HYDROXYCHLOROQUINE (PLAQUENIL) TOXICITY
Objectives

- Hydroxychloroquine (Plaquenil)
  - Indications, MOA, side effects
- Understanding current screening guidelines for HCQ and CQ toxicity

Testing
- Ophthalmic examination
- Automated Visual field
- SD-OCT
- FAF
History

- WWII: need for a safer alternative to quinine (malaria)
- Chloroquine: developed in 1934, was not recognized as a safe antimalarial until 1946 by the US and British
- Elimination of malaria in US (1947-1951)
History

- Interesting side effect:
  - People noted improvement of joint pain

- Hydroxychloroquine developed with improved side effect profile
Medication Indications

- Malaria
- Rheumatoid Arthritis
- Systemic Lupus Erythematosus
- Porphyria Cutanea Tarda
- Post Lyme arthritis
- Sjogren’s
Mechanism of Toxicity

- Not fully understood
- Drug may affect the metabolism of the retinal cells and also bind melanin in the RPE
  - May explain the persistent toxicity after discontinuation of medication
Signs and symptoms of toxicity

- Early stage: asymptomatic
  - Diminished color vision
  - Paracentral scotoma
- Later stages:
  - Visual acuity
  - Peripheral vision
  - Night vision
  - Bull’s eye maculopathy
Medication Side Effects

- Abdominal cramps
- Diarrhea
- Heart problems
- Reduced appetite
- Headache
- Nausea and vomiting
- Tinnitus
Table 1. Factors Increasing the Risk of Chloroquine and Hydroxychloroquine Retinopathy

<table>
<thead>
<tr>
<th>Factor</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of use</td>
<td>&gt;5 yrs</td>
</tr>
<tr>
<td>Cumulative dose</td>
<td></td>
</tr>
<tr>
<td>HCQ</td>
<td>&gt;1000 g (total)</td>
</tr>
<tr>
<td>CQ</td>
<td>&gt;460 g (total)</td>
</tr>
<tr>
<td>Daily dose</td>
<td></td>
</tr>
<tr>
<td>HCQ</td>
<td>&gt;400 mg/day</td>
</tr>
<tr>
<td></td>
<td>(&gt;6.5 mg/kg ideal body weight for short individuals)</td>
</tr>
<tr>
<td>CQ</td>
<td>&gt;250 mg/day</td>
</tr>
<tr>
<td></td>
<td>(&gt;3.0 mg/kg ideal body weight for short individuals)</td>
</tr>
<tr>
<td>Age</td>
<td>Elderly</td>
</tr>
<tr>
<td>Systemic disease</td>
<td>Kidney or liver dysfunction</td>
</tr>
<tr>
<td>Ocular disease</td>
<td>Retinal disease or maculopathy</td>
</tr>
</tbody>
</table>

CQ = chloroquine; HCQ = hydroxychloroquine.
<table>
<thead>
<tr>
<th>HCQ therapy</th>
<th>Low risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose</td>
<td>&lt; 6.5 mg/kg ideal body weight for short individuals 200-400 mg/day</td>
<td>&gt; 6.5 mg/kg ideal body weight for short individuals &gt; 400 mg/day</td>
</tr>
<tr>
<td>Duration of use</td>
<td>&lt; 5 yrs</td>
<td>&gt; 5 yrs</td>
</tr>
<tr>
<td>Cumulative dose</td>
<td>&lt; 1000 g (total)</td>
<td>&gt; 1000 g (total)</td>
</tr>
<tr>
<td>Kidney / liver dysfunction</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Retinal disease or maculopathy*</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Age (with no cut point specified)</td>
<td>elderly</td>
<td></td>
</tr>
</tbody>
</table>

*Note: HCQ = Hydroxychloroquine*

**Table 2. Chloroquine and Hydroxychloroquine Screening Procedures**

<table>
<thead>
<tr>
<th>Timeline</th>
<th>Baseline examination within first year of use. Annual screening after 5 yrs of use.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended Screening Procedures</strong></td>
<td></td>
</tr>
<tr>
<td>Ocular examination</td>
<td>Dilated retinal examinations are important for detection of associated retinal disorders, but should not be relied on for screening (low sensitivity).</td>
</tr>
<tr>
<td>Automated visual field</td>
<td>White 10-2 threshold testing. Interpret with a low threshold for abnormality, and retest if abnormalities appear.</td>
</tr>
<tr>
<td>In addition, if available, perform one or more of the following objective tests</td>
<td></td>
</tr>
<tr>
<td>SD-OCT</td>
<td>Rapid test that can be done routinely, can show abnormalities very early, even before field loss</td>
</tr>
<tr>
<td>mfERG</td>
<td>Valuable for evaluation of suspicious or unreliable visual field loss; may show damage earlier than visual field testing</td>
</tr>
<tr>
<td>FAF</td>
<td>May validate other measures of toxicity; can show abnormalities earlier than field loss</td>
</tr>
<tr>
<td><strong>Not Recommended for Screening</strong></td>
<td></td>
</tr>
<tr>
<td>Fundus photography</td>
<td>Recommended for documentation, especially at baseline, but not sensitive for screening</td>
</tr>
<tr>
<td>Time-domain OCT</td>
<td>Insufficient resolution for screening</td>
</tr>
<tr>
<td>Fluorescein angiography</td>
<td>Use only if corroboration of pigmentary changes is needed</td>
</tr>
<tr>
<td>Full-field ERG</td>
<td>Important for evaluation of established toxicity, but not for screening</td>
</tr>
<tr>
<td>Amsler grid</td>
<td>Use only as adjunct test</td>
</tr>
<tr>
<td>Color testing</td>
<td>Use only as adjunct test</td>
</tr>
<tr>
<td>EOG</td>
<td>Questionable sensitivity</td>
</tr>
</tbody>
</table>

EOG = electro-oculogram; FAF = fundus autofluorescence; mfERG = multifocal electroretinogram; SD-OCT = spectral domain optical coherence tomography.
Screening recommendations as of 2011

- Base line examination before starting medication
- Annual screening after 5 years, unless there is associated risk factors.

**Table 3. Baseline examination for patients treated with HCQ**

<table>
<thead>
<tr>
<th>Subjective tests</th>
<th>Objective tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity for distance/reading</td>
<td>Fundus autofluorescence</td>
</tr>
<tr>
<td>Slit lamp examination (cornea)</td>
<td>or</td>
</tr>
<tr>
<td>Fundus examination</td>
<td>mf ERG</td>
</tr>
<tr>
<td>Automated central perimeter 10-2</td>
<td>or</td>
</tr>
<tr>
<td>(Humphrey visual field 10-2)</td>
<td>OCT- macula</td>
</tr>
<tr>
<td>Fundus photography- optional, if exist pretreatment macular changes</td>
<td></td>
</tr>
</tbody>
</table>
Possible vs. Probable Early toxicity

- **Possible:**
  - Med not medically important: stop; OR
  - follow 3-6 months until evidence to rule in or rule out toxicity.
  - Subtle changes on AVF, SD-OCT, FAF, mfERG → 1st repeat test for verification.

- **Probable:**
  - Clear toxicity (bull’s eye scotoma and depigmentation, bilateral paracentral mfERG, parafoveal abnormalities on FAF, FA or SD-OCT
  - **STOP** medication
  - Re-evaluate in 3 months then annually.
Goal of screening?

- To identify early retinal toxicity
  - AVF 10-2: sensitive for early toxicity
  - SD-OCT: Confirm toxicity in the early stage, some times prior to VF loss.
  - FAF: indicates marked progression in macular toxicity in mild to severe disease
  - mfERG: early detection but little data regarding sensitivity and specificity.
Examination and Testing

- Ophthalmic examination
- Fundus Autofluorescence
- SD-OCT
- Automated Visual Field
Examination and Testing

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Examination and Testing

- **Fundus Autofluorescence**
  - Photoreceptors contain retinoids
  - When damaged they shed outer segments
  - RPE ingest outer segments and store it in liposomes and form lipofuscin
  - Lipofuscin will fluoresce at a 500-800 nm
Examination and Testing

- **Fundus Autofluorescence**
  - Recorded by 2 methods:
    - **cSLO:**
      - rapid scanning of the retina (improve signal to noise ratio and provide higher quality images)
      - Confocal pinhole isolates one plane
    - **Fundus camera:**
      - Image the fluorescence of the retina and RPE at the same time.
      - Only one photograph needs to be taken
Examination and Testing

- **Fundus Autofluorescence**
  - Does wavelength of light matter?
    - **Blue**: tends to be absorbed by xanthophyll pigments
    - **Green**: additional detail in the fovea and the longer wavelength is there is less absorption in the crystalline lens.
    - **Near-infrared**: 790 nm, also stimulate melanin and provides different information about a disease process.
Examination and Testing

- Ophthalmic examination
- Fundus Autofluorescence
- SD-OCT
- Automated Visual Field
Examination and Testing

- Ophthalmic examination
- Fundus Autofluorescence
- SD-OCT
- Automated Visual Field
Summary

- Baseline exam at initiation of treatment, PLUS
  - A thorough ocular exam
  - HVF 10-2 white on white, AND 1 of the following
    - FAF
    - SD-OCT
    - mfERG (not presented in this lecture)
Questions?
References:


