retinal complications. Attendees will be presented with the latest information on Plaquenil, Tamoxifen, Interferons, and other drugs causing maculopathy. Emphasis will be on latest screening guidelines, diagnostic modalities for early detection, and management.
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Course Outline

I. Plaquenil Toxicity

- Hydroxychloroquine sulfate (Plaquenil) and the less used chloroquine-CQ (Arlen) are anti-malarial medications widely prescribed for various dermatologic, rheumatological conditions, such as systemic lupus erythematosus and RA.
- The mechanism of this toxicity is not clearly understood
  - Drug molecule binds to melanin in the retinal pigment epithelium (RPE). Prolong toxic effect
  - This, in turn, leads to disruption and damage to the photoreceptors and outer nuclear and plexiform layer
  - Sparing of the foveal center and the resulting “bull’s eye”
  - Drug molecules also deposit within the corneal epithelium, leading to vortex keratopathy. Thus, anterior segment changes should prompt a thorough retinal examination.
- Risk factors (according to the 2016 AAO guidelines)
  
  **High risk factors:**
  - **Duration of use > 5 years.** The prevalence of hydroxychloroquine sulfate toxicity was 7.5% in those who used the drug longer than five years. Further, the risk of toxicity doubles by 10 years and reaches 20% after 20 years of use.
  - **Dosage > 5.0 mg/kg (real weight).** Hydroxychloroquine sulfate is available in 200 mg tablets and is commonly prescribed two 200mg pills per day — anything above that increase’s macular toxicity risk. Also, Data show “real weight” is better than “ideal weight” for calculating dosage.
    - The drug is stored primarily in melanotic tissue, the liver and kidney, with low concentrations found in a variety of other organs and muscle fat.
    - Thin patients are at increased risk when dose is calculated by ideal weight, as previously recommended.
  - **Renal disease.** As the drug is cleared by the kidney, renal disease effectively increases the circulating level of the drug and the risk of toxicity.
  - **Retinal or Macular disease.** Retinal or macular disease increases the risk because damage makes these ocular areas more susceptible to toxicity.
  - **Tamoxifen use.** Increase the risk of toxicity approximately five-fold. Although the reasons are unclear, they may be related to tamoxifen causing macular toxicity in its own right.
    - Patients taking tamoxifen need careful dosing and screening.

**Lesser Risk Factors**
- **Age.** Elderly patients appear at higher risk, though a recent demographic study
found no significant association between age and risk of toxicity
- **Liver disease.** The liver participates in the metabolism of hydroxychloroquine sulfate, however, no clear association between liver disease and toxicity has been demonstrated.
- **Genetic factors.** There have been suggestions that some patients have a genetic predisposition to hydroxychloroquine sulfate toxicity. That said, a new report suggests that certain genes may be protective, according to the

**Clinical Signs**
- Bilateral granular depigmentation of the RPE in the macula (early sign)
- Bull’s eye maculopathy (concentric rings of hypopigmentation and hyperpigmentation surrounding the fovea)
- Macular edema
- Wide-spread atrophy (late stage)
- Attenuation of retinal arterioles (late stage)
- Optic disc pallor (late stage)

**Diagnosis/management Update:**
- **Automated threshold visual fields.**
  - A central 10-2 white-stimulus
  - For Asian patients, a 24-2 or 30-2 visual fields-recommended because hydroxychloroquine sulfate toxicity often manifests changes beyond the macula in these patients.
- **SD-OCT.**
  - Localized thinning of the photoreceptor layers in the parafoveal region. There is focal disruption of the inner segment (IS)/outer segment (OS) line
  - “Flying saucer” or saucerization sign, with an intact outer retina found directly under the fovea. This creates a “or ovoid appearance.
  - Sinkhole Sign- Displacement of the inner retinal structures toward the retinal RPE with variable loss of the foveal contour
- **Fundus autofluorescence (FAF).** Early parafoveal or extramacular photoreceptor damage as an area of increased autofluorescence that may precede retinal thinning on SD-OCT.
- **Microperimetry.** This allows for specific testing of macular function.
- **Adaptive optics retinal imaging.** This provides automated functional assessment of dark adaptation time, enabling the evaluation of macular cone damage seen with early toxicity.
- **Multifocal electroretinogram (mfERG).** Parafoveal or extramacular depression in early maculopathy.

**Management**
- Baseline eye exam that includes retinal photos within the first year of starting the drug to rule out pre-existing macular or retinal disease with baseline visual fields and SD-OCT.
- Most importantly, communicate baseline findings to prescribing physicians.
  - **High-risk factors,** an annual examination is recommended.
  - If probable or definite toxicity is detected, hydroxychloroquine sulfate should be stopped immediately in consultation with the patient’s rheumatologist.
- Ocular affects may continue even when medications are D/C
II. Tamoxifen Toxicity

- Tamoxifen (Soltamox, Midatech Pharma)
  - Selective estrogen receptor modulator with both anti-estrogen and pro-estrogen activity
  - Important role in the treatment of both early and advanced breast cancer
  - Reduces the incidence of breast cancer up to 50%
  - Standard treatment is five consecutive years. However, the Adjuvant Tamoxifen: Longer against Shorter (ATLAS) trial shows that longer use — up to 10 years.

- Tamoxifen Maculopathy
  - Occur in 6% of patient within 6 months of low dose therapy (20 mg/d to 40 mg/d)
  - Inhibition of glutamate uptake in Müller cells is considered a mechanism of the retinal defects
  - Bilateral white crystalline macular deposits
    - Inner layers of the retina
  - Visual acuity decreases are usually secondary to foveal pseudocyst development ONLY and not pigmentary changes
  - Reversible early, not reversible later

- Guidelines: OCT may help determine co-existing foveal cyst and may consider D/C or lower dose of medication
  - OCT (A)- differentiate between Mac Tel 2 versus Tamoxifen maculopathy

- Other causes of crystalline maculopathy:
  - Canthaxanthin- oral tanning agent. Perifovea crystals located in the outer plexiform layer on SDOCT
  - Nitrofurantoin- oral antibiotic. Circinate distribution of superficial and deep retinal crystals
  - Talc retinopathy- bilateral crystalline micro-intraarteriolar retinal crystals resulting from long-term intravenous drug use

III. Roth Spot

- White-centered hemorrhages (Roth spots)-should prompt the consideration of a possible infective endocarditis (intravenous drug use)

- Represent a rupture of the retinal capillaries with intraretinal hemorrhage and subsequent fibrin-platelet adhesion at the site of the compromised retinal vessel

- IV drug users- the white center may be indicative of a septic embolism caused by a bacteria or fungus.
  - The most common pathogen is *staphylococcus aureus*, followed by *streptococcus bacterium*

IV. Interferon Toxicity

- Use: Anti-inflammatory, anti-tumour, antiviral, and immunomodulatory
  - Multiple sclerosis, hepatitis, and other viral diseases
  - Alfa 2-a subcutaneously/ alfa 2-b intravenously
  - Pegulated interferon
    - More frequent prescribed
    - Long acting form of interferon alpha

- Common ocular side effect:
  - 19% to 69% of adults on interferon therapy
  - Retinal cotton wool spots (CWS) near the ONH, Hemorrhaging, Macular edema
May simulate Purtscher’s retinopathy

- Typically begins within the first three months of treatment
- Reversible after discontinuing therapy
- Overall management is follow-up and co-manage with medical doctor

V. Fingolimod-associated macular edema (FAME)

- Fingolimod (Gilenya) - Oral sphingosine-1-phosphate receptor modulator for the treatment of relapsing-remitting forms of multiple sclerosis (MS)
- Common ocular side effect:
  - Macula Edema (FAME) occurs due to a breakdown of the blood-retinal barrier and vascular permeability
  - Interaction between fingolimod and S1PR1 (sphingosine-1-phosphate (S1P) receptors) present on endothelial cells in retinal vessel
  - Higher dosage are at risk:
    - (1%) in the 1.25 mg group
    - (0.8%) in 0.5 mg group
- Management:
  - Baseline screening patients prior to starting fingolimod
  - Screening after 3–4 months with OCT
    - FAME may be dose dependent
  - Common in patients with diabetes, hypertension, and other vascular disease
  - FAME resolve when medication discontinued
    - 84% of patients had macular edema resolution after fingolimod cessation
  - Persistent FAME
    - Topical steroidal or non-steroidal, intravitreal AVT or steroids (Ozurdex), or oral corticosteroids.

VI. Conclusion

- The aforementioned drugs are important and effective for a number of conditions, but it can lead to devastating vision loss.
- Early detection is key to prevent reduction in visual function.
- Close monitoring is essential, even if the medication has been discontinued.

References: