Archives of
Ophtalmological Research

Review

DOI: 10.51271/AOR-0013

Current diagnosis and screening of hydroxychloroquine retinopathy

Hüseyin Egemen Köse, Mehmet Çıtırık

Department of Ophthalmology, Ankara Etlik City Hospital, Ankara, Turkiye

Received: 05/05/2024 ◆ **Accepted**: 12/07/2024 ◆ **Published**: 26/07/2024

Cite this article: Köse HE, Çıtırık M. Current diagnosis and screening of hydroxychloroquine retinopathy. *Arch Ophthalmol Res*. 2024;1(3):46-49.

Corresponding Author: Hüseyin Egemen Köse, egekose1996@gmail.com

ABSTRACT

Hydroxychloroquine-associated retinopathy is an important cause of progressive visual loss that is increasingly being diagnosed with the growing use of hydroxychloroquine and modern imaging techniques. Hydroxychloroquine acts through complex mechanisms and is commonly used to treat rheumatological and dermatological diseases. Optical coherence tomography, fundus autofluorescence, and automated perimetry are commonly used in retinal clinics for the diagnosis and monitoring of hydroxychloroquine-associated retinopathy. Owing to the potential for irreversible central visual loss with the development of retinopathy, early detection of toxicity is crucial. Advances in technology, wide-field imaging devices, new optical coherence tomography techniques and parameters, fundus autofluorescence techniques, and imaging methods such as optical coherence tomography angiography offer promise for the early detection of toxicity.

Keywords: Hydroxychloroquine retinopathy, microperimetry, multifocal electroretinography, optical coherence tomography, optical coherence tomography angiography, perimetry, wide-field imaging

INTRODUCTION

Hydroxychloroquine (HCQ)-associated retinopathy was first described in the 1960s.[1] Hydroxychloroquine is an antimalarial drug that acts through complex mechanisms as an anti-inflammatory, immunomodulatory, anti-infective, and antithrombotic agent. It is commonly used in many rheumatological diseases due to its low cost and efficacy.[2] Additionally, it has been shown to increase survival in patients with systemic lupus erythematosus (SLE).[3] Hydroxychloroquine is a lipophilic and lysosomotropic drug that accumulates in lysosomes within cells, causing lysosomal instability.[4] Hydroxychloroquine retinopathy poses a threat of blindness by causing progressive visual loss, and toxicity can continue to cause damage even after discontinuation of the drug due to accumulation of hydroxychloroquine in the retinal pigment epithelium melanin.[5,6] The term "bull's eye maculopathy," which was traditionally used to describe the end-stage manifestation characterized by parafoveal pigment epithelial changes, has been replaced by the early detection of outer retinal damage without fundoscopic changes following optical coherence tomography (OCT). Therefore, the early detection of this toxicity is important in ophthalmological practice.

PREVALENCE AND RISK FACTORS

Before the widespread use of OCT and fundus autofluorescence (FAF), the prevalence was thought to be less than 0.5%.[7] However, with the increasing use of OCT and FAF, a prevalence of 7.5% in patients using hydroxychloroquine for more than five years and 20-50% in those using it for more than 20 years has been reported. The dose used in the development of retinal toxicity is the most important factor, with the highest risk of toxicity observed at doses >5 mg/kg/day. It has been suggested that the risk is less than 2% with doses of 4-5 mg/kg/day for less than ten years.[8] Another risk factor is the presence of concomitant renal disease. Current evidence suggests that stage 3 (glomerular filtration rate <60 ml/min/1.73 m^2) and worse renal disease pose additional risk. It has also been found that concomitant use of tamoxifen increases the risk.[8] Since patients using hydroxychloroquine for rheumatological diseases are usually older, and concomitant retinal diseases are possible, which are important for both the differential diagnosis of hydroxychloroquine retinopathy and the resulting visual loss. Currently, there is insufficient evidence that preexisting retinal diseases pose an additional risk for hydroxychloroquine retinopathy. However, the detection

of previous retinal diseases is important for the differential diagnosis of hydroxychloroquine retinopathy.[9] Genetic factors have been suggested to play a role in the development of the disease. In a study using exosome sequencing, the RP1L1, RPGR, RPE65, and CCDC66 genes were associated with the onset of the disease.[10] A recent study in patients with SLE also suggests that the use of selective serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SNRIs), and antiphospholipid syndrome are risk factors for the development of the disease.[11]

HYDROXYCHLOROQUINE RETINOPATHY PATTERNS

These patterns are based on the localization of the affected retinal pigment epithelium-photoreceptor complex in the fundus.

Parafoveal Retinopathy

Defined as defects in the outer retinal layer between 2° and 6°.

Pericentral Retinopathy

Characterized by defects mainly near major retinal vascular arcades rather than parafoveal. A previous study has shown that this type of involvement is common in Asian patients. Additionally, it is noted that patients with this type of involvement are often in more advanced stages, as the defects are detected late on standard tests (OCT and automated perimetry).[12]

Mixed-Type Retinopathy

Characterized by defects in both the parafoveal and pericentral regions.

HYDROXYCHLOROQUINE RETINOPATHY STAGES

HCQ retinopathy can be divided into early, intermediate, and advanced (severe) stages, based on the degree of involvement of the outer retinal layers. In the early stage, defects in the photoreceptor layer are <180°; in the intermediate stage, defects are >180°; and in the advanced stage, combined retinal pigment epithelium defects (mottled hyper-hypoautofluorescence on FAF) are observed.[13] This classification is also important for disease progression. A study found that in early and intermediate stages, outer retinal involvement did not progress for up to 9 years after discontinuation of the drug, while in advanced retinopathy, progression continued for up to 20 years after discontinuation of the drug.[5]

HYDROXYCHLOROQUINE DIAGNOSTIC TESTS

The tests used for the diagnosis of HCQ retinopathy are divided into structural and functional tests.

Functional Tests

Automated perimetry and visual field test: Visual field tests provide information about visual field loss resulting from retinopathy. They are considered subjective tests due to their variable results and dependence on patient compliance.[14] The most common visual field defect is a ring scotoma in intermediate and severe stages, while in early stages, superonasal field defects may be seen, none of these are specific to HCQ retinopathy.[15] The 10-2 test, although commonly used, may miss pericentral defects, which can be detected with the 24-2 and 30-2 tests.[16,17]

Microperimetry: Microperimetry, which combines automated perimetry with real-time fundus photography, can be used to detect functional loss. Its disadvantages are that it is time-consuming and has a long learning curve for patients. Therefore, it has limited use.[16,17]

Electroretinography and multifocal electroretinography: Full-field electroretinography (ERG) is not recommended as a screening tool because widespread photoreceptor damage is usually observed only in severe cases. Multifocal electroretinography (MfERG) is more sensitive than 10-2 visual field test. Unlike full-field ERG.[18] It is an objective test for detecting decreased function due to retinal toxicity, MfERG can detect localized sensitivity changes in the macula, but it is generally expensive and time-consuming. One systematic review suggested that mfERG have the ability to detect HCQ retinopathy more earlier than other tests used in HCQ screening.[19]

Structural Tests

Structural tests can be classified into standard and newly described structural tests. Standard structural tests are easily accessible in routine practice.

Standard structural Tests: These tests mainly include OCT and fundus autofluorescence (FAF). The earliest OCT finding in early retinopathy is the loss of the parafoveal ellipsoid zone.[20-22] In FAF, parafoveal hyperautofluorescence is observed in early stages, while in advanced stages, patchy hypoautofluorescent areas due to RPE loss begin to appear.[23,24] OCT has been found to be more specific than FAF in a study comparing OCT with FAF.[25]

Newly described structural tests and parameters:

- **Newly described OCT techniques and parameters:** Retinal thinning has been detected as a result of hydroxychloroquine use, and can occur in various forms, including parafoveal, perifoveal, mixed, or total macular thinning.[26] Thinning may be more pronounced in any layer of the retina. Thinning of the inner retinal layers may be an early indicator of HCQ toxicity.[27] Outer retinal layer involvement typically occurs in advanced stages. Thinning of the outer nuclear layer has been shown to be associated with HCQ toxicity.[28] Additionally, these parameters examined by OCT can provide insights into progression during follow-up.[29] Studies have shown that thinning occurs not only in retinal layers but also in choroidal layers.[30,31] Because involvement is often parafoveal in Asian patients, wide-field OCT may be useful in detecting these patients.[12,32] En-face OCT is a newly used imaging technique in daily practice that allows visualization of retinal layers in the coronal plane.[33] Studies using en-face OCT have detected HCQ retinopathy, and quantitative measurements of the affected area have been possible with this imaging technique.[34]

- **Newly described FAF techniques and parameters:** Although FAF has long been used in the detection of HCQ retinopathy, new tests based on FAF are being developed. The first is quantitative FAF measurements. Quantitative fundus autofluorescence (FAF) is a imaging method that primarily divides the macular area into segments of 7°-9° and measures the autofluorescence emitted from stimulated photoreceptors using 488 nm light.[35] Increased quantitative FAF signals have been observed in affected eyes, and it has been found that they begin to increase shortly after starting treatment and remain higher years after discontinuation of the drug.[36,37] Near-infrared FAF is another type of FAF that is used. This imaging allows visualization of autofluorescence derived from melanin pigment in the retina.[38] It has been suggested that HCQ retinopathy can be detected without OCT and fundoscopic signs using this imaging technique.[39] Wide-field FAF has been suggested to be useful in Asian patients.[12,32]
- **Newly described optic coherence tomography angiography parameters:** OCTA, which is increasingly used in retinal practice, has been investigated for its usefulness in detecting HCQ retinopathy with various results. A study in 61 patients diagnosed with HCQ retinopathy using MfERG found that decrease in the density of the deep capillary plexus.[40] Another study compared patients with rheumatoid arthritis with a control group and found no difference in vessel densities.[41]

How should imaging methods be used for hydroxychloroquine toxicity, and when?

According to the American Academy of Ophthalmology (AAO) guidelines published in 2011 and 2016, the initial examination was recommended for patients starting hydroxychloroquine, whereas the Royal College of Ophthalmologists (RCO) did not require the first examination. Both guidelines recommend starting annual examinations five years later if the patient has no major risk factors. However, both guidelines recommend starting screening earlier if the patient's dose is >5 mg/kg/day, if tamoxifen is used concomitantly, or if there is concomitant kidney disease (Table). When choosing a test for toxicity screening, AAO suggests that screening can be performed with OCT, FAF, automated perimetry, or mfERG (using wide-field imaging techniques in Asian patients), whereas RCO recommends OCT and FAF (preferably wide-field) as the first step. According to AAO, the presence of subjective findings confirming an objective test is for toxicity diagnosis. According to the RCO, abnormal OCT and FAF findings are diagnostic for toxicity. If a defect is found on OCT or FAF, automated perimetry and mfERG tests should be performed. If retinal toxicity is detected by an ophthalmologist, the rheumatologist or dermatologist should be informed, and the possibility of discontinuing the drug should be discussed because of the risk of central visual loss.[42,43] There is currently no consensus on or documented screening guidelines in our country.

Table. Screening of hydroxychloroquine retinopathy

For AAO	-In patients starting HCQ (hydroxychloroquine) therapy, the initial examination is performed -If there are no major risk factors; --Annual screening is started in the fifth year (OCT, FAF, automated perimetry, MfERG) --In Asian patients, wider field imaging methods --Subjective findings confirming an objective test=toxicity
For RCO	-In patients starting HCQ therapy, the initial examination is not mandatory. If there are no major risk factors; --Annual screening is started in the fifth year. (If possible, with OCT and FAF in wide angle) --Abnormality in OCT and FAF=Toxicity --If abnormality is found in either OCT or FAF; sequentially, automated perimetry and MfERG tests are performed.
Major risk factors:	Dose >5 mg/kg Use of tamoxifen Kidney disease

AAO: American Academy of Ophthalmology, HCO: Hydroxychloroquine, OCT: Optical coherence tomography, FAF: Fundus autofluorescence, MfERG: Multifocal electroretinography, RCO: Royal College of Ophthalmologists

CONCLUSION

HCQ retinopathy is a disease that is encountered more frequently in daily practice due to the increasing use of HCQ, and it is crucial to prevent irreversible vision loss by early detection. Owing to the limitations of commonly used examinations, such as OCT, FAF, and automated perimetry, in detecting early-stage disease, new imaging models for early disease detection are becoming more widespread in retinal clinics. These methods are gradually becoming a part of our daily use and are expected to continue to do so.

REFERENCES

1. Scherbel AL, Mackenzie AH, Nousek JE, Atdjian M. Ocular lesions in rheumatoid arthritis and related disorders with particular reference to retinopathy. A study of 741 patients treated with and without chloroquine drugs. *N Engl J Med.* 1965;273(7):360-366. doi: 10.1056/nejm196508122730704
2. Yates M, Malaiya R, Stack J, Galloway JB. Hydroxychloroquine use: the potential impact of new ocular screening guidelines. *Eye (Lond).* 2018;32(1):161-162. doi: 10.1038/eye.2017.166
3. Alarcón GS, McGwin G, Bertoli AM, et al. Effect of hydroxychloroquine on the survival of patients with systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort (LUMINA L). *Ann Rheum Dis.* 2007;66(9):1168-1172. doi: 10.1136/ard.2006.068676
4. Mindell JA. Lysosomal acidification mechanisms. *Annu Rev Physiol.* 2012;74:69-86. doi: 10.1146/annurev-physiol-012110-142317
5. Pham BH, Marmor MF. Sequential changes in hydroxychloroquine retinopathy up to 20 years after stopping the drug: implications for mild versus severe toxicity. *Retina.* 2019;39(3):492-501. doi: 10.1097/IAE.0000000000002408
6. Schroeder RL, Gerber JP. Chloroquine and hydroxychloroquine binding to melanin: Some possible consequences for pathologies. *Toxicol Rep.* 2014;1:963-968. doi: 10.1016/j.toxrep.2014.10.019
7. Morsman CD, Livesey SJ, Richards IM, Jessop JD, Mills PV. Screening for hydroxychloroquine retinal toxicity: is it necessary? *Eye (Lond).* 1990;4(Pt 4):572-576. doi: 10.1038/eye.1990.79
8. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. *JAMA Ophthalmol.* 2014;132(12):1453-1460. doi: 10.1001/jamaophthalmol.2014.3459
9. Yusuf IH, Issa PC, Ahn SJ. Hydroxychloroquine-induced retinal toxicity. *Front Pharmacol.* 2023;14. doi: 10.3389/FPHAR.2023.1196783

10. Chiu HI, Cheng HC, Wu CC, et al. Exome sequencing and genome-wide association analyses unveils the genetic predisposition in hydroxychloroquine retinopathy. *Eye (Lond)*. doi: 10.1038/s41433-024-03044-x

11. Trefond L, Lhote R, Mathian A, et al. Identification of new risk factors for hydroxychloroquine and chloroquine retinopathy in systemic lupus erythematosus patients. *Semin Arthritis Rheum*. 2024;66:152417. doi: 10.1016/j.semarthrit.2024.152417

12. Melles RB, Marmor MF. Pericentral retinopathy and racial differences in hydroxychloroquine toxicity. *Ophthalmology*. 2015;122(1):110-116. doi: 10.1016/j.ophtha.2014.07.018

13. Marmor MF. Comparison of screening procedures in hydroxychloroquine toxicity. *Arch Ophthalmol*. 2012;130(4):461-469. doi: 10.1001/archophthalmol.2011.371

14. Marshall E, Robertson M, Kam S, Penwarden A, Riga P, Davies N. Prevalence of hydroxychloroquine retinopathy using 2018 Royal College of Ophthalmologists diagnostic criteria. *Eye (Lond)*. 2021;35(1):343-348. doi: 10.1038/s41433-020-1038-2

15. Anderson C, Blaha GR, Marx JL. Humphrey visual field findings in hydroxychloroquine toxicity. *Eye (Lond)*. 2011;25(12):1535-1545. doi: 10.1038/eye.2011.245

16. Pfau M, Jolly JK, Wu Z, et al. Fundus-controlled perimetry (microperimetry): application as outcome measure in clinical trials. *Prog Retin Eye Res*. 2021;82:100907. doi: 10.1016/j.preteyeres.2020.100907

17. Rohrschneider K, Bültmann S, Springer C. Use of fundus perimetry (microperimetry) to quantify macular sensitivity. *Prog Retin Eye Res*. 2008;27(5):536-548. doi: 10.1016/j.preteyeres.2008.07.003

18. Lai TYY, Ngai JWS, Chan WM, Lam DSC. Visual field and multifocal electroretinography and their correlations in patients on hydroxychloroquine therapy. *Doc Ophthalmol*. 2006;112(3):177-187. doi: 10.1007/s10633-006-9006-0

19. Tsang AC, Ahmadi Pirshahid S, Virgili G, Gottlieb CC, Hamilton J, Coupland SG. Hydroxychloroquine and chloroquine retinopathy: a systematic review evaluating the multifocal electroretinogram as a screening test. *Ophthalmology*. 2015;122(6):1239-1251.e4. doi: 10.1016/j.ophtha.2015.02.011

20. Omri S, Omri B, Savoldelli M, et al. The outer limiting membrane (OLM) revisited: clinical implications. *Clin Ophthalmol*. 2010;4:183-195. doi: 10.2147/opth.s5901

21. Chen E, Brown DM, Benz MS, et al. Spectral domain optical coherence tomography as an effective screening test for hydroxychloroquine retinopathy (the "flying saucer" sign). *Clin Ophthalmol*. 2010;4:1151-1158. doi: 10.2147/OPTH.S14257

22. Rodriguez-Padilla JA, Hedges TR, Monson B, et al. High-speed ultra-high-resolution optical coherence tomography findings in hydroxychloroquine retinopathy. *Arch Ophthalmol*. 2007;125(6):775-780. doi: 10.1001/archopht.125.6.775

23. Kellner S, Weinitz S, Farmand G, Kellner U. Cystoid macular oedema and epiretinal membrane formation during progression of chloroquine retinopathy after drug cessation. *Br J Ophthalmol*. 2014;98(2):200-206. doi: 10.1136/bjophthalmol-2013-303897

24. Kellner U, Renner AB, Tillack H. Fundus autofluorescence and mfERG for early detection of retinal alterations in patients using chloroquine/hydroxychloroquine. *Invest Ophthalmol Vis Sci*. 2006;47(8):3531-3538. doi: 10.1167/iovs.05-1290

25. Cukras C, Huynh N, Vitale S, Wong WT, Ferris FL, Sieving PA. Subjective and objective screening tests for hydroxychloroquine toxicity. *Ophthalmology*. 2015;122(2):356-366. doi: 10.1016/j.ophtha.2014.07.056

26. Kim KE, Ahn SJ, Woo SJ, et al. Use of OCT retinal thickness deviation map for hydroxychloroquine retinopathy screening. *Ophthalmology*. 2021;128(1):110-119. doi: 10.1016/j.ophtha.2020.06.021

27. Gil P, Nunes A, Farinha C, Teixeira D, Pires I, Silva R. Structural and functional characterization of the retinal effects of hydroxychloroquine treatment in healthy eyes. *Ophthalmologica*. 2019;241(4):226-233. doi: 10.1159/000495308

28. Casado A, López-de-Eguileta A, Fonseca S, et al. Outer nuclear layer damage for detection of early retinal toxicity of hydroxychloroquine. *Biomedicines*. 2020;8(3). doi: 10.3390/biomedicines8030054

29. Melles RB, Marmor MF. Rapid macular thinning is an early ındicator of hydroxychloroquine retinal toxicity. *Ophthalmology*. 2022;129(9):1004-1013. doi: 10.1016/j.ophtha.2022.05.002

30. Ahn SJ, Ryu SJ, Joung JY, Lee BR. Choroidal thinning associated with hydroxychloroquine retinopathy. *Am J Ophthalmol*. 2017;183:56-64. doi: 10.1016/j.ajo.2017.08.022

31. Polat OA, Okçu M, Yılmaz M. Hydroxychloroquine treatment alters retinal layers and choroid without apparent toxicity in optical coherence tomography. *Photodiagnosis Photodyn Ther*. 2022;38:102806. doi: 10.1016/j.pdpdt.2022.102806

32. Lee DH, Melles RB, Joe SG, et al. Pericentral hydroxychloroquine retinopathy in Korean patients. *Ophthalmology*. 2015;122(6):1252-1256. doi: 10.1016/j.ophtha.2015.01.014

33. Leitgeb RA. En face optical coherence tomography: a technology review [Invited]. *Biomed Opt Express*. 2019;10(5):2177-2201. doi:10.1364/BOE.10.002177

34. Ahn SJ, Joung J, Lee BR. En face optical coherence tomography ımaging of the photoreceptor layers in hydroxychloroquine retinopathy. *Am J Ophthalmol*. 2019;199:71-81. doi: 10.1016/j.ajo.2018.11.003

35. Greenberg JP, Duncker T, Woods RL, Smith RT, Sparrow JR, Delori FC. Quantitative fundus autofluorescence in healthy eyes. *Invest Ophthalmol Vis Sci*. 2013;54(8):5684-5693. doi: 10.1167/iovs.13-12445

36. Reichel C, Berlin A, Radun V, et al. Quantitative fundus autofluorescence in systemic chloroquine/hydroxychloroquine therapy. *Transl Vis Sci Technol*. 2020;9(9):42. doi: 10.1167/tvst.9.9.42

37. Greenstein VC, Lima de Carvalho JR, Parmann R, et al. Quantitative fundus autofluorescence in HCQ retinopathy. *Invest Ophthalmol Vis Sci*. 2020;61(11):41. doi: 10.1167/iovs.61.11.41

38. Abdolrahimzadeh S, Ciancimino C, Grassi F, Sordi E, Fragiotta S, Scuderi G. Near-infrared reflectance imaging in retinal diseases affecting young patients. *J Ophthalmol*. 2021;2021:5581851. doi: 10.1155/2021/5581851

39. Kellner S, Weinitz S, Kellner U. Spectral domain optical coherence tomography detects early stages of chloroquine retinopathy similar to multifocal electroretinography, fundus autofluorescence and near-infrared autofluorescence. *Br J Ophthalmol*. 2009;93(11):1444-1447. doi: 10.1136/bjo.2008.157198

40. Akhlaghi M, Kianersi F, Radmehr H, Dehghani A, Naderi Beni A, Noorshargh P. Evaluation of optical coherence tomography angiography parameters in patients treated with Hydroxychloroquine. *BMC Ophthalmol*. 2021;21(1):209. doi: 10.1186/s12886-021-01977-5

41. Esser EL, Zimmermann JA, Storp JJ, Eter N, Mihailovic N. Retinal microvascular density analysis in patients with rheumatoid arthritis treated with hydroxychloroquine. *Graefes Arch Clin Exp Ophthalmol*. 2023;261(5):1433-1442. doi: 10.1007/s00417-022-05946-6

42. Marmor MF, Kellner U, Lai TYY, Melles RB, Mieler WF. American Academy of Ophthalmology. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 Revision). *Ophthalmology*. 2016;123(6):1386-1394. doi: 10.1016/j.ophtha.2016.01.058

43. Yusuf IH, Foot B, Lotery AJ. The Royal College of Ophthalmologists recommendations on monitoring for hydroxychloroquine and chloroquine users in the United Kingdom (2020 revision): executive summary. *Eye (Lond)*. 2021;35(6):1532-1537. doi: 10.1038/s41433-020-01380-2