Quinine toxicity identified after 40 years

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Abstract

This brief report describes a case of suspected ocular quinine toxicity. Most case reports of quinine toxicity have detailed descriptions of the acute clinical picture, laboratory results, electrodiagnostic findings, and patients' progress. In this case, such detail is not possible since the patient presented to our unit about 40 years after the incidence of suspected quinine toxicity. The late clinical picture of this case is nonspecific, so it was only after an electrodiagnostic test and detailed drug history that the presumptive diagnosis of ocular quinine toxicity was made retrospectively. This case illustrates that a detailed drug history is important in ophthalmology.

Key words: Quinine toxicity, Electroretinogram

Introduction

Since the first documentation of ocular quinine toxicity by Giacomini in 1841,[1,2] there have been many reports of various features of quinine toxicity. A history of quinine use plus the presence of typical quinine toxicity features of cinchonism (nausea, vomiting, diarrhea, tinnitus, deafness, flushing, diaphoresis, headache)[1] and other ocular and systemic signs and symptoms enables the correct diagnosis of quinine toxicity to be made. Various laboratory tests will confirm the diagnosis. However, if the history of quinine use is not immediately apparent, and the patient presents to a clinician years after the drug toxicity occurred, it may be difficult to reach the correct diagnosis.

Case report

A 66-year-old Chinese lady was referred to our clinic in 1998 for the management of bilateral blurred vision. She gave a history of a relatively sudden decrease in visual acuity 40 years previously. She did not consult a doctor at that time because her vision partially improved after several days. After that episode, she had no significant visual problems except for nyctolopia. She sought medical advice at this time since her visual acuity had further decreased during the past year. Her past health was unremarkable except for the recent diagnosis of hypertension and gout. She denied any history of trauma, operation, severe blood loss, significant medical diseases, or any notable drug use, except for drugs for gout and hypertension. Her family history was unremarkable.

Examination showed best-corrected visual acuity of 6/24 in her right eye, and 4/60 in the left eye. Her pupils were normal size and there was no relative afferent pupillary defect. She missed half the plates of the pseudochromatic Ishihara color test. Moderate nucleosclerosis was noted in both eyes, which could account for her recent decrease in vision. Fundal examination showed bilateral optic disc pallor. The retinal vessels were markedly attenuated (**Figure 1**). There was no definite pathological cupping suggestive of glaucoma and her intraocular pressure was 15 mm Hg in both eyes. There were some pigmented clumps at the posterior pole, but no bony speckles. Her visual fields were markedly constricted bilaterally (**Figure 2**).

Differential diagnosis for a female patient with a sudden bilateral drop in visual acuity during her twenties followed by nyctolopia, constricted visual fields, bilateral disc pallor and attenuated retinal vessels may include:
- bilateral retinal vascular diseases such as anterior ischemic optic neuropathy (AION), central retinal vein occlusion (CRVO), or central retinal artery occlusion (CRAO)
- hereditary chorioretinopathy such as retinitis pigmentosa sine pigmento
- optic neuropathy such as Leber's optic neuropathy or bilateral optic neuritis in multiple sclerosis
- ocular drug toxicity.
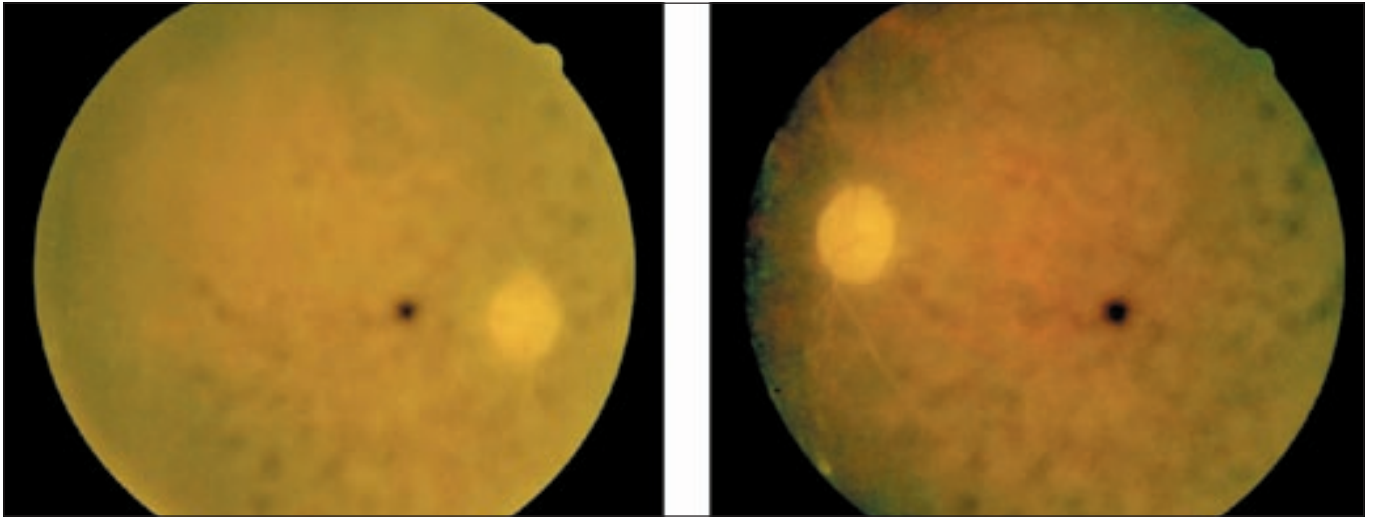
Figure 1. Fundus pictures showing bilateral optic disc pallor and markedly attenuated retinal vessels. The view was blurred because of nucleosclerosis.

Bilateral AION, CRVO or CRAO are rare in youth unless other diseases such as coagulopathy, connective tissue diseases, or vasculitis are present. There was no significant history of drug use except for antihypertensive drug therapy and allopurinol during the past few years. Bilateral optic neuritis may give rise to such a clinical picture, although vessel attenuation is not common. Leber's optic neuropathy which occurs in females in 15 to 45% of the cases reported was a possibility. Although retinitis pigmentosa sine pigmento seldom gives rise to a rapid decrease in visual acuity, her other ocular features (nyctolopia, disc pallor, vessel attenuation, bilateral involvement, visual field constriction) were compatible and an electroretinogram (ERG) was indicated.

In this situation, various investigations can be done to exclude different diseases. We decided to perform electrodiagnostic tests, which are readily available in the clinic, to differentiate between optic neuropathy and chorioretinopathy. In the visual evoked potential test, waveforms were poorly detected and the result was difficult to interpret. However, some interesting findings were detected in her ERG (**Figure 3**).

There were markedly attenuated ERG waveforms in both scotopic and photopic phases. Her scotopic blue flash ERG and 30 Hz flicker photopic ERG were almost extinguished. However, there were some residue A waves in the scotopic white flash ERG and photopic white flash ERG.

There are several ocular diseases that will give rise to decreased B wave amplitude as compared to A wave in ERG:
- congenital stationary night blindness (type 1,3 Oguchi's disease)
- juvenile retinoschisis
- optic atrophy
- CRAO
- CRVO[3]
- intraocular foreign body (siderosis bulbi)[3,4]
- drug toxicity such as quinine.[4]

Congenital stationary night blindness was unlikely in this case. The diagnosis was not retinitis pigmentosa sine pigmento because there should be a marked decrease in both A and B waves. There was no evidence of intraocular foreign body and the picture was not that of retinoschisis,
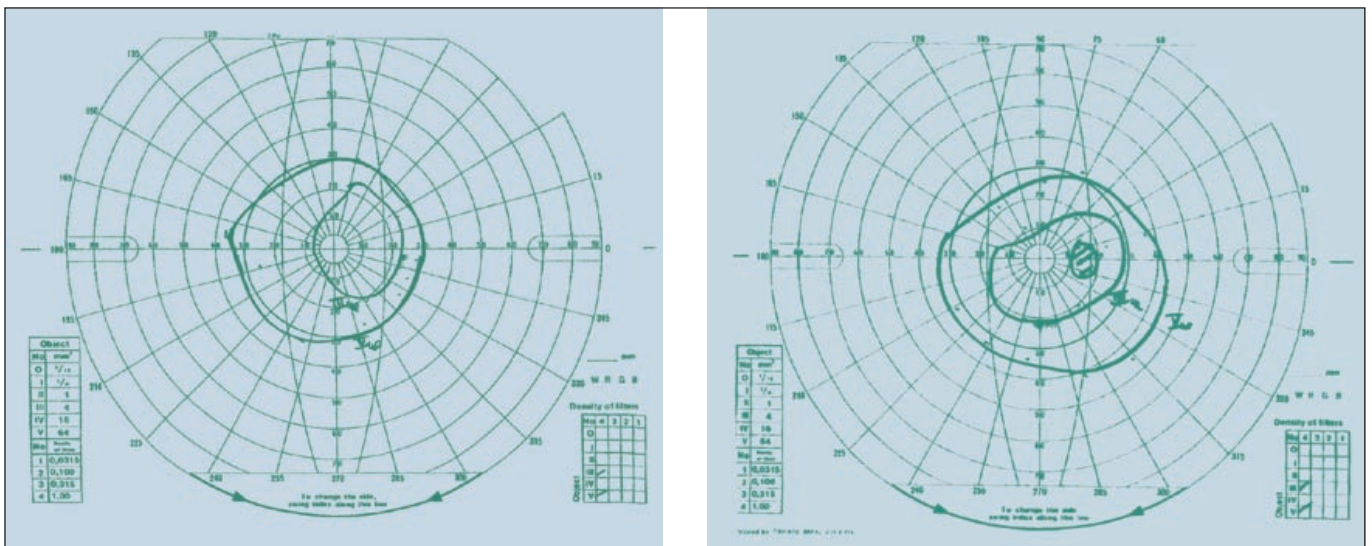
Figure 2. Goldmann perimetry showing constricted bilateral visual fields.
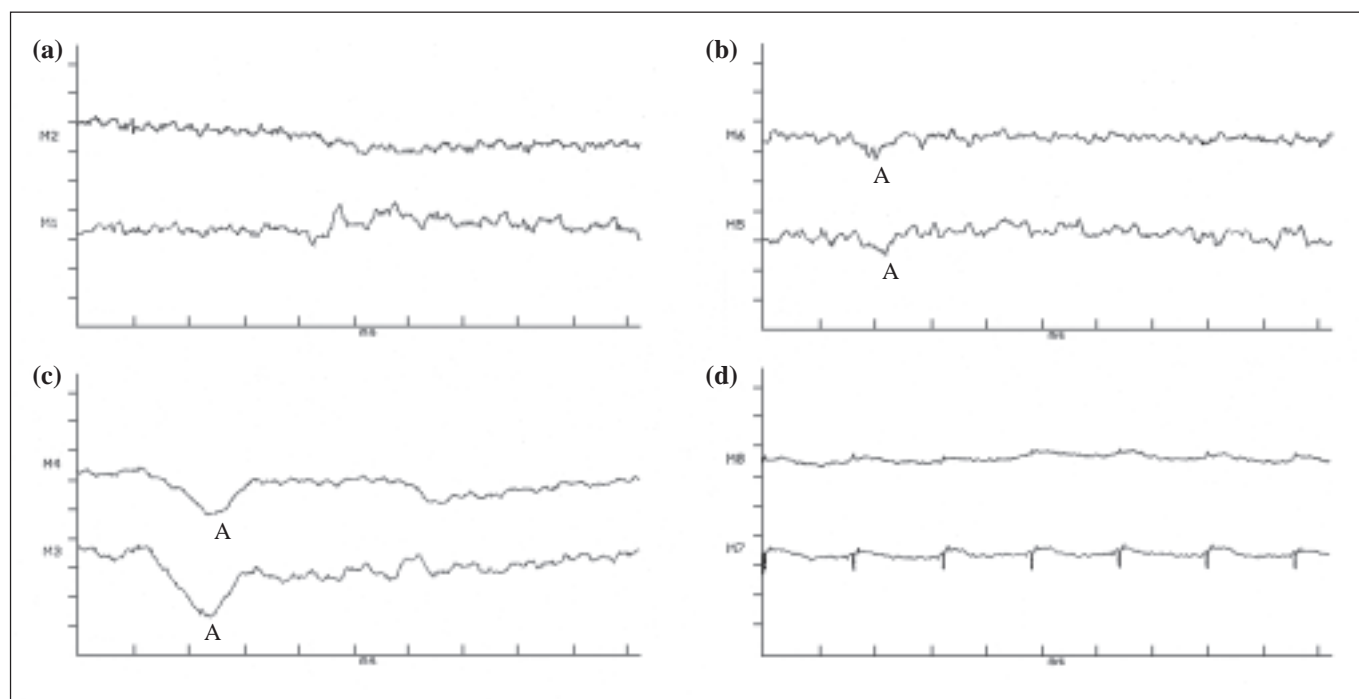
Figure 3. Electroretinogram with the upper waves representing the right eye and the lower waves representing the left eye. (a) Scotopic blue flash, (b) scotopic white flash, (c) photopic white flash, (d) photopic, 30 Hz flicker, white flash.

nor was there any history of systemic medical diseases or vascular events such as severe bleeding, operation or hypotension that would give rise to bilateral CRVO or CRAO. Before we considered further investigations, we decided to review her history again with direct questions. This time she finally admitted that she once had a self-induced abortion shortly before the episode of visual decrease. She could not remember any features of cinchonism but she did have severe systemic upset after the abortion. She did not know what drug she took for the abortion, but she claimed that it was known as a 'drug for chill and rigor'. Quinine was once used as a first-line antimalarial treatment. Severe blood loss secondary to abortion may also give rise to vascular spasm and thus CRAO. However there should not be improvement afterwards as there was in this case and the patient could not remember experiencing severe blood loss. Although it was too late for further confirmatory laboratory tests, the history and clinical features suggest that she had probably suffered from ocular quinine toxicity 40 years previously.

Discussion

In ophthalmology, a correct diagnosis can almost always be made with a detailed history and careful examination. This case illustrates that an important part of the history may somehow be missed. This lady might not have thought that her abortion history was significant, or she may have felt embarrassed to give such history at the first visit. Also, pregnancy and drug history may often be missed in history taking. For ocular drug toxicity, quinine and methanol are the two most important chemicals that should be considered when there is acute visual loss.[1] Other therapeutic agents such as 4-aminoquinoline (chloroquine, hydoxychloroquine),

phenothiazines, digitalis, tamoxifen, desferoxamine, tranexamic acid, cisplatinum, ergot derivative, or combined antihypertensive drugs (α-methyldopa with propanolol)[5] may cause ocular toxicity by various mechanisms and should be considered for unexplained visual deficits.

Use of quinine

Quinine, an alkaloid derived from the bark of the cinchona tree, was first imported to Europe from Peru in the 17th century as an antipyretic.[1,2] It is an optical isomer of quinidine, which has cardiac effects. Its use as an antipyretic was later superseded by non-steroidal anti-inflammatory drugs such as salicylates. Quinine was also used as a first-line anti-malarial drug although it was later replaced by other drugs such as chloroquine because of its toxicity.[1] Quinine is used to flavor carbonated drinks or tonic water because of its bitter taste. One study shows that 100 mg of quinine taken in tonic water is sufficient to produce positional abnormalities in electro-nystagmography.[6] Quinine was also used as an adulterant in heroin because its bitter taste disguised dilution. Due to its oxytocic activity, quinine was used intravenously to induce abortion. Since its oxytocic activity is ineffective when taken orally, repeated oral doses may give rise to overdose.[1,7] Nowadays, the commonest therapeutic use of quinine is for nocturnal muscle cramp, although this use is not well proven.[1]

Pharmacokinetics of quinine

Quinine is almost completely absorbed from the gut and its peak plasma concentration is at about 3 hours post-ingestion. 75% is metabolized by the liver, kidneys, and muscle and 25% is excreted unchanged in urine.[1] The average lethal

dose is generally considered to be 8 g and quinine toxicity can occur when taking more than 4 g orally. Although quinine toxicity occurs mostly after deliberate or inadvertent overdose, toxicity may occur at the normal therapeutic dosage.[1,8,9] Ocular toxicity has been noted after dosages as low as 0.13 g,[10] which may be due to some idiosyncratic action.[2,8]

Quinine toxicity

In one study, the mean time of onset of minor symptoms after quinine overdose was $3^1/_2$ hours.[11] Occasionally, visual loss may not occur until days or weeks after taking the drug.[2] In one case report, a patient developed visual loss 3 days after taking a therapeutic dose of quinine for muscle cramp.[2]

Cinchonism is a classic syndrome of quinine toxicity, the features of which include nausea, vomiting, diarrhea, tinnitus, deafness, vasodilation, diaphoresis and headache.[1] In general, quinine toxicity can be grouped into cardio-toxicity, neurotoxicity, and ocular toxicity.

Cardiotoxicity
Most of the mortality from quinine toxicity is due to cardio-toxicity and the reported mortality rates range from 0 to 6.25%.[12-14] Quinine has a class 1a type of anti-arrhythmic drug action and thus may cause SA node block/arrest, high degree atrio-ventricular block, complete atrio-ventricular dissociation, ventricular tachycardia, ventricular fibrillation, or torsade de pointe in overdose. It also has α-adrenergic antagonistic effects and thus may cause myocardial depression, vasodilation, and hypotension.[1,13,15-17] Dyson *et al* found that 50% of their patients with quinine toxicity had cardio-toxicity,[13] while Boland *et al* found that 4% of their patients had intractable ventricular dysarrhythmia.[14]

Neurotoxicity
Neurotoxic features of quinine overdose may include ataxia, headache, vertigo, syncope, confusion, and delirium.[1,15,16] Coma and convulsion may occasionally occur, especially in children with cardiotoxicity.[1,14] Tinnitus is common, occurring in 38% of reported cases.[1] Deafness may occur in severe poisoning.[14,15,17] However, the mechanism of neuro-toxicity and ototoxicity is controversial.[1]

Ocular toxicity
The features of ocular toxicity range from mild clouding of vision to complete loss of light perception depending on dosage.[1-2] Approximately 17% to 47% of reported cases of quinine toxicity have ocular toxicity.[14,18] In one study, visual loss occurred in every patient with a plasma quinine level of ≥ 10 mg/l.[13] Usually, the onset of visual loss occurs about 6 to 9 hours after the onset of other symptoms. Typically, a patient with quinine toxicity will have systemic upset several hours after taking the drug, necessitating rest. Then the patient may wake up to discover the visual loss. There is also a markedly constricted visual field and color vision defect. Examination may show pupil dilation with or without vermiform pupil movement. There may also be

denervation hypersensitive pupil response to 0.125% pilocarpine.[19] These pupil effects may be due to the direct toxic effect of quinine to the iris parasympathetic nerves, the neuromuscular junction of the iris, or the sphincter pupillae, or they may be due to the curare-like effects of quinine, inhibiting the release of acetylcholine at the neuro-muscular junction.[19] Sometimes iris atrophy may be seen due to the sclerosing effect of quinine on the vessels.[19]

It was once thought that vasoconstriction was the mechanism of ocular toxicity because of the disc pallor and vessel attenuation. However, during the initial period, when the vision loss is most severe, the fundi usually look normal or show some macular edema only.[1,19] Typically, disc pallor and vessel attenuation occur days after the drug toxicity and may take months to fully develop when there is already visual improvement — a paradox of quinine toxicity.[19] Also various electrodiagnostic studies show that there is a toxic effect to various layers of the retina. Usually, during the initial 24-hour period, ERG is normal. This may suggest that the electrically neutral zone, the ganglion cell layer, is affected. Subsequently, there is a markedly diminished B wave suggesting inner retinal layer or bipolar cell layer damage. However, other studies show that there is early electro-oculographic abnormality suggesting retinal pigment epithelium/photoreceptor damage and demonstrated ERG abnormality as early as 12 hours.[18] Thus, it is generally believed that various layers of the retina may be affected by quinine. With time, the ERG abnormality may improve but may not return to normal and there will be a residual decrease in B wave amplitude.

Laboratory evaluation

Laboratory tests can be done to diagnose quinine toxicity, assess the severity of toxicity, and estimate the prognosis. Thin layer chromatography can be useful although it cannot differentiate between quinine and its optical isomer quinidine. Immunoassay is the most accurate method of measurement.[1]

Treatment

Various methods had been tried to improve the ocular outcome in quinine toxicity. These aim at either decreasing quinine absorption, increasing quinine elimination or decreasing the supposed vasoconstriction effect of quinine. After quinine overdose, there will usually be some vomiting, thus decreasing the amount of quinine absorbed. Gastric lavage and repeated activated charcoal ingestion have been tried but may not be effective since quinine is almost completely absorbed within 3 hours.[1] Acid diuresis, peritoneal dialysis, hemodialysis, or exchange transfusion have all been used to enhance quinine elimination with equivocal results.[1,15,18] Recent studies show that acid diuresis may not increase quinine removal or decrease its half life but may worsen cardiotoxicity and therefore should not be used.[1,15,18] Vaso-dilators have been used to counteract the supposed vasocon-striction effect of quinine. Intravenous sodium nitrate, CO_2 inhalation, retrobulbar vasodilators, and anterior chamber

paracentesis to reduce intraocular pressure are some of the historical methods.[9] The National Poisons Unit of the United Kingdom recommends intravenous nitrates as treatment for ocular toxicity when arterial vasoconstriction can be seen on fundoscopy.[9] Sympathetic denervation by stellate ganglion block has also been tried in various studies.[9,11,19] However there are risks of pneumothorax, intra-arterial injection, phrenic nerve injury, or recurrent laryngeal nerve palsy[11] and this method is now out of favor. A recent report of two cases of quinine ocular toxicity shows successful treatment with hyperbaric oxygen therapy, presumably due to the vasodilation effect.[20] However, a prospective study for this therapy will be difficult to perform.

Conclusion

Although ocular quinine toxicity is a horrifying condition as complete vision loss may occur, the natural course of the condition is partial or full return of central visual acuity over several hours to days.[1,2,9] There will also be improvements in color vision, visual field, and pupil response with time. Permanent visual deficits may occur in 27% of cases[1] and the risk of blindness increases as the ingested dose and the plasma quinine level increase.[12,13] In one series, a plasma quinine level of above 15 mg/l was associated with some permanent ocular damage.[12] Optic disc pallor and vessel attenuation will usually remain.

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