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Subjective and Objective Screening Tests for Hydroxychloroquine Toxicity

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Objective: To compare subjective and objective clinical tests used in the screening for hydroxychloroquine retinal toxicity to multifocal electroretinography (mfERG) reference testing.

Design: Prospective, single-center, case control study.

Participants: Fifty-seven patients with a previous or current history of hydroxychloroquine treatment of more than 5 years' duration.

Methods: Participants were evaluated with a detailed medical history, dilated ophthalmologic examination, color fundus photography, fundus autofluorescence (FAF) imaging, spectral-domain (SD) optical coherence tomography (OCT), automated visual field testing (10-2 visual field mean deviation [VFMD]), and mfERG testing. We used mfERG test parameters as a gold standard to divide participants into 2 groups: those affected by hydroxychloroquine-induced retinal toxicity and those unaffected.

Main Outcome Measures: We assessed the association of various imaging and psychophysical variables in the affected versus the unaffected group.

Results: Fifty-seven study participants (91.2% female; mean age, 55.7±10.4 years; mean duration of hydroxychloroquine treatment, 15.0±7.5 years) were divided into affected (n = 19) and unaffected (n = 38) groups based on mfERG criteria. Mean age and duration of hydroxychloroquine treatment did not differ statistically between groups. Mean OCT retinal thickness measurements in all 9 macular subfields were significantly lower (<40 μm) in the affected group ($P < 0.01$ for all comparisons) compared with those in the unaffected group. Mean VFMD was 11 dB lower in the affected group ($P < 0.0001$). Clinical features indicative of retinal toxicity were scored for the 2 groups and were detected in 68.4% versus 0.0% using color fundus photographs, 73.3% versus 9.1% using FAF images, and 84.2% versus 0.0% on the scoring for the perifoveal loss of the photoreceptor ellipsoid zone on SD-OCT for affected and unaffected participants, respectively. Using a polynomial modeling approach, OCT inner ring retinal thickness measurements and Humphrey 10-2 VFMD were identified as the variables associated most strongly with the presence of hydroxychloroquine as defined by mfERG testing.

Conclusions: Optical coherence tomography retinal thickness and 10-2 VFMD are objective measures demonstrating clinically useful sensitivity and specificity for the detection of hydroxychloroquine toxicity as identified by mfERG, and thus may be suitable surrogate tests. *Ophthalmology 2014;■:1–11 © 2014 by the American Academy of Ophthalmology.*

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Hydroxychloroquine is widely used in the treatment of various autoimmune diseases, but has the potential to cause severe retinal dysfunction and vision loss.[1] Current guidelines from the American Academy of Ophthalmology (AAO) recommend starting annual ophthalmic screening within 1 year of initiating hydroxychloroquine therapy. The guidelines further recommend that patients receiving hydroxychloroquine therapy for more than 5 years be evaluated using automated 10-2 visual field testing plus one or more of the following objective tests: spectral-domain (SD) optical coherence tomography (OCT), multifocal electroretinography (mfERG), or fundus autofluorescence (FAF) imaging.[1] The current recommendations exclude lower-yield tests such as color vision, and instead focus on subjective and objective tests believed to be associated with early toxicity.

Screening for hydroxychloroquine toxicity in the general ophthalmic community presents practical challenges. Although disparate testing methods can reveal changes consistent with hydroxychloroquine toxicity,[2,3] some methods, such as mfERG, are not widely available. Other imaging and psychophysical tests may not identify early changes associated with toxicity with high sensitivity and specificity and often rely on subjective expert interpretation where thresholds for determining toxicity are not well established. The optimal algorithm for hydroxychloroquine toxicity screening using different methods is still being debated.[4,5]

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Considerations for screening recommendations include accessibility, reliability, ease of interpretation, and cost of testing. A recent article by Browning[4] reported that revisions in the AAO hydroxychloroquine screening guidelines from the 2002 version to its current revised 2011 version resulted in a 40% increase in total associated health expenditure costs, rising from an estimated $29 million to $40.7 million. Both Marmor[5] and Browning[4] point out in their exchange that the AAO guidelines do not explicitly discuss that a certain level of expertise is needed to interpret mfERG, visual field, and OCT data.[5] They recommended that further studies are needed to assess the relative usefulness of testing methods and to optimize guidelines to identify those affected by hydroxychloroquine toxicity.

In several recent studies, mfERG assessment has been considered to be the gold standard test for the detection of hydroxychloroquine toxicity because it has the dual characteristics of being both an objective test and a direct measure of retinal function (Invest Ophthalmol Vis Sci 2013;54:3597; Invest Ophthalmol Vis Sci 2013;54:5037; Invest Ophthalmol Vis Sci 2013;54:5105).[6] Hydroxychloroquine toxicity typically manifests on mfERG testing as a characteristic ring of depressed responses in the perifoveal regions of the macula.[7,8] An increase in the ratio of central-to-paracentral response amplitudes (i.e., an increased R1-to-R2 ratio) is diagnostically useful, providing high sensitivity and specificity in predicting toxicity.[6] However, mfERG testing is not available in most ophthalmology practices and requires specialized training to perform and analyze the test results.

The purpose of this study was to evaluate the findings of subjective and objective screening tests recommended by the current AAO guidelines in a prospective study of participants receiving long-term hydroxychloroquine therapy. Study participants had at least 5 years of hydroxychloroquine therapy and were identified using mfERG as the reference gold standard as having or not having hydroxychloroquine toxicity. These 2 groups then were evaluated with various testing methods suggested by the AAO 2011 guidelines including (1) automated visual field testing, (2) SD-OCT imaging, (3) fundus photography, (4) FAF imaging, and (5) visual acuity measurements. The results of these tests were evaluated for association with the presence or absence of hydroxychloroquine toxicity as defined by mfERG testing to establish which tests could best serve as surrogates for mfERG testing results. These findings may help to enable screening ophthalmologists to have a more targeted approach, with more widely available tests, to identify patients with hydroxychloroquine toxicity.

Methods

Study Participants

This prospective case-control study was conducted at the eye clinic of the National Eye Institute, National Institutes of Health, Bethesda, Maryland. Inclusion criteria included a current or previous history of hydroxychloroquine treatment for a total duration exceeding 5 years and an absence of concomitant retinal disorders (e.g., diabetic retinopathy, retinal vein occlusion, age-related macular degeneration, or Stargardt's disease). Information on patient characteristics, including demographics, medical history, body weight and height, duration and cumulative dose of hydroxychloroquine therapy, and diagnostic indications for hydroxychloroquine treatment, were obtained by medical history evaluation.

The study protocol and informed consent forms were approved by a National Institutes of Health–based institutional review board and the study was registered at www.clinicaltrials.gov (identifier, NCT01145196). The study protocol adhered to the tenets of the Declaration of Helsinki and complied with the Health Insurance Portability and Accountability Act.

Study Procedures

All participants underwent a comprehensive ocular examination, including best-corrected visual acuity testing using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol, slit-lamp examination, and dilated fundus examination. In addition, all patients underwent mfERG testing, automated visual field testing, and retinal imaging, including SD-OCT, FAF imaging, and color fundus photography. Testing was performed in both eyes of all participants.

Visual Field Testing and Analysis

Perimetric assessment was performed using a standard 10-2 Humphrey Visual Field Analyzer (Humphrey Instruments, Inc, San Leandro, CA) with a white test spot. The visual field mean deviation (VFMD) values, representing deviation from age-matched normal eyes, were obtained from the visual field output.

Multifocal Electroretinography Testing and Analysis

Multifocal ERG testing was performed according to the International Society for Clinical Electrophysiology of Vision guidelines,[9] based on the 61-hexagon stimulus pattern of the VERIS Clinic system (Electro-Diagnostic Imaging, Inc, Redwood, CA). Each hexagon elicits a waveform consisting of a negative trough (N1), followed by a positive peak (P1), followed by another negative trough (N2). The 61 hexagon responses were grouped into 5 concentric rings (R1–R5), as shown in Figure 1. The average amplitude, measured as (P1–N1), was assessed for each ring outside the R1 hexagon. The average response densities (nanovolts per degrees squared) within concentric rings from the center (ring 1) to the periphery (ring 5) were generated by the mfERG VERIS software (Fig 1A). The ring ratios of the mfERG were defined as ratios of the central hexagon amplitude (R1) to each of the peripheral ring amplitudes (R2–R5). These ratios were calculated for all tested eyes.

Spectral-Domain Optical Coherence Tomography Imaging and Analysis

We evaluated both the objective quantitative retina thickness in all ETDRS subfields as well as the subjective assessment of the OCT of all participants by 2 masked educated graders (C.C., N.H.). Foveal-centered SD-OCT volumes were obtained for both eyes from each participant on the Cirrus-HD system (Carl Zeiss Meditec, Inc, Dublin, CA) using the macular cube 512×128 scan pattern. The macular thickness map was divided into 3 concentric circles based on the ETDRS grading grid: a central circle (0.5 mm or 1.5° radius) centered on the fovea, a concentric inner ring (1.5 mm or 5° radius), and a concentric outer ring (3 mm or 10° radius). Radii at 45° and 135° angles were used to divide the circles into the 9 ETDRS subfields: the central subfield and 4 inner and 4 outer subfields (temporal, superior, nasal, and inferior subfields; Fig 1B). Mean retinal thicknesses in each of the 9 subfields were generated by the manufacturer's software version 6.5.0.772 (Carl Zeiss Meditec, Inc).