Delayed-onset chloroquine retinopathy

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SUMMARY Delayed-onset chloroquine retinopathy was diagnosed in a patient seven years after cessation of treatment by a total dose of 730 g of chloroquine for rheumatoid arthritis. Visual functions continued to deteriorate after the diagnosis. Periodic examinations by ophthalmoscopy and by functional tests such as EOG and visual fields should be continued in patients at risk of delayed-onset chloroquine retinopathy after discontinuance of the drug.

Chloroquine and hydroxychloroquine have been used in the treatment of rheumatoid arthritis and discoid and systemic lupus erythematosus since the early 1950s. Towards the end of the same decade serious ocular complications became apparent. Corneal deposits due to chloroquine were first noted in 1958.¹ A retinopathy with visual loss was confirmed by Hobbs *et al.*² and Sternberg *et al.*³ in 1959. Similar observations with hydroxychloroquine were subsequently reported, and this entity became well documented over the years.

The retinal findings are usually bilateral and vary from mild non-specific changes consisting of fine pigment mottling of the macula with loss of foveal reflex to the characteristic pattern described as the 'bull's eye' lesion with granular hyperpigmentation of the perifoveal area surrounded by a concentric zone of depigmentation which is encircled by another ring of pigment.⁴ In advanced cases attenuated retinal arterioles, pallor of the optic disc, and a generalised pigmentary retinal disturbance resembling retinitis pigmentosa were described.

Several factors have been reported to predispose the retina to the development of chloroquine toxicity. These are daily dosage, duration of treatment, serum drug level, age of patient, and specific drug used.^{5,6} However, a review of the literature suggests that the daily dosage is the most important risk factor. Recommendations by Mackenzie⁷ limit the daily dosage to 3.5 to 4.0 mg/kg of chloroquine or 6.0 to 6.5 mg/kg of hydroxychloroquine, based on lean body weight. The patient should be subjected to an annual ocular examination and biennial if he is 65 years old or more. Treatment should be adjusted for

pharmacokinetic variables such as renal failure. Adherence to these safety rules should reduce the retinopathy to a minimum and prevent loss of vision.

We present a case of severe advanced chloroquine retinopathy which began seven years after discontinuation of the drug. Delayed onset chloroquine retinopathy, the proper term for such a condition, is little known, poorly understood, and only a few reports of it exist.

Case report

A 50-year-old woman had been under our care since 1965, when she was diagnosed as having seropositive rheumatoid arthritis. Cryotherapy failed because of a severe rash, and she was started on chloroquine tab. 250 mg once daily in 1966. She was treated with the same dosage for the following eight years, with a good response. Throughout the years tests of visual acuity and ophthalmoscopy were performed at regular intervals and were found to be within normal limits. In 1974 chloroquine therapy had been discontinued because of a possible drug-related polyneuropathy, with symptoms of muscle weakness and wasting. Electromyography (EMG) showed loss of motor units, fibrillations, and impaired conduction. Visual acuity tests and the fundi were normal. As the disease had been under control, with only mild arthralgia, the patient was put on brufen (Motrin) tab. 400 mg twice daily. She continued with this treatment for the next six years. In total she was treated with 730 g of chloroquine. In late 1982, almost seven years after discontinuation of the chloroquine therapy, she started to complain for the first time of visual disturbances.

The patient was referred to the eye clinic and presented with difficulty in reading. The visual acuity

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Fig. 1 Visual fields 10 years after cessation of chloroquine treatment, showing a large scotoma in the upper part of the visual field.

Fig. 2 Visual fields 11 years after cessation of chloroquine treatment, showing further increase in the size of the scotoma.

was 20/60 in the right eye with best correction, and 20/60 in the left eye improved with correction to 20/40. The anterior segment was normal. The fundus examination revealed the typical bull's eye appearance of chloroquine retinopathy in both eyes.

On colour testing the patient could not recognise any of the American optical Hardy-Rand-Rittler (A-O HRR) colour testing plates. The visual field examination showed paracentral scotoma in both eyes.

The electro-oculogram (EOG) was disturbed. The Arden ratio was 1.65 in the RE and 1.9 in the LE. The electroretinogram (ERG) was abnormal, and decreased amplitudes of a waves (40–50 μ V) and b waves (160–190 μ V) were noted.

On follow-up examination at the eye clinic three years after the onset of symptoms the patient's visual acuity was unchanged, but a deterioration in the visual field with enlargement of a relative paracentral scotoma was found. This was unnoticed by the patient, because it was confined to the upper visual field (Figs. 1, 2).

The EOG results, which in 1981 were 165% in RE and 190% in LE, varied in the four years of follow-up from 120% to 140% in both eyes.

Discussion

Progression of visual loss after cessation of treatment by chloroquine or hydroxychloroquine has been reported in single case reports over the years. The interval between the last dosage of the drug and the development of retinopathy ranged from 1 year to 10 years.^{8,9} Scherbel *et al.*⁴ and Okun *et al.*¹⁰ reported cases in which the onset of a pigmentary retinopathy started 18 and 33 months after chloroquine therapy had been discontinued.

Some cases have progressed to extreme deterioration of vision. Burns described two cases of delayed onset chloroquine retinopathy at two to four years and at five years after discontinuation of chloroquine.¹¹ Carr and co-workers reported a five-year follow-up of 10 patients after discontinuation of therapy. The majority of their patients with chloro-

quine retinopathy remained stable. A few patients in the early stages of retinopathy returned to normal, whereas some showed progressive maculopathy.¹² Similar observations are shared by Brinkley *et al.*, who followed up seven patients for a period of 10 years after discontinuation of the treatment.¹³ Our patient had a lag period of seven years between discontinuation of chloroquine and the onset of visual disturbances.

During the course of her treatment with chloroquine she had regular ophthalmoscopy and visual acuity examinations done, which were all within normal limits. Electrophysiological examinations were not available at that time. The patient consumed an approximate total dose of 730 g during the eight years of treatment with chloroquine. Rarely, ingestion of 100 g of chloroquine may cause a retinopathy. The risk becomes significant when the total dosage exceeds 300 g.¹⁴ Nylander reported a 50% increase of retinopathy in patients receiving a cumulative dose which exceeds 900 g of chloroquine.¹⁵ Ogawa *et al.* recently reported a survey on 68 chloroquine retinopathy patients who had instituted a lawsuit against chloroquine manufacturers.¹⁶ The total dosage per patient ranged from 45 to 674 g (mean 274 g) and the duration of therapy from 16 to 129 months (mean 51 months). All patients had visual field defects and none showed improvement. On the contrary, progression was noted in 10 patients after discontinuation of chloroquine therapy. In five of these cases the progressive impairment continued for more than five years after chloroquine therapy was stopped.

The pathogenesis of the retinopathy related to chloroquine is not fully known. Histological examinations show evidence of destruction of rods and cones and migration of pigment clumps.¹⁷ Antimalarial compounds are known to bind to melanin, and chloroquine has been shown to be deposited in the melanin-containing tissues of the eye (the iris, choroid, and pigment epithelium of the retina) in concentrations many times in excess of those in other body tissues.^{10,18} It has also been shown that small amounts of antimalarial drugs may be recovered from the urine even years after their discontinuation, mainly owing to slow release of the residue bound to melanin.¹⁹ It has therefore been suggested that this binding to the melanin may be related to the toxicity,¹⁷ and it is postulated that the high affinity for the melanotic tissues may cause the delayed onset of the retinal toxicity to the drug.

Though delayed onset of chloroquine retinopathy is rare, we wish to emphasise its severity and suggest the need for follow-up by functional tests such as those of the visual fields and EOG. They should probably be done on all patients who have received 300 g of chloroquine or more. There is no other way to know which patient is liable to suffer from delayed-onset chloroquine retinopathy.

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