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Retinal toxicity due to hydroxychloroquine: frequency in an Ophthalmology ambulatory

Toxicidade retiniana pela hidroxicloroquina: frequência em um ambulatório de Oftalmologia

Aluisio Rosa Gameiro Filho[1], Raquel de Melo e Souza[2], Fernando Moreira dos Santos[2], Rita de Cássia Marques Cardoso[3], Patrícia Correa de Mello[2], Aderbal de Albuquerque Alves Jr.[4]

Abstract

Hydroxychloroquine is widely used by rheumatologists for the treatment of various diseases, such as systemic lupus erythematosus and rheumatoid arthritis because of its safety and low cost. However, it can cause retinal abnormalities. Until today, there is no Brazilian protocol for screening for retinal changes in these patients. We reviewed the medical records and optical coherence tomography of all patients who had attended at Hychloroquine Ambulatory of HFSE, in the period from March/ 2015 until November/2016.

Keywords: *Hydroxycloroquine/toxicity; Retina/drug effects; Rheumatic diseases/drug therapy*

Resumo

A Hidroxicloroquina é amplamente utilizada por reumatologistas para o tratamento de várias condições, como os lúpus eritematoso sistêmico e artrite reumatoide, pelo seu baixo custo e relativa segurança. Porém, esta droga pode causar danos à retina. Até o presente momento, não há protocolo brasileiro para o screening de alterações retinianas devido ao uso desta medicação. Foi realizada revisão de prontuário e análise de imagens de tomografia de coerência óptica de pacientes atendidos no período de Março de 2015 a Novembro de 2016 no ambulatório de Hidroxicloroquina do Hospital Federal dos Servidores do Estado do Rio de Janeiro.

Descritores: Hidroxicloroquina/toxicidade; Retina/efeito dos fármacos; Doenças reumáticas/tratamento farmacológico

[1] Programa de Residência em Oftalmologia, Hospital Federal dos Servidores do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.
[2] Setor de Retina, Hospital Federal dos Servidores do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.
[3] Programa de Residência em Reumatologia, Hospital Federal dos Servidores do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.
[4] Serviço de Retina e Vitreo, Hospital Federal dos Servidores do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.

Instituição: Hospital Federal dos Servidores do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.

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Introduction

Hydroxychloroquine (HCQ) is a well-known option for the treatment of systemic diseases, due its good cost/benefit. Nowadays, this drug is widely used in the treatment of systemic lupus erythematosus (SLE), as well as for other inflammatory or/and dermatologic diseases, such as Rheumatoid arthritis, scleroderma and dermatopolymyositis. Recently, this drug is being considered for auxiliary treatment for diabetes, dyslipidemias and in the adjuvant treatment of cancer.[1-3] Hydroxychloroquine prescription increased more than 30% over the 1990s. [4,5]

Retina toxicity due to hydroxychloroquine is one of the most important collateral effects of the use of this drug, and it is even more important in patients who use Chloroquine. It can cause macular alterations, like the well-known bulls eye lesion, for mechanisms not yet fully known. This toxicity can lead to visual loss, ranging from mild cases until great loss of visual field, that can limit patient's autonomy.

Retinal changes due the use of HCQ do not have treatment, however recent studies shows that central visual field can be preserved if the damage is recognized before the impairment of retinal pigment epithelium (RPE).[6] Thereby, the early screening of visual changes in patients taking this medications becomes so important, even more, if we take in consideration that the progression these changes can occur even with the cessation of the drugs. The American Academy of Ophthalmology (AAO) published recently their new recommendations for screening in patients using HCQ.

In this study we evaluate the alterations in OCT (optical coherence tomography) in patients using HCQ, followed at Hospital Federal dos Servidores do Estado do Rio de Janeiro (HFSE).

Methods

Cross-sectional study that used retrospective database and medical reviews of all the patients attended at Hydroxychloroquine Ambulatory of HFSE, in the period from March, 2015 until November, 2016. Patients followed in this sector are the ones who take HCQ, or, less frequently Chloroquine, that were referred by Rheumatology from our Hospital, following our hospital protocol. During this period, 436 patients attended at our ambulatory. We used Heidelberg Spectralis to perform the OCTs.

Results

We evaluated 436 patients. 409 were woman (93.8%) and 27 were man (6.2%). The mean age was 48 years old (sd:13.19) ranging from 19 to 82 years old. The mean HCQ dose was 5,33 (sd:0.926) ranging from 2.32 to 7.5 mg/kg/day. All patients had the previous diagnosis of SLE and used HCQ. None of the patients used Cloroquine during the period of the study. 418 patients had no abnormalities in OCT, 22 of these (5.3%) were man and 396 (94.7%) were woman. The mean age was 47.51 years (SD:13.22). The mean dose of HCQ was 5.33 mg/kg/day (SD: 0.913) ranging from 2.32 to 7.5.

Only 18 (4.3%) patients had any sort of abnormality in the OCT due to HCQ use. 13 (72.2%) were woman and 5 (27.8%) were man, The mean age was 56.72 years (SD:8.65), ranging from 42 to 73 years old. The mean time of SLE diagnosis between these patients was 17.37 (sd:6.78) ranging from 7 to 32 years. The mean dose was 5.00 mg/kg/day (sd:1.25) ranging from 3.09 until 6.7. Only 6 (33.3%) of these patients refered the previous use of Cloroquine. 08 (44.4%) had no previous use, and we did not had information about the previous use of Cloroquine in 4 patients.

We divided OCT abnormalities in three groups: patients with early change in the junction line of inner and outer segments of photoreceptors (line IS/OS or ellipsoid line), as it can be seen in figure 1; the second group, characterized by thinning of perifoveal outer nuclear layer, with the typical image of flyer saucer (Figure 2); and the third group, which is the later stage, in which foveal atrophy can be found.

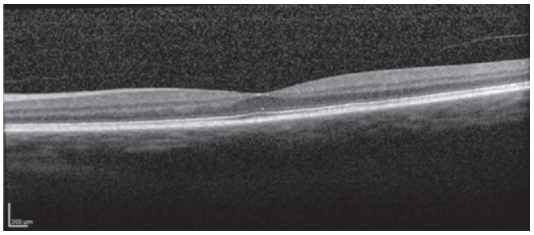

Figure 1: Early abnormalities in SD-OCT. There is loss of integrity of IS/OS zone.

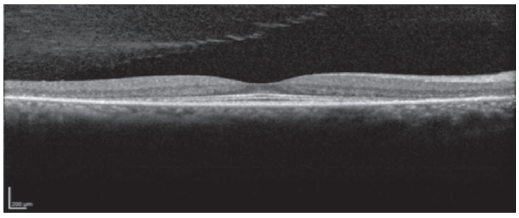

Figure 2: Flyer saucer sign.

Of our 18 patients, 7 had early changes in ellipsoid line; 9 had the flyer saucer sign and only 2 had foveal atrophy in SD-OCT analysis.

The mean age of patients with early abnormalities in OCT was 53.16 years old, the mean time of SLE diagnosis was 15.8 years, the mean duration of HCQ use was 6.6 (±5.3) years and the mean daily dose of HCQ used at the time of the research was 5.13 (±1.7) mg/Kg. When we analyzed the same data of patients with flyer saucer sign, we found that the mean age was 57.88, the mean time of SLE diagnosis was 16.77 (± 8.05) years, the mean duration of HCQ was 12.25 (±5.06) and daily dose used at the time of the research was 4.83 mg/Kg (±1.51). In patients with late stages of OCT abnormalities, the mean age was 59,5 years old, the mean time of SLE diagnosis was 24 (±5.65) years, the mean time of HCQ use was 10 years (±8.48) and the daily dose used at the time of research was 5.5 mg/Kg.

Discussion

4-aminoquinolone derivatives were originally reserved for malaria treatment and prophylaxis, although, in present days have a widespread use in the control of inflammatory and rheumatological diseases, and is also a key drug in the treatment of numerous diseases, in special SLE. Howbeit, since 1957,[7] there are reports in literature of retinal toxicity caused by these drugs, and, even though being described more than 60 years ago, until today, the complete and exact fisiopatologhy is not yet known.

Currently, it is believed that the primary damage is caused in the photoreceptors, with posterior degeneration of external nuclear layer and RPE disruption.[8] The damage usually affects the macula, for this reason, some studies suggests that the light absorption, or even cone's metabolism may play an important role in the etiology

of the lesion, but still without very concrete data.[1] Some authors say that these drugs can connect to melanin, which can be responsible or even extend retinal damages.[9] The classic retinal change is bull's eye maculopathy, characterized by depigmentation of parafoveally RPE, sparing the fovea.

It is important to say that, although less commented, other ocular damages can occur as a result of the use of HCQ: subcapsular cataract, cornea vercilatta, anterior uveitis and optic neuropathy, disturbance in periocular muscles, among others.[10]

Considering that currently there is no treatment for HCQ's retinopathy, a screening is extremely important, however, there is no Brazilian protocol for screening in patients who use HCQ yet. The American Academy of Ophthalmology published recently in 2016(1) their screening recommendations, which say that the most important risk factors for the development of retinal toxicity are:

- Daily dose: dosage >5mg/kg/day of HCQ or >3mg/kg/day of Chloroquine. An important change in that this dose refers to real weight, not ideal weight as it was in AAO's previous recommendations, due to the fact that the This is due to the fact that, using the ideal weight would result in overdosage in leaner individuals;

- Duration of use: more than 5 years of use. Wolfe et al. [9] showed in his study with 3995 patients that the mean retinal toxicity was 6,5 cases per 1000 users, however, this number falls to 3/1000 if only patients with less than 5 years of use are taken in account. In users for more than 10 years, this number raises to 20/1000;

- Renal disease: HCQ and Chloroquine both have renal excretion, so, if the is any abnormality in renal clearance, the circulation level of the drugs increase;

- Tamoxifen use: for unknown reasons, the concomitant use between HCQ and Tamoxifen increases the risk of retinal damage in 5 times; [1,10]

- Previous retinal disease;

AAO also considers as risk factors: age (eldery patients have a higher risk); liver diseases; genetic conditions such as polymorphisms in cytochrome P450.

The 2016 AAO's recommendations [1] proposes that the first evaluation should be done in the first year of starting the drugs, as a baseline evaluation, to establish a a record of fundus appearance and functional status. The primordial exam, should be the fundus examination. OCT and visual field may be useful, but are not indispensable in this moment.

The posterior screening evaluations will depend on some factor: if the patient has no major risk factor, the evaluation could be made annually, starting 5 years after starting the use of the drug. On the other hand, in patients with major risk factor, screening should start earlier. For both groups, the evaluation should be made one time per year, with:

- SD-OCT (spectral domain optical coherence tomography): an objective and highly specific exam, that shows thickening of photoreceptors layer;

- Automated visual field: highly sensitive. Pattern 10-2 field has high resolution of macula, however, in Asian patients, the initial damage is manifested beyond the macula, so, a 24-2 or 30-2 examination is preferable;

Some additional exams can be useful, such as:

- Multifocal eletroretinogram (mfERG): similar in sensitivity as automated visual field;

- Fundus autofluorescence: can reveal photoreceptors damage even before SD-OCT;

AAO do not recommend the following exams as screening: fundus examination; TD-OCT (time domain optical coherence tomography); color vision tests; Amsler grid; electro-oculogram.

In HFSE, we followed our own protocol, which recommends fundus examination in the first evaluation, as baseline, and annual screening with SD-OCT.

Conclusion

Hydroxychloroquine is a well-known option for the treatment of multiple systemic diseases, and it use is rising considerably over the last few years, due to patient's highly tolerance for this drug and its excellent cost/benefit. One of the most commons adverse effects of this drug is the retina toxicity, that is irreversible and can lead to visual loss, that can in severe cases limit patient's autonomy. Due to the fact that this lesion cannot be treated, a screening protocol is necessary. Currently there is no Brazilian protocol for this screening. In our hospital, we use a modified AAO 2016 recommendation, with an initial fundoscopy and an annual OCT, even after the first year of use of the drug.

This toxicity can lead to visual loss, ranging from mild cases until great loss of visual field, that can limit patient's autonomy, howbeit, if this alteration are observed in early stages, the progression can be avoided. Other exams can be used in the screening, like visual acuity and visual field. New studies are necessary to create an adequate Brazilian protocol for this disease.

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Corresponding author:
Aluisio Rosa Gameiro Filho
Rua R. Sacadura Cabral, 178 - Saúde, Rio de Janeiro, RJ, Brazil.
Zip code: 20221-903
E-mail: agameirofilho@yahoo.com.br