REVERSIBLE BINOCULAR VISUAL LOSS IN TEMPORAL ASSOCIATION WITH ARTESUNATE-AMODIAQUINE TREATMENT IN A CHILD ON MEFLOQUINE CHEMOPROPHYLAXIS

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SUMMARY

A case of an acute reversible visual loss in a 10-year-old child who was on mefloquine prophylaxis, and was treated with artesunate-amodiaquine for an acute febrile illness diagnosed clinically as uncomplicated malaria, is reported. On admission the patient could not perceive light and had bilateral papilloedema. She was treated with dexamethasone and recovered her sight gradually over a 21-day period. There has been no previous report to our knowledge, of an association between acute visual loss and mefloquine, amodiaquine, or artesunate in the published literature, even though mefloquine is associated with blurring of vision, and antimalarials of the quinoline class have been associated with retinopathy (during long term use). While causality is difficult to ascribe in this case, it may be prudent to avoid the use of quinoline-based antimalarials for treating acute malaria in travelers taking mefloquine prophylaxis, because information on the safety of concurrent use of artemisinin combination therapies and mefloquine, or other recommended prophylactic regimens, is limited.

Case Report

A ten-year-old female child of Ghanaian parentage, weight, 47kg, resident of New York City, travelled with her parents from the USA in May 2008 to visit relatives in Ghana. She had started mefloquine prophylaxis (250mg weekly) in the USA prior to departure, and had taken the first dose one week before travel. She was in good general health and her past medical history was unremarkable.

One week after arrival in Ghana, she developed an acute febrile illness with headache and myalgia, for which she was diagnosed and treated presumptively for uncomplicated malaria with a standard dose of artesunate-amodiaquine at a private clinic in Accra - while continuing the weekly mefloquine prophylaxis.

One week after the febrile episode (by which time 3 weekly doses of mefloquine had been taken), she noticed blurring of vision in her left eye just before going to sleep. On waking the next morning, she reported to her parents that "all she can see is blackness all around." She was seen at the Children's Emergency Department of Korle Bu Teaching Hospital, and was found to have dilated (7-8mm) pupils that reacted sluggishly to light, zero visual acuity, and she could not perceive light. She did not admit to taking any routine medications, she had no family history of similar illness, there was no history of systemic envenomation, and she denied any history of recent head trauma.

Fundoscopic examination on admission showed pink, hyperaemic discs with blurred margins bilaterally, consistent with papilloedema. Her blood pressure was 100/70mmHg, and results of conducted laboratory investigations were as follows: Haemoglobin, 13.1g/dl, WBC, 8.6 x 10^9/L, with a neutrophil differential of 60.5%, and lymphocyte differential of 25.2%, and platelet count, $470 \times 10^3/\mu L$. The erythrocyte sedimentation rate was 8mm fall/hour, malaria parasites were not seen on the blood film, and haemoglobin genotype was, "AA." Computerized cranial tomography (CT scan) and magnetic resonance imaging (MRI) of the brain were both normal.

She was started on oral dexamethasone, 2mg, twice daily, and advised to stop the mefloquine. She reported perceiving i) "occasional flashes of rainbow" (on Day 3 of admission), ii) "shadows of examiner's fingers" (by Day 5 of admission), and iii) colour –albeit rudimentary (by Day 6). On day 10, she reported that she could identify "colours as well as shapes of objects". She was discharged from hospital on this day (10) to continue dexamethasone at home. She reported on a review visit (Day 14) that she could "read license plates of vehicles from a distance".

Ophthalmologic examination on this day showed unaided visual acuity of 6/18 in both eyes; and pinhole visual acuity done at the ophthalmology department was, 6/12 and 6/18 in the right and left eyes, respectively. The oral dexamethasone dose was adjusted to 2mg once daily, and by day 21, unaided visual acuity was 6/12 and 6/9 in the right and left eyes, respectively. She had regained full sight and had no complaints on subsequent visits.

DISCUSSION

This case of an acute, painless, reversible, visual loss, which occurred in association with sequential administration of antimalarials for prophylaxis and treatment, highlights two issues that have not been adequately addressed in treatment guidelines: i) the potential for adverse interactions to occur between newly introduced therapeutic antimalarials (e.g., ACT's) and existing prophylactic regimens, and ii) the basis for discontinuation and resumption of chemoprophylaxis in travelers who receive antimalarial treatment for breakthrough malaria infections while remaining in an endemic area.

Mefloquine, a blood schizonticide that is widely used for both treatment and prophylaxis of malaria, has not been previously linked with acute visual loss. Mefloquine has, however, been associated with blurring of vision,[1-3] and a range of neuropsychiatric effects, including visual illusions.[4] A single case of visual (field) loss has also been reported in a traveler on mefloquine prophylaxis, but no change in visual acuity was reported in this subject.[5] Mefloquine has also been shown to cause retinal degeneration as well as lens opacification in animals, especially during long term use.[6] Mefloquine-associated adverse effects occur more commonly in adults than in children,[7] more frequently in females and first-time users,[8, 9] and more commonly in those of low body mass index.[10]

Treatment (3 day course) doses of amodiaquine have also not been previously linked to acute visual loss; however, the 4-aminoquinoline class of antimalarials, to which amodiaquine belongs, are associated with retinopathy during long term use.[11]

An episode of acute bilateral visual loss following a febrile illness in a child could be due to conditions such as optic neuritis, which may be caused by viral infection, and could also be associated with immunizations. Most cases of optic neuritis, however, involve the optic disc, with disc oedema, which may be evident as disc enlargement on imaging. Also, enhancement of the optic nerve in the orbit or intracranial segment of the optic nerve or of the chiasm is helpful in confirming diagnosis of optic neuritis, but both CT and MRI in this case did not reveal any such abnormalities. Furthermore, it has been reported that, administration of oral corticosteroids in patients with optic neuritis may, paradoxically, lead to recurrent attacks in those treated compared with those unreated,[12] while a gradual but progressive improvement was observed in this case.

The visual loss could be also due to visual pathway or functional disorders, retinal disease, or its origin could be cortical, and the constellation of presenting findings - in the absence of structural brain abnormalities – makes a diagnosis of optic neuropathy likely.

Optic neuropathy may be due to ischaemic, compressive, infiltrative, toxic, traumatic, nutritional or hereditary causes. The apparent absence of other signs on physical examination and the observed clinical course, as well as absence of a suggestive medical history makes a diagnosis of optic neuropathy from causes other than toxic, unlikely, though not impossible in this patient. Furthermore, reported findings from imaging studies in optic neuropathy are inconsistent, ranging from absence of abnormalities, to optic nerve enhancement.

Vaphiades[13], for instance, reported optic nerve enhancement in optic neuropathy, however, the majority of the reported literature regarding ischaemic optic neuropathy (ION) do not find any MRI abnormalities. Rizzo et al, in contrast, compared the MRI findings of ION with MRI findings of optic neuritis in patients with multiple sclerosis (MS) and found that only 5 of 32 patients with clinical diagnoses of ION demonstrated MRI abnormalities.[14] The sudden loss of vision experienced in this case, therefore, based on imaging studies alone, would not make optic neuropathy likely, though the absence of nerve enhancement does not exclude optic neuritis either.

The possibility of an association between the visual loss and administered drugs may also be supported in part by the observation that, the time of first occurrence of the visual loss (approximately on day 21 of start of mefloquine intake; and 4 days after completing artesunate-amodiaquine course) overlapped with reported times of high plasma concentrations of both mefloquine[15] and desethylamodiaquine[16] - the active metabolite of amodiaquine. This time-course of events may, therefore, support a possible, albeit temporal, association between high doses of the parent drug or metabolites of the respective antimalarial drugs, alone or in combination, and the visual loss.

Furthermore, the prophylactic dose of mefloquine that the child reportedly took (250mg) is slightly higher than the 5mg/kg dose of mefloquine that is recommended for children.

A direct causal relationship remains undetermined in this case, as the differential diagnosis of an acute visual loss in a child with an undiagnosed febrile illness (or at least unconfirmed malaria), may not be straightforward, especially in the absence of viral studies. However, the possibility of a potentiation of as-yet unreported effects of the respective antimalarials cannot be ruled out, since antimalarials structurally related to both amodiaquine and mefloquine (e.g., hydroxychloroquine), are associated with ocular toxicity.[17]

There are still gaps (and even conflicts), among guidelines and health authorities with respect to recommendations for the choice of chemoprophylactic agents, and indications for use of specific antimalarials for standby or emergency treatment in travelers on chemoprophylaxis who develop acute malaria.[18] For these reasons, it may be prudent to avoid the use of antimalarials such as amodiaquine, or other quinoline-based antimalarials for treatment of acute malaria in travelers who are already taking related drugs (e.g., mefloquine) for prophylaxis. Further studies on the safety of ACTs in patients taking different prophylactic antimalarial regimens are warranted.

REFERENCES

1. Ronn AM, Ronne-Rasmussen J, Gotzsche PC, Bygbjerg IC. Neuropsychiatric manifestations after mefloquine therapy for Plasmodium falciparum malaria: comparing a retrospective and a prospective study. *Trop Med Int Health* 1998;3(2):83-8
2. Van Riemsdijk MM, Ditters JM, Sturkenboom MC, Tulen JH, Ligthelm RJ, Overbosch D, et al. Neuropsychiatric events during prophylactic use of mefloquine before travelling. *Eur J Clin Pharmacol* 2002; 58(6):441-5
3. Potasman I, Beny A, Seligmann H. Neuropsychiatric problems in 2,500 long term young travelers to the tropics. *J Travel Med* 2000;7(1):5-9
4. Bornat F-X, Nater B, Robyn L, Genton B. Prolonged visual illusions induced by mefloquine (Lariam): a case report. *J Travel Med* 2001;8:148-9
5. Melo MM, Ciriano JP, van Genderen PJ. Narrow vision after view-broadening travel. *J Travel Med* 2008;15(4):278-80
   Available at:
   www.fda.gov/medWatch/safety/2002/lariam. (Accessed 2010 December 3)
6. Croft A, World M. Neuropsychiatric reactions with mefloquine chemoprophylaxis. *Lancet* 1996;347:326
7. Schlagenhauf P, Steffen R, Lobel H, Johnson R, Letz R, Tschopp A, et al. Mefloquine tolerability during chemoprophylaxis: focus on adverse effect assessments, stereochemistry and compliance. *Trop Med Int Health* 1996;1(4):485-94
8. Schlagenhauf P, Tschopp A, Johnson R, Nothdurft HD, Beck B, Schwartz E, et al. Tolerability of malaria chemoprophylaxis in non-immune travelers to sub-Saharan Africa: multicentre, randomized, double blind, four arm study. *BMJ* 2003;327(7423):1078
9. Van Riemsdijk MM, Sturkenboom MC, Ditters JM, Tulen JH, Ligthelm RJ, Overbosch D, et al. Low body mass index is associated with an increased risk of neuropsychiatric adverse events and concentration impairment in women on mefloquine. *Br J Clin Pharmacol* 2004;57(4):506-12
10. Tehrani R, Ostrowski RA, Hariman R, Jay WM. Ocular toxicity of hydroxychloroquine. *Semin Ophthalmol* 2008;23:201-9
11. Beck RW, Cleary PA, Anderson MM, Keltner JL, Shults WT, Kaufman DI, et al. A randomized controlled trial of corticosteroids in the treatment of acute optic neuritis. *N Engl. J. Med* 1992;326:581-8
12. Vaphiades MS. Optic nerve enhancement in hypotensive ischaemic optic neuropathy. *J Neuroophthalmol* 2004;24:235-236
13. Rizzo JF 3rd, Andreoli CM, Rabinov JD. Use of magnetic resonance imaging to differentiate optic neuritis and nonarteritic anterior ischaemic optic neuropathy. *Ophthalmology* 2002;109:1679-1684
14. Svensson US, Alin H, Karlsson MO, Bergqvist Y, Ashton M. Population pharmacokinetic and pharmacodynamic modelling of artemisinin and mefloquine enantiomers in patients with falciparum malaria. *Eur J Clin Pharmacol* 2002;58:339-51
15. Adjei GO, Kristensen K, Goka BQ, Hoegberg LC, Alifrangis M, Rodrigues OP, et al. Effect of concomittant artesunate administration and cytochrome P4502C8 polymorphisms on the pharmacokinetics of amodiaquine in Ghanaian children with uncomplicated malaria. *Antimicrob Agents Chemother* 2008;52:4400-6
16. Tehrani R, Ostrowski RA, Hariman R, Jay WM. Ocular toxicity of hydroxychloroquine. *Semin Ophthalmol* 2008;23:201-9
17. 18. Chen LH, Wilson ME, Schlagenhauf P. Controversies and misconceptions in malaria chemoprophylaxis for travelers. *JAMA* 2007;297:2251-63