Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Relatively spared central multifocal electroretinogram responses in acute quinine toxicity

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Summary

A 71-year-old man was investigated with electrodiagnostic testing 4 months after a deliberate quinine overdose. Initially he was admitted to intensive care unit with visual acuity (VA) of perception of light in both eyes. VA recovered to 6/6 right eye and 6/12 left eye, though severely constricted fields were noted. Slow stimulus (base period of 83 ms) multifocal electroretinogram (ERG) showed electronegative responses outside the inner 5 degrees, with a reduced but electropositive response seen in this central area. It appears that in this case of bilaterally negative ERGs that the macula/fovea (which has a vascular supply through the choroid) is relatively spared as is seen in bilateral vascular electronegative ERGs. This may indicate that quinine toxicity to the retina may be secondary to effects similar to vascular occlusion or severe ischemia during the acute phase of quinine poisoning.

BACKGROUND

This case resulted in severe visual loss from misuse of a drug that is used commonly in older people. Although partial visual recovery occurred, this was severely disabling. Our findings suggest ischaemic / occlusive type events happening in the posterior retinal circulation with relative sparing of choroidal circulation during the acute phases of quinine poisoning.

CASE PRESENTATION

A 71-year-old gentleman was admitted to the hospital in an unconscious state after a deliberate overdose of quinine with alcohol. The quantity of quinine taken was unknown. He was not known to be an alcoholic. Medical history included gastritis, nocturnal night cramps, etc. Drug history included omeprazole, nosulph, quinine, zopiclone and sildenafil. No ophthalmic history was noted.

The patient remained in the intensive care unit where he was managed medically. He regained consciousness a few days later and had severe visual loss in both eyes. A bedside ophthalmic examination revealed a visual acuity (VA) of perception of light (bilaterally), clear ocular media, sluggishly reactive pupils, normal optic discs and severe colour vision defect.

An examination 12 days later revealed a VA of 6/9 OD and 6/12 OS. Colour vision was 0/15 both eyes on the Ishihara test plates. Visual fields were severely constricted to confrontation. Pupils were sluggish and foveal stippling was noted bilaterally. No optic disc pallor was noted. Humphrey 120 full field test showed a severe visual field defect in the right eye and was abandoned for the left eye as the patient kept falling asleep.

INVESTIGATIONS

Electrodiagnostic testing was carried out 4 months after his overdose (figure 1). International Society for Clinical Electrophysiology of Vision standard electroretinogram (ERG) was recorded with gold leaf electrode. Standard flash in the light response was much reduced and of near negative morphology. The 30 Hz flicker response was reduced and delayed. There was no discernable response to the dim flash in the dark (after 20 min dark adaptation) and standard flash revealed a normal A-wave with an attenuated B-wave. Multifocal electroretinogram (mfERG) were recorded to 19 hexagons with a 4:1 distortion out to 21 degrees radius using a slow stimulus of base period 83 ms with a short sequence n=9. 4 runs of 47 ms were averaged together. Recording was made with 2–200 Hz bandpass. White hexagons were 100 cd/m² against dark hexagons and surround of 0.1 cd/m². The slower stimulus rate tends to elicit response closer in morphology to that recorded from an isolated flash.¹ Responses outside the central hexagon (inner 5 degrees) were electronegative. Responses in the inner 5 degrees were electropositive but still of reduced amplitude and delayed implicit time. Pattern-reversal visual evoked potentials (PVEPs) were performed to a range of check-sizes and these produced significantly delayed responses down to the smallest check-size.

DIFFERENTIAL DIAGNOSIS

Our findings suggest ischaemic/occlusive type events happening in the posterior retinal circulation with relative sparing of choroidal circulation during the acute phases of quinine poisoning.

Figure 1 Visual field of severely affected right and left eyes after recovery (Humphrey 24-2 visual field).

Figure 2 Left normal, middle quinine, right central retinal vein occlusion, top displays individual hexagon responses, bottom ring averages, note the ring averages to quinine have their scale expanded by a factor of 2 (figure provided by Richard Hagan).

OUTCOME AND FOLLOW-UP

A review 7 weeks after the overdose revealed a VA of 6/6 OD and 6/12 OS. The field loss had not recovered (figure 2). Mild pallor of optic discs was noted temporally in both eyes along with pigmentation at foveae.

DISCUSSION

Quinine was historically used for the prevention of malaria. With the advent of newer drugs the indications for quinine have reduced to nocturnal night cramps and falciparum

malaria with chloroquine resistance.¹ Quinine toxicity known as cinchonism may induce tinnitus, headaches, hot and flushed skin, nausea, abdominal pain and visual disturbances (including temporary blindness).² Life-threatening features may include arrhythmias and convulsions. Treatment may be difficult.³ Toxicity appears to be dose related. Langford *et al* report visual toxicity in 80% of individuals taking more than 5 g but only 1% in patients taking less than 1 g.⁴

The exact mechanism for visual loss after quinine toxicity is still unclear. The 'paradox of quinine' phenomenon

was described in 1919 as the patient not being able to see when the retinal vessels have normal calibre, but regains good VA even when there is retinal artery constriction.⁵

Reported ERG features in quinine toxicity are normal or enlarged A-wave (photoreceptor) with an abnormal electrooculography.^{6–8} This may reflect activity of retinal pigment epithelium-photoreceptor complex. This may suggest pre photoreceptor and post photoreceptor dysfunction. In our experience the slow mfERG is similar to that of mf ERG in central retinal vein occlusion.

Brinton *et al* describe a case similar to ours where a patient suffered severe visual loss to perception of light and subsequently recovered with loss of visual field and optic disc pallor.⁹

A stellate ganglion block to minimise the effects of quinine toxicity may be tried. Previously this has shown no apparent benefit to the affected eye.^{10 11}

Our patient showed signs of optic nerve injury secondary to the overdose of quinine. This was consistent with the optic disc pallor appearing approximately 7 weeks after the quinine overdose.

Delayed pattern visual evoked potential has also been reported in this context.⁶ In our case, the PRVEP remained very delayed; 150 ms left eye (VA 6/12) and 130 ms right eye (VA 6/6) (possibly more than expected with a negative ERG). Our case also shows abnormal rod and cone pathway damage indicative of neuroretinal damage to the optic nerve and ganglion cell layer of the retina based on electrophysiologic testing. This may be similar to the changes described by Verdon *et al*¹² giving further confidence to the findings.¹³ It appears that in our case of quinine toxicity, the macula/fovea (which is supplied by the choroid) may be relatively spared (negative ERGs) similar to unilateral vascular electronegative ERGs.

The authors hypothesise that visual loss in these patients may be due to a temporary shutdown or severe compromise of choroidal and retinal arterial circulation. This may correlate well with the severe visual loss seen early on in severe quinine toxicity. It is possible that the retinal nerve fibre layer, photoreceptors and ganglion cells may eventually survive after an initial period of choroidal and retinal vasculature shutdown due to rich choroidal circulation and permeation of nutrients through a thinner retinal pigment epithelial layer at the fovea. Generalised atrophy of the peripheral retinal responses on the ERG and the constriction of the peripheral visual field may be explained by constriction of the central retinal vessels (mimicking a vascular occlusion) affecting the optic nerve and peripheral retina through a thicker peripheral retinal pigment epithelium.

It may well be that in the acute phase the ganglion cells are involved with severe visual loss when the ERG is often seen as normal. Whether the peripheral damage in the retina is caused at this stage or later has not been determined.

An indocyanine green retinal and choroidal angiography during the acute phase of quinine toxicity may reveal

whether the above hypothesis is correct. In our patient this was not possible as the patient was resuscitated and ventilated in the intensive care unit.

Advances in the management of quinine over dosage may be possible with increased understanding of the mechanism of toxicity.

Learning points

- ▶ Severe visual loss may be expected in quinine poisoning with doses in excess than 5 g.
- ▶ The visual loss may be due to transient constriction of retinal vessels which may cause ganglion cell loss and neurologic injury.
- ▶ The macular area may be spared due to its underlying choroidal circulation.
- ▶ If retinal vasoconstriction is the cause of this rare entity, there may be a role of vasodilators in the acute management of quinine toxicity with visual impairment.
- ▶ In these cases, as the retina is affected, visual fields will get constricted and optic atrophy may set in. However on mfERG, fovea is relatively spared.

Competing interests None.

Patient consent Obtained.

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