

EXTENDED REPORT

Detecting chloroquine retinopathy: electro-oculogram versus colour vision

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Aim: To investigate the relative sensitivity and specificity of two tests of retinal function (the electro-oculogram (EOG) and a computerised colour vision test) in screening for ocular toxicity caused by chloroquine and hydroxychloroquine.

Methods: 93 patients with rheumatic diseases receiving long term chloroquine and hydroxychloroquine therapy were followed for an average of 2.6 years. Clinical examination, an EOG, and a quantitative test of colour vision were carried out every 6 months.

Results: Mild fundus changes were observed in 38 patients. Four patients developed typical bull's eye maculopathy, three of whom had received 250, 365, and 550 g total dose of chloroquine, and one 1500 g of hydroxychloroquine. Statistical analysis of all patients showed that for those with no fundus changes or stippled pigmentation a number showed elevation of tritan threshold, so that if macular stippling is a sign of mild retinopathy the test on tritan changes has a 64% sensitivity and 63% specificity for an upper threshold value of 7%. All four patients with bull's eye lesions showed a marked disturbance of tritan colour vision, with a threshold of 14.8%, a sensitivity of 75%, and a specificity of 94%. For protan colour vision a threshold of 10% gives 75% sensitivity and 91% specificity. By contrast, neither an absolute nor a relative EOG reduction was a valid criterion for early or late chloroquine retinopathy. In advanced retinopathy an Arden coefficient (AQ) <180% yields 50% sensitivity and 54% specificity. When AQ <160% is the threshold, sensitivity does not increase but specificity rises to 82%. Occurrence of marked corneal deposits on clinical examination yields 50% sensitivity and 90% specificity in this situation.

Conclusion: Screening for chloroquine retinopathy can be improved by using a sensitive colour test. Disturbance of the tritan axis appears to occur first. A normal test result on computerised colour testing virtually excludes any retinopathy by antimalarials. The EOG is of little diagnostic value.

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Ocular toxicity caused by antimalarials was first described in the literature as early as 1957.^{1,2} As antimalarials were found effective not only for treatment and prophylaxis of malaria but also for many rheumatoid diseases they are used ever more frequently nowadays and are given as a long term medication. The risk of ocular toxicity is therefore considerable. The incidence of early retinopathy in ophthalmologically unmonitored patients was estimated in an early review by Bernstein³ as 10% for chloroquine and 3–4% for hydroxychloroquine. Advanced retinopathy had an incidence of 0.5%. These risks might be reduced substantially by regular observation and testing.

Some degree of corneal deposits (verticillata) can be demonstrated in most patients taking chloroquine, but these changes very rarely impair vision.⁴ Corneal deposits occur more frequently with chloroquine than with hydroxychloroquine,⁵ are located in the epithelium and subepithelial stroma^{6,7} and are mostly reversible.⁷ By contrast, retinopathy is a severe ocular side effect presenting with bilateral, reproducible, and permanent visual field abnormalities.⁸ Early retinal changes consist of a pigmentary stippling or granular appearance of the macula, with the patient still being asymptomatic. Advanced retinopathy may show the typical "bull's eye" maculopathy associated with impaired visual acuity and central visual field defects.⁹ These changes of advanced maculopathy are irreversible and may progress even after cessation of the drug.^{10,11}

Screening strategies for antimalarial toxicity are still controversial, because there is a difficulty in defining the early stages of retinopathy, and in well monitored patients, the incidence of retinopathy is low. Macular changes and transient

defects in visual field testing as well as in colour vision testing may be symptoms of a "pre-retinopathy," but are difficult to differentiate from other causes such as age related changes. While all screening strategies include visual acuity testing and a dilated fundus examination, and many include fundus photographs, other tests like fluorescein angiography¹² or more frequently visual field tests ranging from Amsler grid¹³ to automated macular perimetry^{14–16} have been used. Also, various colour vision tests have been proposed¹⁷ and different electrophysiological tests (EOG and ERG) have been evaluated.^{18–25} The efficiency of all such ophthalmological screening procedures is controversial. This is reflected in surveys of current practice patterns showing quite inhomogeneous results.²⁶ Recently, proposed screening requirements are more and more limited to clinical tests,^{16,27} and for hydroxychloroquine no routine ophthalmological screening is recommended by the Royal College of Ophthalmologists.⁹ The recent recommendations of the American Academy of Ophthalmology¹⁶ adopt screening intervals after a baseline examination for both antimalarials because of the anticipated risk to the patient. The proposed routine screening includes an ophthalmological examination and visual field testing by an Amsler grid or Humphrey 10-2. Optional tests include colour testing, fundus photography and fluorescein angiography, and multifocal ERG. The EOG is not recommended by the American Academy as a screening test.

Therefore the aim of the current study was to investigate, if screening for ocular toxicity of antimalarials can be improved by adding the EOG—as it theoretically shows retinal pigment epithelium and rod/cone interactions—and by colour vision testing. For colour vision testing a computerised test

developed by Arden,²⁸ known to be more sensitive than most other colour tests²⁸⁻³⁰ was applied.

METHODS

Retinopathy

The definition of retinopathy caused by antimalarials is controversial. Subtle retinal changes such as pigmentary stippling or granular appearance of the macula with the patient still being asymptomatic (and not exhibiting defects in visual field testing) may be the first signs of retinopathy.^{31, 32} In those cases colour vision is known to be already reduced.^{17, 31, 33} In established retinopathy bilateral, reproducible, and permanent visual field abnormalities are found additionally.⁸ In more advanced cases also visual acuity may be impaired and the typical "bull's eye" maculopathy can be seen.⁹

Therefore in this study two forms of retinopathy were distinguished. A "mild form" of retinopathy was defined by pigmentary macular changes but without reproducible defects on Amsler and static macular visual field testing (Humphrey, 10-2 program). A second group of patients with "advanced" maculopathy distinguished in accordance with previous use⁸ showed advanced macular changes—that is, typical bull's eye appearance and reproducible, bilateral visual field defects.

Patients

Retrospectively all patients monitored between 1983 and 2000 at our electrophysiological department for antimalarial toxicity were identified from the records. Inclusion criteria were at least one complete examination for toxicity including clinical examination, EOG, and colour vision testing. Patients with other causes for macular changes such as diabetes, central serous retinopathy, retinitis pigmentosa, or age related macula degeneration were excluded. Therefore, from 98 identified patients, five with age related macula degeneration were excluded. In those five patients three had normal EOGs and colour vision, one exhibited only a disturbance in tritan axis, and one patient had an abnormal EOG <160% Arden coefficient and a defect in the tritan axis. Also, patients with other ocular disorders interfering with colour vision such as advanced cataracts, or diseases affecting the optic nerve such as former optic neuritis or glaucoma were excluded. None of the remaining 93 patients had any of these disorders.

A final total of 93 patients were included in the study. Of those, 66 (71%) were female and 27 male. The reason for medication with antimalarials was in 37 patients (40%) rheumatoid arthritis, in 36 patients (39%) systemic lupus erythematosus, in six patients other collagenoses, and in the remaining 14 patients various other rheumatic diseases. A total of 16 patients (17%) received hydroxychloroquine, while the majority received chloroquine (83%). Regular examinations were performed every 6 months. In the analysis three monitoring visits were included: baseline examination, last available examination, and one intermediate examination dividing time into equal intervals. If the medication was discontinued for any reason, the last examination was the examination in which it was decided to stop the drug. A total of 61 patients were seen more than once, 51 patients were followed several times. Mean age when starting follow up was 50.8 (SD 17.6) years, mean follow up time 2.6 (SD 2.9) years. On every examination besides clinical examination, EOG and colour vision testing as described below were performed. Amsler visual field testing was only performed when a maculopathy was suspected.

In total, 51 out of 93 patients were totally normal. A mild retinopathy (as defined above) was found in 38 patients and four patients showed an advanced retinopathy. In patients without retinopathy the mean cumulative dose at last follow up visit was 297 g chloroquine (SD 298 g) and 324 g hydroxychloroquine (228 g). Those exhibiting mild retinopathy had received total doses of 280 g (286 g) chloroquine and 153 g

(153 g) hydroxychloroquine, not statistically different from those without retinopathy. Those patients with advanced retinopathy had received a total dose of chloroquine of 250, 365, and 550 g respectively (mean 400 g; $p=0.6$) and one patient had received 1500 g of hydroxychloroquine. However, only one of these had been previously monitored at our institution. In two of those four cases we had long term records of body weight available and the dose given far exceeded the recommended 3 mg/kg/day for chloroquine and 6.5 mg/kg/day for hydroxychloroquine.

EOG

Electro-oculography was carried out on all patients in accordance with the standards of International Society for Clinical Electrophysiology of Vision (ISCEV).³⁴ Pupil dilatation with 1% tropicamide was performed before pre-adaptation. Horizontal fixation targets were approximately 30° apart, silver-silver chloride electrodes were placed according to ISCEV standards. Recording was performed with a Jaeger-Toennies "multiliner" system (Hoechberg, Germany) and finally the Arden ratio (Arden quotient, AQ) between the lowest dark adapted point (dark trough) and highest light point (light peak) was calculated.³⁴ In all people except one, the EOG was repeated one or more times.

Colour vision test

The computerised colour vision test by Arden was used. The details of the method are described in detail elsewhere.²⁸⁻³⁰ In brief, the system uses a calibrated 21 inch colour monitor to present random letters as targets to be identified. The letters are of equal luminance to the background, and can only be recognised because their hue differs from the background. The colour of the letters can be varied along a chosen colour-confusion axis. That all stimuli are equiluminant with the background is ensured by a preliminary adjustment (in every patient) of the relative luminance of the red and green and green and blue phosphors. Then a modified binary search is carried out to determine the threshold colour contrast along protan and tritan colour confusion lines. The resulting threshold should not exceed 8.0% in normal probands and is known to be almost independent of age.³⁰ The thresholds of 8.0% for protan and tritan axis were used according to Berninger *et al*,³⁰ where 7.0% was found as an extreme value for protan axis and 7.9% for tritan axis in normals. The threshold represents a deviation of more than 3 SD for protan and 2 SD for tritan from the normal mean. Completeness of follow up examinations was identical to that of the EOG.

Statistics

Data were collected and analysed using SPSS 10.0 for Windows (SPSS Inc, Chicago, IL, USA). On all tests $p<0.05$ was considered significant. Unless otherwise specified for comparisons of means the parametric T test was used. At the begin of analysis a comprehensive graphical analysis of all results by means of scatter plots and box plots was performed to identify possible influencing factors. The patients receiving chloroquine and hydroxychloroquine were combined for assessment of the diagnostic tests, as both drugs show very similar toxicities, although with different probabilities. Receiver operating characteristic (ROC) curves were calculated with SPSS 10.0 as a statistical standard method to investigate the figure of merit for diagnostic tests. For assessment of diagnostic value the sensitivity and specificity were calculated manually (sensitivity = number of patients where the test result is abnormal and who have the disease/all patients with the disease; specificity = normals with a normal test result/all normals). The positive and negative predictive values were also calculated as common in statistical analysis. For this, it was assumed that the prevalence of retinopathy (that is, occurrence at some time during therapy) in patients receiving chloroquine was 10%.

Table 1 EOG in retinopathy

EOG criteria	Mild retinopathy	Advanced retinopathy	Normals
AQ<180 "abnormal"	23	2	23
AQ>180 "normal"	15	2	27
	Sensitivity 61%	Sensitivity 50%	Specificity 54%
AQ<160 "abnormal"	12	2	9
AQ>160 "normal"	26	2	41
	Sensitivity 32%	Sensitivity 50%	Specificity 82%
Reduction of AQ>20% "abnormal"	8		6
Reduction of AQ<20% "normal"	20	1	26
	Sensitivity 29%	*	Specificity 81%
Reduction of AQ>30% "abnormal"	3		5
Reduction of AQ<30% "normal"	25	1	27
	Sensitivity 11%	*	Specificity 84%

Sensitivity and specificity of EOG to screen for chloroquine retinopathy. Different cut-off criteria are listed.
*Cannot be assessed validly due to the low patient number.

Table 2 Arden colour vision test in retinopathy

Test results	Mild retinopathy	Advanced retinopathy	Normals
Protan axis "abnormal"	8	3	6
Protan axis "normal"	29	1	45
	Sensitivity 22%	Sensitivity 75%	Specificity 88%
Tritan axis "abnormal"	22	4	17
Tritan axis "normal"	15	0	34
	Sensitivity 60%	Sensitivity 100%	Specificity 67%
Acquired colour defect	[3]	1	3
No acquired colour defect	[31]		44
	[Sensitivity 10%]*	*	Specificity 94%

Sensitivity and specificity of the computerised Arden colour test to screen for chloroquine retinopathy.
*Cannot be assessed validly due to the low patient number.

RESULTS

EOG

The results of EOG testing are summarised in Table 1. The highest sensitivity of 61% is achieved when using an AQ of 180 for discriminating between normal and abnormal EOGs. However, then only 54% specificity is obtained. When a prevalence of 10% retinopathy is assumed, this would yield a positive predictive value of only 13%, which means that only 13% of those patients with an abnormal EOG have retinopathy. The corresponding negative predictive value is 93%—that is, 93% of patients with a normal EOG do not have retinopathy. This has to be compared with the assumed 90% of patients who do not develop retinopathy anyway. Some other criteria like AQ 160% as a limit, or a reduction of AQ more than 20% or 30% over time are listed in Table 1. None of them shows significantly better characteristics for screening. There are no large differences between considering all maculopathies and only advanced maculopathies.

Colour vision

Analysis of the Arden colour vision test is summarised in Table 2. While an absolute defect in the protan axis is found in only 22% of cases with mild retinopathy, this criterion yields a sensitivity of 75% in advanced maculopathy. Disturbances of the tritan axis are less specific (67%), but show 100% sensitivity in patients with advanced retinopathy. When looking at acquired colour defects only, they are found to be very specific. As several patients entered the series with disturbances in colour vision and only one patient with advanced retinopathy could be followed while developing retinopathy, the sensitivity cannot be assessed validly in this study. When calculating the

positive predictive value, again, for advanced retinopathy an abnormal protan axis yields 41% and an abnormal tritan axis yields 25%. For the negative predictive value 96.9% are obtained for protan and 100% for tritan axis. This means that a normal test result on Arden colour test virtually excludes any more advanced retinopathy by antimalarials.

Corneal deposits

A distinct cornea verticillata was seen in five of 51 patients without maculopathy, in five of 38 patients with mild retinopathy and in two of the four patients with advanced maculopathy. This yields 13% sensitivity for mild macular changes and remarkable 50% sensitivity for advanced retinopathy at 90% specificity. For advanced retinopathy a positive predictive value of 36% and a negative predictive value of 94% is obtained.

Effect of age

To investigate if age related changes have a role in the diagnostic tests, regression analysis was performed. For the EOG no significant effect was found in the patients treated with antimalarials: $EOG\ AQ = 198 - 0.47 \times age$. For the colour test a significant, but small effect of age was found for both, the protan ($p=0.03$) and larger for the tritan axis ($p<0.001$).

$$\text{Protan threshold} = 3.75 + 0.064 \times age$$

$$\text{Tritan threshold} = 1.81 + 0.129 \times age$$

When only the subgroup of patients who never developed any retinopathy was examined, a similarly significant, but smaller effect in size remained:

$$\text{Protan threshold} = 4.56 + 0.037 \times age$$

$$\text{Tritan threshold} = 3.60 + 0.070 \times age$$

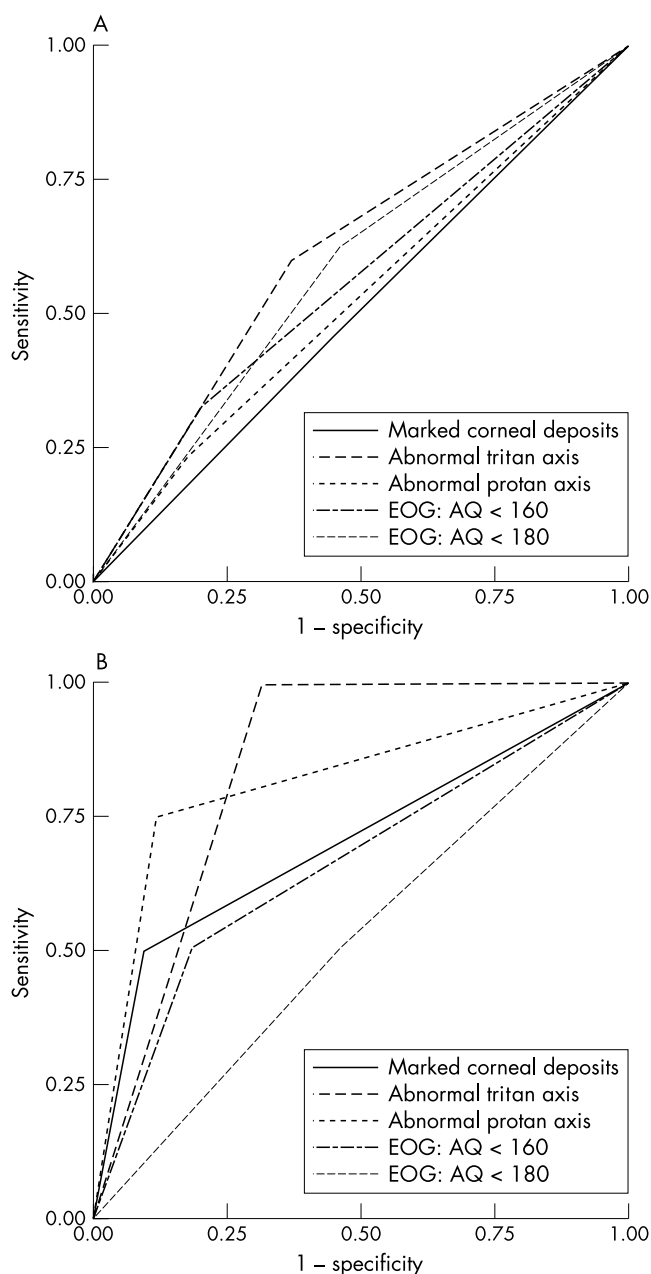


Figure 1 (A) ROC curves for mild retinopathy. (B) ROC curves for advanced retinopathy. One can see that in mild retinopathy (A) none of the tests shows a receiver operating characteristic (ROC) curve distinctly different from the diagonal and is therefore suitable for screening. In advanced retinopathy (B) as defined by existing visual field defects, a defect colour vision in protan and tritan axis offer good characteristics for screening. Marked corneal deposits show similar fair characteristics as does the best criteria using the EOG, an AQ of smaller than 160%. The other absolute and relative cut offs for the EOG show even worse test characteristics.

ROC analysis

The results obtained with the given cut-off limits are summarised as ROC curves in Figure 1. While for mild retinopathies (Fig 1A) no test shows suitable test characteristics (all curves are close to the diagonal), for advanced retinopathies (Fig 1B) a disturbance of protan and tritan axis in the Arden colour test shows a distinct curve. The area under the curve representing diagnostic quality is highest for tritan changes (0.840) and still very high for changes in protan axis (0.815).

Optimising thresholds

To investigate, whether the cut-off points derived from studies on normal people and previous literature results can be further optimised, ROC analysis was performed. The patients

on antimalarials without any sign of retinopathy served as controls. For mild retinopathies the best test characteristics are obtained for a change in the tritan axis. A threshold of 6.2% provides 75% sensitivity and 39% specificity, a threshold of 7.0% gives 64% sensitivity and 63% specificity. The test characteristics for all other tests are less suitable as shown above.

For advanced retinopathy both the tritan and protan axis show acceptable test characteristics. The screening characteristics of EOG are no better than chance and therefore will not be shown. For the tritan axis a threshold of 8.5% still gives 100% sensitivity and 75% specificity, a threshold of 14.8% yields 75% sensitivity and 94% specificity. For the protan axis, a threshold of 6.1% yields 100% sensitivity at 62% specificity and a threshold of 10.0% gives 75% sensitivity and 91% specificity.

ANOVA

To account for possible cross correlations an analysis of variance (ANOVA) was calculated. The covariates and factors included were the age, accumulated total dose of antimalarials, AQ of the EOG, protan threshold, tritan threshold, and occurrence of marked corneal deposits. For prediction of a mild retinopathy occurrence of marked corneal deposits was the only significant factor ($p=0.04$), while all other tests yielded not statistically significant results. For prediction of an advanced retinopathy a disturbance of the protan axis was highly significant ($p=0.01$), while all other factors were not statistically significant. The high R^2 of 0.45 indicates a good overall prediction of the model.

DISCUSSION

Electrophysiology

Testing of patients taking chloroquine with the EOG was introduced early and showed promising first results.^{18, 35} The EOG is believed to show the interaction between retinal pigment epithelium and rods of the human eye³⁶ and was therefore considered to be a valid diagnostic tool.^{18, 37} However, it soon was noticed that screening for antimalarial toxicity by EOG requires a baseline testing owing to high inter-individual variations.¹⁸ It also became obvious, that an Arden quotient (AQ) of 180% is not an appropriate cut off for diagnostic testing.^{21, 38} Because of 10% intra-individual variance a cut off of 20% reduction of AQ was proposed.^{23, 39} Furthermore, it was noted that a reduction of EOG occurred frequently not only because of chloroquine medication but also by the course of the rheumatic disease itself.^{24, 25, 40, 41} Therefore in the present study the "normals" were defined as patients treated for rheumatic diseases but without any evidence of chloroquine retinopathy. But even given this control group, a rather limited diagnostic value of EOG was found. An absolute cut off of AQ=180% was found completely unsuitable and a cut off of AQ=160% yielded good specificity but very low sensitivity. No improvement could be achieved by using relative reductions within the same patient or ROC analysis. Therefore, given the relatively time consuming process of EOG measurement including dark adaptation³⁴ its use as a screening test appears little justified.

The ERG was also evaluated for screening for chloroquine toxicity,^{18, 19} but never found to be a more suitable screening test than the EOG.^{18, 23-25, 42, 43} It therefore was not evaluated in this study although it is nowadays performed with similar frequency as the EOG.²⁶ Until now only case reports regarding the pattern ERG are available,⁴⁴ while the multifocal techniques such as the multifocal ERG seem to be promising for detecting chloroquine retinopathy.^{45, 46} However, multifocal techniques are not yet routinely applied and further studies with larger patient series are required.

Colour vision

Defects in colour vision are known to occur with antimalarial treatment that causes retinal toxic changes⁴⁷ and may precede fundus changes.³¹ However, reported changes may be subtle and frequently are not detected by conventional colour testing.^{8 33 35 48-50} The first changes resulting from retinal toxicity occur with blue-yellow (that is, tritan) colours, while protan defects occur in more advanced cases.^{51 52} This explains why every colour test is not equally applicable. Recently, Vu and Easterbrook¹⁷ compared different clinical colour tests on patients with established retinopathy and normal patients with rheumatic diseases. They found that the Standard Pseudoisochromatic Plates Part 2 (SPP-2) had the best test characteristics for screening, yielding a sensitivity of 93% and a specificity of 88%.

In contrast with this plate based test, in our study colour vision testing is performed by a computerised colour test. Besides several other testing possibilities, this test allows a very exact and fast determination of individual colour vision on the protan and tritan axis.²⁸⁻³⁰ Based on our patient database this method allowed a sensitivity of 100% with 67% specificity for defects on the tritan axis, while defects on the protan axis yielded 75% sensitivity and 88% specificity. With adjustment of the thresholds even 100% sensitivity at 75% specificity can be obtained using the tritan axis. Those results are comparable to those of the SPP-2 published by Vu *et al.*¹⁷ However, not all patients were seen shortly after starting chloroquine medication so unfortunately no valid evaluation of the intra-individual changes during therapy was possible. This fact is important as some, especially male patients, may have an inborn defect in colour vision thus falsely reducing specificity.³⁰ One main advantage of the computerised test used is that even in those patients with a congenital or possible deficiency due to the rheumatic disease itself a further reduction in colour vision can be monitored. The findings of Vu *et al.*¹⁷ that earlier defects are more on the tritan axis, while more advanced defects also involve the protan axis, are confirmed by our results. On the other hand tritan changes are less specific, as they are more easily affected by other systemic and ocular changes such as media opacities by, for example, cataracts.⁵⁴ The computerised colour test used in our study has the advantage that it is relatively insensitive to disturbances in colour perception due to age.³⁰ Still, some age related changes can be found. They lie in the same range as known from normal probands.^{30 55} In an ANOVA, however, this small effect of age proved insignificant compared to the large changes in developing retinopathy.

Corneal deposits

Corneal deposits are known to occur in the corneal epithelium and superficial stroma. In experiments with albino rats a more peripheral localisation and a dose dependent effect was found.⁵⁶ The dose dependent corneal changes in corneal epithelium and anterior stroma could be confirmed on patients *in vivo* by confocal microscopy.⁷ It is also known that up to 95% of patients on chloroquine (in contrast with approximately 10% of patients taking hydroxychloroquine) exhibit corneal deposits.⁵ A correlation with overdosage, especially in hydroxychloroquine, has been discussed,⁵ but unfortunately most reports do not even mention corneal status.^{10 11 57 58} The importance of carefully examining the cornea for a verticillata^{4 5 27} as it may hint at retinopathy is supported by our results: for advanced retinopathy 50% sensitivity and 90% specificity were obtained for a marked cornea verticillata, which is comparable to the results of EOG testing. In ANOVA the occurrence of corneal deposits was even found a statistically significant predictor of mild retinopathy. Therefore careful slit lamp examination (with dilated pupil) of the cornea gives easily obtainable, valuable additional information on the probability of retinopathy.

Visual field testing

Visual field testing is frequently performed for monitoring,²⁶ since it was first proposed by Hart *et al* in 1984.¹⁴ Definite maculopathy is defined by Easterbrook as reproducible bilateral field defects,^{8 59} while early maculopathy does not show visual field defects.⁶⁰ The use of Amsler grid for testing is inexpensive and fast and therefore is frequently recommended.^{13 16 26 27 32} However, it is very dependent on the compliance of the patient and non-specific as approximately 6% of the normal population has defects.⁴⁹ Amsler grid testing may still give valuable hints and allows a less frequent use of automated static perimetry.²⁷ Although routinely many centres use static 10-2 automated perimetry, only few reports exist regarding its suitability for screening. Easterbrook found 91% sensitivity and 58% specificity for a red perimetry,⁴ which is in the range of colour vision tests. Therefore perimetry often is only performed, if other risk factors for retinopathy such as abnormal Amsler testing, abnormal colour vision, or long lasting therapy are present.²⁷ However, further prospective studies regarding 10-2 white perimetry are needed.

Experimental data

Several experimental studies on animals and cell cultures may influence the clinical attitude towards further screening considerations for retinopathy. While early studies assumed a binding of chloroquine to melanin caused retinal toxicity^{61 62} it is nowadays well known that melanin is not at all concerned in ocular toxicity.⁶³ This is supported by the fact, that retinopathy can be reproduced equally both in albino and in pigmented rabbits, rats and cats.⁶⁴⁻⁶⁸ The early histopathological reports of retinal changes showed membranous cytoplasmic bodies predominantly in the ganglion cells of the retina in humans,⁶⁹ monkey⁷⁰ and rodents,⁷¹ whereas the pigment epithelium showed only changes in very advanced retinopathy. Regarding the underlying mechanism, lipid complex accumulation causes ganglion cells to develop complex-containing lysosomes, Mueller and bipolar cells being first affected.⁶⁵ It appears that changes of the retinal pigment epithelium occur only in later stages as a secondary effect.⁶³ As far as it is known, chloroquine forms complexes with gangliosides impairing further degradation⁷² finally leading to a accumulation of lipid complexes in the neuroretina.^{73 74} Ultimately this may cause irreversible damage to rods and cones even after cessation of the drug.^{75 76} Here, the interference of chloroquine with DNA may play a part.^{62 73 74}

From this mechanism of first impairing ganglion cell function it becomes clear that in early chloroquine retinopathy screening strategies must focus on those cells. This may explain why the normal EOG and ERG are not as effective as expected but colour vision is a sensitive test as it is in glaucoma.²⁹ Of the electrophysiological tests, theoretically the pattern ERG should be the most effective.⁷⁷ As the retinopathy occurs predominantly in the macula, multifocal techniques are promising⁴⁵ and visual field testing can be limited to the central 10°.

CONCLUSIONS

When the recommended 3 mg chloroquine and 6.5 mg hydroxychloroquine per kilogram ideal body weight are not exceeded, the risk for retinopathy is low.⁷⁸ As hydroxychloroquine appears to be very safe, less frequent or even no monitoring is necessary for this drug. Regular screening is, however, indicated for patients taking chloroquine and should consist of vision testing, corneal and fundus examination, and Amsler as well as colour vision testing. Further tests such as fundus photography, automated visual field testing, and fluorescein angiography may be required in suspect cases to differentiate other retinal changes. It could be shown that EOG screening is of limited value, whereas the proposed automated colour vision test offers high diagnostic value. It is best

to have a baseline examination when retinopathy can still be excluded because of a low total chloroquine dose—for example, within the first 6 months.

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