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Hydroxychloroquine ototoxicity in a patient with systemic lupus erythematosus*

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Dear Editor,

We report the case of a 51-year-old female patient who presented with alopecia and erythematous atrophic plaques with some areas of hyperpigmentation on the face and scalp in 2006. At the time,

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she was diagnosed with chronic cutaneous lupus erythematosus after a histologic report of a biopsy taken from the scalp, and started treatment with topical corticosteroids. In 2011, she developed fever, weight loss, fatigue and arthritis of the proximal and distal metacarpophalangeal joints, hands, elbows and shoulders. Hydroxychloroquine 5mg/kg/day (400mg/day) was commenced. Three years after regular use of the medication, she complained of tinnitus and bilateral hearing loss. Liminar tonal audiometry showed moderate neurosensory hearing loss on the left ear and mild to moderate on the right ear. The abnormalities found on the audiometry are suggestive of hydroxychloroquine toxicity. Antiphospholipid antibodies were negative, aiding in the exclusion of lupus erythematosus neurosensory dysacusia. The medication was discontinued, and four months later she still complains of tinnitus and dysacusia. She is undergoing clinical follow-up.

Hydroxychloroquine is a relatively safe drug, with uncommon side effects, except for retinopathy associated to the use in high doses.¹ Drug-related ototoxicity is defined by a transient or permanent disturbance of the auditory and/or vestibular function induced by therapeutic substances.² Many drugs have the potential of causing vestibulocochlear toxicity and, although the antimalarial activity of hydroxychloroquine is the same as the chloroquine sulfate, its toxic potential is significantly lower.^{2,3} Its derivatives, chloroquine and hydroxychloroquine, are widely used in connective tissue disease, adverse effects as cutaneous hyperpigmentation and retinopathy are known and usually monitored in those using these drugs.^{1,2}

Quinine-induced ototoxicity is manifested by auditory and vestibular dysfunction; however, its exact mechanism is yet not well established. The drug is absorbed by the gastrointestinal tract and most of it is deposited in the tissues, with only a minimal portion excreted.² Chloroquine builds up and remains selectively fixed to melanocytes, and high levels of the drug are present in the stria vascularis, retinal pigment, skin, hair follicle and endocrine glands.¹ Ototoxicity is related to the destruction of the stereocilia in varying degrees, reducing the neuron population, altering the support structures, causing atrophy of the stria vascularis and potentially leading to ischemia.¹ Melanin is present in the inner ear in highly vascular areas, thus, blood vessels are usually surrounded by melanocytes. In this context, it is believed that the buildup of chloroquine is responsible for a vascular injury and degenerative changes in the planum semilunatum and stria vascularis. These abnormalities of the epithelial tissues could result in an alteration of the structure of the endolymph, leading to damage of the cellular receptor.² The buildup and long-term retention of antimalarial in melanocytes of the inner ear could explain the late onset of lesions and the relationship with elevated cumulative doses.²




The main symptoms associated to the use of antimalarials are tinnitus, neurosensory hearing loss and vertigo. Hearing loss is considered irreversible, with the report of some exceptions.² Seçkin¹ reports a case of ototoxicity with HCQ in a patient with rheumatoid arthritis who developed mild bilateral neurosensory dysacusia and tinnitus. After discontinuation of the treatment, she improved of the tinnitus and on the audiogram.

In view of a clinical suspicion, the diagnosis can be made with brain evoked response audiometry (BERA).^{2,4} In these cases, the hearing loss should be differentiated from lupus dysacusia, characterized by sudden or rapidly progressing neurosensory hypacusis, with reduced response on the audiometry evaluations. Inflammatory tests and the presence of antibodies will help in the differentiation.⁵

There are reports in the literature of partial improvement after early therapy with steroids and vasodilators.^{3,4} The drugs used have anti-inflammatory effects and could control the hypersensitivity reaction of the vessels to antimalarials, restoring the blood supply for the inner ear.^{3,4} Thus, one must be vigilant regarding any sign or symptom related to hearing changes in patients using these medications, so that the diagnosis can be made early enough to allow for the reversal of the picture. Although rare, HCQ ototoxicity is a severe complication that impairs functional activities and quality of life of the patients and can appear after relatively short periods of use and in low doses. With this study, we aim to alert for the ototoxic potential of the antimalarials and suggest that patients be carefully advised about this complication when they start treatment. We also suggest a periodic audiology assessment of the patients using antimalarials for a prolonged and regular period so that eventual ototoxic changes can be detected early, therefore avoiding possible irreversible damage. □

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CASE LETTERS ▼

Fixed drug eruption to nimesulide: an exuberant presentation confirmed by patch testing*

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Dear Editor,

Currently, cutaneous adverse drug reactions are a growing problem in which diagnosis can be challenging due to the existence of multiple drugs, diverse pharmacological interactions and symptoms that mimic a large variety of skin diseases. We report a case of a 23-year-old female patient that presented a 3-year history of dysuria, vulvar bleeding and painful oral ulcerations that healed spontaneously in approximately 10 days (Figure 1). The episodes were sporadic, but the symptoms became more exuberant with every relapse, leading to conjunctival hyperemia and eyelid edema. Systemic lupus erythematosus and Behçet's disease were considered. Laboratory tests, including viral serologies, ANF, ESR and ANCA showed normal results and pathergy test was negative.

Although a definite diagnosis was not reached, the patient was started on prednisone 0.5mg/kg/day and azathioprine 150mg/day with partial clinical control. Even though the patient was on immunosuppressant drugs, erythematous macules appeared on the lower limbs, which regressed within a few hours. However, in every recurrence, the lesions extended to the trunk and became more numerous, pruritic, erythematous and violaceous, leaving residual pigmentation (Figure 2). At this moment, we hypothesized fixed drug eruption with cutaneous and mucous involvement. The patient reported occasional use of nimesulide to treat a possible viral infection of the upper respiratory tract.

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