Early Plaquenil Toxicity Detected without Bull’s Eye Maculopathy

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Case History

- A 79 year old Hispanic female reports for her annual exam
- (-) visual complaints

Medical History:

- **Lupus** x 14 years
- Type 2 DM x 11 years
  - BS: 190 this AM; A1c: 7
- HTN
- Hyperlipidemia
- Hypothyroidism
Medications

- **Plaquenil—200mg qd** x 6-7yrs
- Diclofenac Sodium (Voltaren)
- Glyburide
- Metformin
- Lipitor
- Levothyroxone (synthetic thyroid hormone)
- Citalopan (antidepressant)
## Exam Findings

- **VA:**
  - 20/20 OD, OS

- **SLEx:**
  - (-) corneal deposits (verticillata) OU
  - (-) rubeosis OU
  - **Pseudophakia** OD, OS

### Internal Examination:
- **C/D ratio:**
  - 0.35/0.35 OD, 0.45/0.5 OS

### Macula:
- **Dark, grainy** OD, OS
- (-) foveal light reflex OD, OS
- (-) bull’s eye maculopathy OD, OS
- (-) DR OD, OS
- (-) Peripheral retinal findings OU
10-2 VF Results OU

OD: Reliable VF with a few mild, paracentral defects
OS: Unreliable VF with nasal defects probably due to edge of trial lens. Pt. had difficulty keeping her head in machine during testing of the left eye.
Spectral Domain (SD) OCT Findings

(-) Photoreceptor integrity line defects (PIL) paracentrally

(-) Photoreceptor integrity line defects (PIL) paracentrally
Management

**Assessment:**
Is there *early* Plaquenil toxicity present?
- VF defect OS (with ? reliability)
- Normal SD-OCT OS

**Options:**
- Repeat the VF OS
- Send the patient for specialized testing
- Bring the patient back in 1 year to repeat the VF because the SD-OCT is normal

**Plan:**
- Elected to repeat VF OS in 1 month
Repeat VF 10-2 O.S.

- Again, there are issues with reliability and a number of points are depressed along the inferior/nasal aspect of the field.

- So, after analyzing this printout, previously performed VFs were reviewed (see next slide).
Previously missed paracentral points shown in these VFs did not repeat on retesting.

This visit is the first time she is giving repeatable VF defects.

Cataract Surgery 2011
Management

Assessment:
- Same question: Is this early Plaquenil toxicity?
- Repeatabile, inf/nasal VF defect (?) reliability
- Normal SD-OCT

Plan:
- Repeat VF OS again in 3 months
- However, patient wanted a definitive answer regarding possible toxicity
- Decision was made to refer to a retinal specialist for specialized objective testing (mfERG and/or FAF)
A mfERG was performed two weeks later
The patient’s mfERG results in 3 dimensional form:
- Paracentral depression OD, OS
- Peak of the mfERG is significantly reduced OD, OS
Management

Retinal Specialist:
- Recommends d/c Plaquenil

Assessment:
- Suspect early Plaquenil toxicity since two out of three tests performed were abnormal
  - Normal SD-OCT
  - Repeatable, questionable VF defects OS
  - Abnormal mfERG findings OU

Plan:
- Recommended to patient and rheumatologist to discontinue the Plaquenil
Antimalarial Drugs

- In the U.S., these drugs are used primarily for their **anti-inflammatory effects** in the tx. of **auto-immune conditions** such as *rheumatoid arthritis* and *lupus*.

- The exact mechanism by which antimalarial drugs cause toxicity is not well understood¹.

- Antimalarial drugs are believed to **bind to the melanin in the RPE** which prolongs exposure of these medications **and their toxic effects** at the macula¹.
Antimalarial Drugs

- Fewer side effects occur with Plaquinil (Hydrochloroquine) than with Aralen (Chloroquine).

- It’s estimated that approximately 10-20% of patients taking Chloroquine and 3% of patients taking Hydroxychloroquine develop toxicity.

- It’s rare for side effects to occur with Plaquinil if the medication is dosed properly.

- **Side effects:** Blurred vision, bull’s eye maculopathy, scotoma, vortex keratopathy, headache, accommodative dysfunction, whitening of eyelashes, phototoxicity.
Bull’s Eye Retinopathy

- Early macular toxicity can cause **stippling or mottling of the RPE**

- Next, **granular pigmentation** and loss of the normal foveal reflex can occur

- It’s believed (but not proven) that if **early macular changes are detected** and the medication is stopped, any toxicity that has occurred can be **reversed**.¹

- If the maculopathy continues to progress, **concentric zones of hyperpigmentation and depigmentation** (seen below) can form, causing **irreversible** toxicity.

- Later disease findings include peripheral bone spicules, vasculature attenuation, and disc pallor (can **mimic retinitis pigmentosa**)¹

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Examples of other patients with Bull’s Eye Maculopathy

Photos courtesy of Dr. Jane Ann Grogg and Dr. Anna Bedwell, Indiana University School of Optometry
Another patient with Bull’s Eye Maculopathy and the corresponding FA

Photos courtesy of Dr. Jane Ann Grogg, Indiana University School of Optometry
Testing for Antimalarial Drug Toxicity

American Academy of Ophthalmology 2011 Guidelines\textsuperscript{19}

- BVA
- Dilated fundus exam
  - Be sure to perform DFE within the first year of antimalarial drug use
  - 10-2 central threshold automated visual fields with a \textbf{white} target
  - Subtle, \textit{repeatable} visual field defects should be taken seriously and are an indication to do \textit{objective} testing

- At least one of the following \textbf{objective} tests should be performed during routine screening if available:\textsuperscript{19}
  - Spectral Domain (SD) Optical Coherence Tomography (OCT)
  - Multifocal Electroretinogram (mfERG)
  - Fundus Autofluorescence (FAF)
Testing for Toxicity

Visual Fields:

- Early drug toxicity can cause bilateral, relative paracentral scotomas\(^4\)

- Defects can be present BEFORE definitive signs are seen on fundus examination.

- A white-on-white 10-2 threshold visual field is recommended.\(^{19}\)
  - Want to pay close attention 2-6 degrees from fixation\(^{21}\)
Testing for Toxicity

Visual Fields:

- If VF defects are **repeatable**, then perform **objective testing** such as:
  - SD-OCT
  - mfERG and/or FAF

- Some experts suggest that if the VF is **unreliable** ---or--- shows multiple loci w/at least **-4dB** on **pattern deviation**, objective testing is warranted

**If the -4dB rule mentioned above is applied to the visual fields in the case report, the left VF is clearly abnormal, but the right VF, the one deemed as reliable and WNL...could actually be considered suspicious for toxicity (see next slide)**
10-2 VF Results OD

Initial Review

Reliable

2013

WNL

O.D.

Second Review

Reliable

2013

-4dB

-4dB

2 points, -4dB

-5dB

? Abnormal

O.D.
SD (Spectral Domain) OCT

- With early Hydrochloroquine retinopathy, SD-OCT can detect outer layer retinal abnormalities
- Specifically, SD-OCT can detect loss of the perifoveal photoreceptor inner segment/outer segments line (PIL)
- At the macula, an ovoid appearance can appear (described as “flying saucer” sign by Chen, et al)\(^1\)

![Normal SD-OCT and Abnormal SD-OCT](image)

*Displacement of inner retinal structures
- Black arrows point to PIL loss
- Loss of foveal depression
- Normal outer retinal structures between black arrows

Photo courtesy Dr. Anna Bedwell, Indiana University School of Optometry
Multifocal ERG (mfERG):

- A mfERG can help confirm the presence of retinal toxicity when perimetry or other tests detect abnormalities\(^\text{11}\)

- Generates an array of local ERG responses that corresponds to the central 40 degrees

- mfERG is better than full field ERG at detecting local changes in the macula

Of note, mfERG can vary 10-30% from session to session and to find definitive changes, a series of mfERG recordings needs to be done\(^\text{9,10}\)

Significant cataracts can affect the outcome of the mfERG\(^\text{12}\)

- In studies, 20-60% of patients receiving Plaquinil were found to have mfERG abnormalities—however, clinically significant hydroxychloroquine toxicity is quite rare\(^\text{2}\)
Fundus Autofluorescence (FAF)

- FAF can be used to detect early RPE alterations in retinal disorders

- Areas of early photoreceptor damage can appear to have increased fluorescence around the macula from an accumulation of outer segment debris\(^{17,19}\)

- In some instances, auto-fluorescence has detected abnormalities before visual field testing\(^{19}\)

- More studies on autofluorescence are needed to determine its sensitivity in relation to other testing\(^{19}\)
**Follow-Up Frequency**

- *No universally accepted standards exist* regarding methods of screening, follow-up frequency, or judging risks for patients taking antimalarial drugs

- Follow-up needs to determined by the patient’s *RISK* for developing toxicity
## Risk Assessment

### American Academy of Ophthalmology 2011 Guidelines

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of use</td>
<td>&gt; 5 years</td>
</tr>
<tr>
<td>Cumulative dose</td>
<td>&gt;1000 g (total) HCQ</td>
</tr>
<tr>
<td></td>
<td>&gt;460 g (total) CQ</td>
</tr>
<tr>
<td>Daily Dose</td>
<td></td>
</tr>
<tr>
<td>Hydroxychloroquine (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>Chloroquine (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>

Duration and Toxicity

- The longer the patient is on an anti-malarial drug, the more likely they are to develop toxicity.

- However, there is an extremely low chance of toxicity within the first **five** years of usage of the drug.

- Revised guidelines recommend:¹⁹
  - **Baseline** examination within first year of usage of *Plaquenil* (Hydrochloroquine) or *Aralen* (Chloroquine)
  - Annual screening after **5 years** of use

**Interesting, The Royal College of Ophthalmologists in Great Britain does NOT recommend routine screening for toxicity with antimalarial drug use.**
Cumulative Dose and Risk

- **Cumulative dose** is now considered a more critical factor in developing toxicity than daily dose/kilogram (which older literature focused upon)\(^\text{19}\)

- Research has shown that the risk of toxicity begins to increase sharply towards 1\% after approximately 5 to 7 years of use\(^\text{19}\)

- A cumulative dose that increases the risk of retinal toxicity:
  - **1000g (total) Hydroxychloroquine (HCQ)**
  - **460 g (total) Chloroquine (CQ)**

- Cumulative dose of 1000g HCQ is reached in **7 years** with the daily dose of **400mg**\(^\text{19}\)

- Cumulative dose of 460g CQ is reached in **5 years** with the typical daily dose of **250mg**\(^\text{19}\)
Case Report Patient:

- Reported that she had been on Plaquenil around 6 to 7 years
- However, upon further investigation it turns out that the patient had been taking:
  - 400mg of Plaquenil for 3 years: 146 grams
  - 200mg of Plaquenil for 11 years: 803 grams

Cumulative dose: **949 grams TOTAL** after **14** (not 7!) years of use

- One more year of Plaquenil use for this patient would have placed her over the 1000 gram mark, which puts her at higher risk for toxicity
Daily Dosage and Risk

**Daily dosage levels are still important**

- The patient’s **height** and **weight** are important factors in dosing the medication
- Experts recommend that daily doses be limited to **400 mg Hydroxychloroquine** or **250mg Chloroquine**

**Dosage levels that can cause toxicity:**

- > 6.5 mg/kg **Hydroxychloroquine** (Plaquenil)\(^\text{19}\)
- > 3 mg/kg **Chloroquine** (Arlen)

**With Plaquenil:**

- Plaquenil is manufactured in **only a 200 mg tablet**
- The typical dosage is either **200 or 400 mg per day**
- **200 mg** daily puts anyone under **68 pounds** at risk\(^1\)
- **400 mg** of Plaquenil daily puts anyone under **135 pounds** at a higher risk for toxicity
- Therefore, **200mg of Plaquenil** daily is going to be a **safe** dosage for virtually all adults\(^\text{13}\)
Physique and Risk

- If a person is **overweight and/or short in stature**, the typical dose of antimalarial drugs may be too high since these drugs *don’t accumulate in fat and bone*\(^1,13,14,19\)

- Dosing for overweight and/or short individuals should be based on the basis of height, by finding an estimation of "**ideal body weight**" and not actual weight\(^1,19\)

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**How to define if someone is overweight?**

Determine the patient’s BMI (Body Mass Index using the National Heart Lung and Blood Institute formula)

The patient is at higher risk for toxicity if the number is **25** or higher\(^15\)
  - A BMI of 25 is considered clinically overweight
  - A BMI of 30 is considered clinically obese
Dosing for “Ideal” Body Weight

To determine Ideal Body Weight several different formulas can be used.

Listed below are formulas most often used in the literature:

- Women—100 lbs at 5 feet
  - Add 5 lbs/extra inch of height
- Men—110 lbs at 5 feet
  - Add 5 lbs/extra inch of height

---OR---

- Women--45.5 kg + 2.3 kg (height (inches)-60)
- Men--50 kg + 2.3 kg (height(inches)- 60)
Calculating Safe Maximum Daily Dosage
(Case Report Patient)

- My patient in the case report was 5’2 and 146 pounds
- Her BMI number was 26.3 for her height and weight

To determine the safe maximum daily dosage:

1. Calculate ideal body weight:
   - 100lbs + (2” x 5lbs) = 110 pounds is ideal body weight for case report patient

2. Convert ideal body weight to kg:
   - 1kg = 2.2 lbs
   - (patient’s ideal body weight, 110lbs) / 2.2lbs = 50kg

3. Multiply by 6.5 mg/kg/qd x 50kg = 325 mg which is the safe maximum daily dosage for this patient
Calculating Safe Maximum Daily Dosage of Antimalarial Drugs

Another way to calculate the safe maximum daily dosage finding the daily dosage level in mg/kg for patient is:

- \((\text{Dosage pt. is taking in mg})/\text{pt. ideal weight in kg}\)

Case Report Patient:

- \(200\text{mg/50kg} = 4 \text{ mg/kg}\) (the patient daily dosage level is well below 6.5 mg/kg level that can cause toxicity issues)
Physique and Risk

THIN patients:
- Remember to calculate the Plaquenil dosage for a thin patient on ACTUAL, not ideal, body weight\(^{20}\)
  - Ideal body weight will be higher than actual, possibly leading to overdosing

Height:
- Just as you pay attention to weight as a potential risk factor for toxicity, you also have to think about height
- It is possible to calculate the ideal body weight and safe maximum dosage for any given height
- From there, it is possible to determine that:
  - Any woman shorter than 5’7 and any man shorter than 5’5 should NOT be taking 400mg/daily or risks being overdosed
Plaquenil risk factor calculators are available on-line.

The calculator shown on this slide is from Eye Dock and is available as an app for your smart phone.

If you plug in height, weight, daily dosage and number of years on the drug, this calculator gives you the patient’s BMI, cumulative dose, and safe maximum daily dosage.
Other Risk Factors for Toxicity

- **Advanced age**\(^{19}\)
  The elderly are believed to be more at risk to develop toxicity

- **Renal/liver disease**\(^{19}\)
  Antimalarial drugs are cleared both through the kidney and liver

- **Concomitant retinal disease**\(^{19}\)
  For example, age related macular degeneration
Testing **Not** Recommended for Routine Screening

**Color Vision:**
- Color vision can be abnormal in early toxicity with Plaquenil and Aralen.
- Color vision testing has never been very sensitive or specific for antimalarial drug toxicity.
- Studies show that mixed color defects (meaning both red/green and blue/yellow) can occur in early toxicity\(^7\).
- Experts now feel that color vision should be used as a supplemental test and does not need to be performed during routine screenings.
- However, it would be prudent to perform color vision testing on all males during their initial visit to detect any underlying congenital color deficiencies.\(^19\)
Testing **Not** Recommended for Routine Screening

**Amsler Grid**
- A red Amsler grid may be more effective at detecting early paracentral scotomas because the red target functions as a dim, white target
- High false positive rates occur with red Amsler grids
- The Amsler grid should **NOT** be used in place of a 10-2 threshold testing

**Fundus Photography:**
- Can be performed at the baseline exam to document the fundus appearance
Testing **NOT** Recommended for Routine Screening

**Fluorescein Angiography:**
- Can be performed to ensure that macular tissues are healthy and to help distinguish antimalarial drug toxicity from other types of acquired maculopathies\(^\text{1,4}\)

**Full field Electroretinogram (ERG):**
- **Full Field ERG/EOG** measures the entire retina as one unit.
- It is not sensitive to early toxic changes\(^\text{2}\)
- Only shows abnormalities in late chloroquine or hydrochloroquine toxicity\(^\text{1}\)
- These tests help judge how severe or widespread the damage is once toxicity has been established\(^\text{1}\)

**Time-Domain (TD) OCT:**
- The resolution of a time domain OCT instrument is not sufficient to detect early toxic changes\(^\text{19}\)
Visual Fields vs. SD-OCT
Which is more reliable for detecting toxicity?

- **Question**: If the VF is questionable or unreliable, but the SD-OCT results are normal, can you hold off repeating a questionable VF until the following year?
  - Unsure

- An interesting retrospective study done by Dr. Marmor looked at 2289 patients who had taken a cumulative dose of HCQ greater than 1000g.\(^{23}\)
  - The study found:
    - 150 patients had ocular toxicity\(^{23}\)
    - Approximately 10% of toxic cases had a normal SD-OCT but a parafoveal ring scotoma on VF!!\(^{23}\)
    - However, 90% of toxic patient had both an abnormal VF and SD-OCT, but no patients had just an abnormal OCT and a clear VF
Visual Abnormalities Detected

- **If questionable early toxicity is noted:**
  - Begin following the patient every 3-6 months for changes
  - Obtain specialized testing (if not already performed) such as multifocal ERG, fundus autofluorescence, or spectral domain OCT

- **If definite changes are noted at the fundus or there are repeatable defects on the VF or other testing:**
  - Discontinue the drug immediately
  - Re-evaluate in 3 months after discontinuation of the drug (visual function can continue to deteriorate after the drug is discontinued because it can take anywhere from months to years for these meds to clear the blood)
Clinical Pearls

Optometrists need to ensure that all patients taking antimalarial drugs are properly dosed to prevent ocular complications

- Calculate and record the **cumulative** dose on ALL patients taking Plaquenil
  - If there is any question when the patient started the drug, or the number of years on Plaquenil:
    - Contact the prescribing doctor, so that you can correctly figure out the cumulative dose for the patient

- Calculate **ideal** body weight and compare to **actual** weight
  - Go with the **lower** of the two numbers

- Calculate and record the **daily dosage level** and let the prescribing doctor know if the patient is overdosed

- Pay close attention to **subtle, VF defects**
  - Especially those points missed between 2 and 6 degrees from fixation
References


References

