PEER REVIEWED LETTER

Severe, Reversible Dysphagia from Chloroquine and Hydroxychloroquine Myopathy

Farrah J. Mateen, B. Mark Keegan

Can. J. Neurol. Sci. 2007; 34: 377-379

Chloroquine and hydroxychloroquine are 4-aminoquinoline medications used in the treatment of malaria, amebiasis, connective tissue diseases, and skin disorders.[1] A generalized toxic neuromyopathy can occur with their use. We report an 89-year-old man with severe, relatively isolated and reversible dysphagia related to combined chloroquine and hydroxychloroquine myopathy.

An 89-year-old man presented with a 3-year history of progressive oropharyngeal dysphagia with both solids and liquids. He had no fatigability of chewing or swallowing but had difficulty propelling the bolus back to his posterior pharynx. His dysphagia was profound, and he had lost over 20 pounds of weight. He twice developed aspiration pneumonia. He was otherwise in good health and had longstanding morphea profunda, a circumscribed, localized sclerosis of the skin and underlying soft tissues involving his chest, back, buttocks, and limbs. The morphea was diagnosed 18 years previously, and was successfully treated with hydroxychloroquine 200 mg twice daily by mouth for 18 years in addition to chloroquine 500 mg thrice weekly for the previous two years. He was not treated with cholesterol-lowering medications or other medications associated with myopathy.

Swallowing studies demonstrated dysphagia and a cricopharyngeal bar. A cricopharyngeal myotomy was recommended by his local physicians. On flexible laryngoscopic assessment and review by an otolaryngologist, he had normal vocal cord motion, normal mucosa and no mass lesions. Poor tongue base propulsion and poor laryngeal elevation were found.

On neurological examination, he had dysarthria and mild, symmetrical weakness involving the deltoids (4/5 MRC grading) and the neck flexors (4/5). He had focal weakness of the left toe extensors and the posterior and anterior tibialis from a prior L5 radiculopathy but otherwise no demonstrable diffuse or proximal lower extremity weakness. Motor strength in the face was normal with normal pharyngeal motion and no tongue atrophy or fasciculations. Muscle stretch reflexes were normal in the upper extremity and mildly reduced in the lower extremities with flexor plantar responses bilaterally. Sensation revealed only slight age-appropriate vibratory sensory deficit.

Creatinine kinase (CK) was elevated at 557 units/litre (normal <336 U/l). Anti-acetylcholine receptor, anti-striated muscle antibody, β-hexosaminidase, serum protein electrophoresis and other basic laboratory studies were normal. Magnetic resonance imaging of the brain showed age-related changes only. Nerve conduction studies of the median and ulnar nerves revealed reduced amplitude of compound muscle action potentials, but nerve conduction studies were otherwise age appropriate. Two hertz repetitive stimulation, at rest, to the ulnar nerve, was normal. Electromyography demonstrated small amplitude, short duration motor units with multiple fibrillation potentials consistent with an active myopathy in multiple muscles including the masseter, biceps brachii, deltoid, triceps, flexor digitorum profundus, tibialis anterior, vastus medialis, thoracic and lumbar paraspinal muscles. There was no evidence of myotonia.

A muscle biopsy of the right deltoid showed vacuolar changes with prominent increases in lysosomal enzyme activity in both vaculoated and nonvacuolated fibres (Figure 1), consistent with a toxic myopathy.

Upon discontinuation of the chloroquine with continuing hydroxychloroquine treatment, the patient's weight loss halted and the CK normalized; however, his dysphagia persisted. Hydroxychloroquine was then discontinued. Seven months later, his dysphagia fully resolved. He returned to his normal weight and resumed his normal daily activites, including golfing. The CK level had declined to 141 U/l. A repeat EMG showed improvement in the myopathic changes. A repeat radiological study confirmed improvement in swallowing function and no aspiration despite stability of the cricopharyngeal bar. His morphea profunda was treated with topical triamcinolone.

Discussion

Both hydroxychloroquine and chloroquine cause an iatrogenic neuromyopathy,[1,2] but the etiology of their toxicity is uncertain. Also called 'antimalarial myopathy' because of the common use of these drugs to prevent malaria, a diffuse,

From the Department of Neurology, Mayo Clinic College of Medicine, Rochester MN, USA.

Received January 9, 2007. Accepted in final form April 23, 2007.

Reprint requests to: B. Mark Keegan, Department of Neurology, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN, 55905, USA.

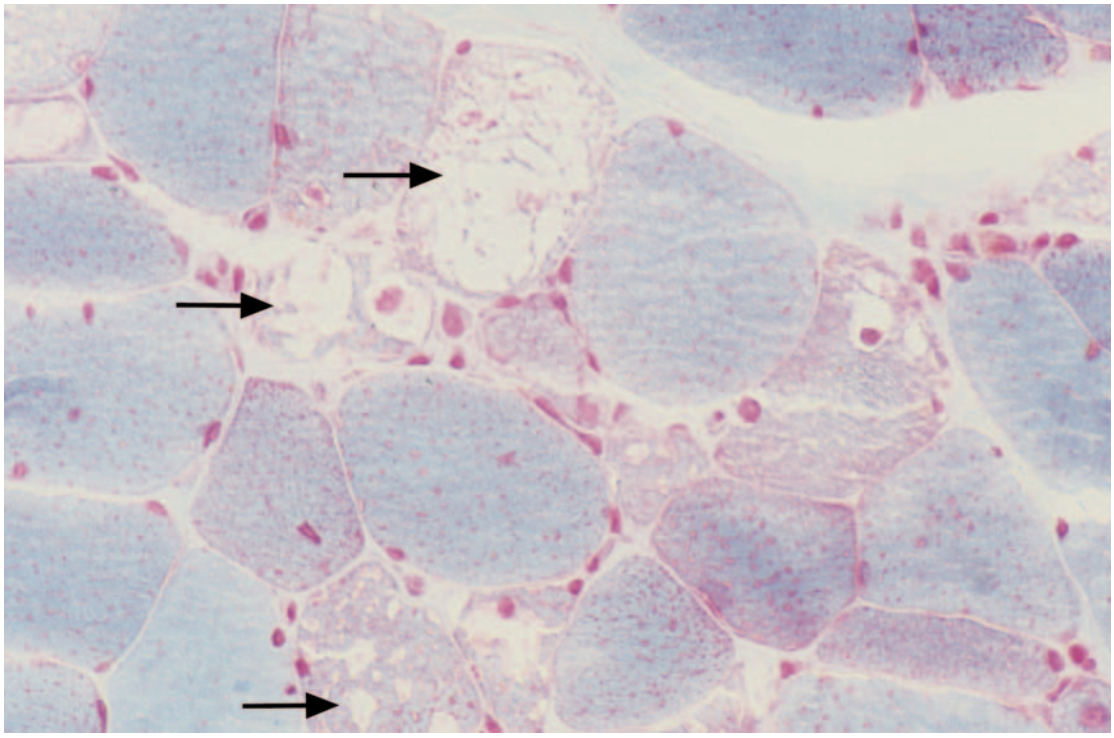

Figure 1A. *Trichrome stain x 100 (deltoid muscle). Arrows point to characteristic vacuoles with increased lysosomal activity.*

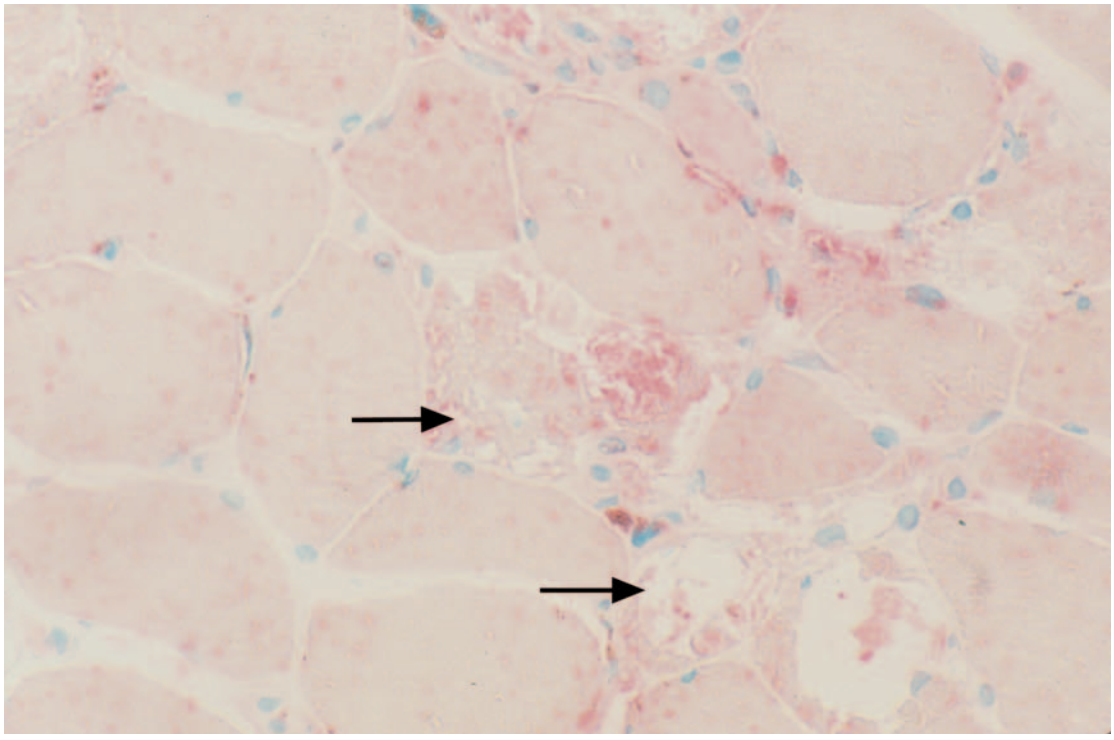

Figure 1B. *Acid phosphatase x 100 (deltoid muscle). Multiple fibers display increase of acid phosphatase activity within the vacuoles and in numerous nonvacuolated fibers.*

https://doi.org/10.1017/S0317167100006880 Published online by Cambridge University Press

proximal myopathy is characteristic. Previously thought to be uncommon,[1] a recent prospective series of more than 100 patients on either chloroquine or hydroxychloroquine estimates that the prevalence of clinical myopathy may be as high as 6.7% with an annual incidence of 1.2%. Cardiomyopathy has been reported rarely,[3] as has respiratory compromise due to phrenic nerve and diaphragmatic involvement.[4]

The quinines have also been reported to induce a myasthenia gravis-like syndrome which may present with severe dysphagia. One case,[5] with positive acetylcholine receptor antibodies, was associated with ptosis, dysarthria, ophthalmoplegia and fatigable weakness as well as neuromuscular junction blockade on repetitive nerve conduction studies. Our case, in contrast, demonstrated no antibody or electromyographic evidence of neuromuscular junction failure and thus points to a primarily myopathic cause for his dysphagia. Likewise, the improvement of his symptoms with medication cessation suggests a myopathic process, rather than a sclerotic one related to his morphea profunda. A sclerotic process would not be expected to improve following discontinuation of his active treatment.

Myopathies known to be associated with prominent early dysphagia include polymyositis, inclusion body myositis, and oculopharyngeal muscular dystrophy. This case demonstrates that chloroquine and hydroxychloroquine can cause a profound, yet reversible, dysphagia and may do so with little clinical evidence of diffuse myopathy. Although EMG demonstrated myopathic features in a diffuse, proximal distribution in our patient, as is typical of approximately half of biopsy-proven antimalarial myopathy cases with elelvated enzymes,[6] this patient had no clinical complaints regarding his limbs or general strength. Moreover, his dysphagia did not respond to selective discontinuation of chloroquine, and only resolved after both quinines were stopped. Therefore, an interaction between these drugs is unlikely.

No report of myopathy from the quinines has been reported until after at least six months of continued intake.[6] Presumably, there is an accumulation of the toxic effects of chloroquine or hydroxychloroquine over time in some individuals, with autophagic vacuoles (arrows, Figure 1) and lysosomal protease activity being found in greater amounts with continued use. This remains speculative, however, since experimental studies of toxicity have thus far been performed on *ex vivo* human blood[7] and *in vitro* animal glandular tissue,[8] but not directly on human muscle tissue.

The importance of symptomatic reversibility is clinically important in our patient, who avoided a cricopharyngeal myotomy. Thus, severe, reversible dysphagia may occur with long-term chloroquine and hydroxychloroquine treatment, and should be added to the differential diagnosis of myopathies associated with prominent dysphagia.

Acknowledgments

The authours thank Dr. Duygu Selçen for her assistance with the figures of muscle pathology.

References

1. Engel AG, Franzini-Armstrong C, editors. Myology. 3rd ed.United States of America:McGraw-Hill; 2004. p. 1699-700.
2. Estes ML, Ewing-Wilson D, Chou SM, Mitsumoto H, Hanson M, Shirey E, et al. Chloroquine neuromyotoxicity. Clinical and pathologic perspective. Am J Med. 1987;82: 447-55.
3. McAllister HA Jr., Ferrans VJ. Chloroquine-induced cardiomyopathy. Arch Pathol Lab Med. 1987;111:953-6.
4. Seguin P, Camus C, Leroy J, Le Tulzo Y, Jouannic I, Thomas R. Respiratory failure associated with hydroxychloroquine neuromyopathy. Eur Neurol. 1995;35:236-7.
5. Sghirlanzoni A, Mantegazza R, Mora M, Pareyson D, Cornelio F. Chloroquine myopathy and myasthenia-like syndrome. Muscle Nerve. 1988;11:114-9.
6. Casado E, Gratacós J, Tolosa J, Martínez JM, Ojanguren I, Ariza A, et al. Antimalarial myopathy: an underdiagnosed complication? Prospective longitudinal study of 119 patients. Ann Rheum Dis. 2006;65:385-90.
7. Fedorko M. Effect of chloroquine on morphology of cytoplasmic granules in maturing human leukocytes – an ultrastructural study. J Clin Invest. 1967;46(12):1932-42.
8. Kumamoto T, Araki S, Watanabe S, Ikebe N, Fukuhara N. Experimental chloroquine myopathy: morphological and biochemical studies. Eur Neurol. 1989;29(4):202-7.