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Chloroquine myopathy

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Chloroquine (7-chloro-4(4-diethylamino-1-methylbutylamino)quinoline) is one of the more effective and less toxic of the quinoline derivatives that were introduced as antimalarials during and after World War II (Grollman, 1965). It also proved useful in the treatment of amoebiasis, in rheumatoid arthritis, and in certain skin diseases. With the long-term ingestion of the drug a number of side effects appeared, perhaps the most serious of which were those involving the eye, with reversible corneal (Calkins, 1958) and irreversible macular changes (Hobbs, Sorsby, and Freedman, 1959; Ormrod, 1962). Since 1963 there have been occasional suggestions that chloroquine may also injure peripheral nerve and muscle. There are still only a few descriptions of such chloroquine neuropathy or myopathy, and in several of these the drug was used in treating patients with possible or proven collagen diseases. In these latter instances the cause of the muscle change is perhaps open to some doubt, as the histological finding that is probably characteristic of chloroquine toxicity to muscle, a vacuolar myopathy, also occurs in systemic lupus erythematosus (Pearson, 1964).

Because the condition is rare, is potentially reversible, and possibly not well known, it has seemed worth recording a further instance of vacuolar myopathy due to chloroquine, particularly when this occurred in a patient in whom there was no question of underlying collagen disease.

CASE REPORT

A 54-year-old mother of two children presented with a two-year history of recurrent cystitis. She had received various antibiotics but no nitrofurantoin. For approximately two years she had also been troubled by low back pain attributed to lumbar spondylosis. Eight months before her referral she was given a proprietary tablet containing chloroquine phosphate 40 mg., prednisone 0·75 mg., and acetylsalicylic acid 200 mg., as treatment for backache. She took this in a dose of six tablets a day for seven weeks, with a further four and a half weeks on half dosage. She was then treated with chloroquine phosphate, 750 mg. a day, till her referral five months later.

While she was receiving the combined therapy (*i.e.* some six months before her presentation) she realized that her thighs were becoming weak. Soon after she noted weakness in her arms. The weakness increased steadily in all limbs and her vision began to blur. In the two months before her referral she occasionally saw double and noted some tingling in the left forearm and hand. She had no other symptoms apart from losing 3 kg. in weight over the six months.

There was nothing of relevance in the past history. A maternal aunt 20 to 30 years before had had wasted muscles, but no further description could be obtained.

On examination of the patient the only significant abnormalities were in the eyes and nervous system. The media of both eyes appeared cloudy but there were no cataracts or retinal abnormalities. External ocular movements were normal except for severe restriction of conjugate upward gaze. There was no disturbance of sensation or of cerebellar function to clinical testing. The muscles of face, jaws, pharynx, and trunk were spared, but otherwise there was generalized symmetrical weakness of the musculature. This particularly involved trapezii, sternomastoids, shoulder girdles, quadriceps, and other hip flexors. The glutei, hamstrings, and the muscles of the hands and feet were only slightly weakened. The affected muscles were wasted in proportion to their weakness, but the wasting was nowhere marked. On palpation the involved muscles felt boggy rather than flabby. There was no fasciculation or myotonia. Tendon reflexes were symmetrical though inactive, but the abdominal muscle reflexes were of normal briskness. Plantar responses were flexor.

An injection of neostigmine (1·5 mg.) did not alter the weakness.

The clinical diagnosis was that of myopathy, possibly due to chloroquine.

An ophthalmologist (Dr. O. Salkeld) reported that each cornea showed a generalized haze with radiate lines of opacity, an appearance consistent with the effects of chloroquine. No retinopathy was seen.

There was no albuminuria. Microscopic examination of urine was normal. Blood urea was reported as 65 mg.% but an intravenous pyelogram was normal. The serum electrolytes and a glucose tolerance test were both normal.

The serum lactate dehydrogenase measured 223 international units (normal range 0-240 i.u.); aldolase 3·9 units per ml. (normal range 3-8 units per ml.); glutamate-oxaloacetate transaminase 58 Karmen units (normal range 9-32); glutamate-pyruvate transaminase 43 Karmen units (normal range 5-30); creatine kinase levels were within normal limits.

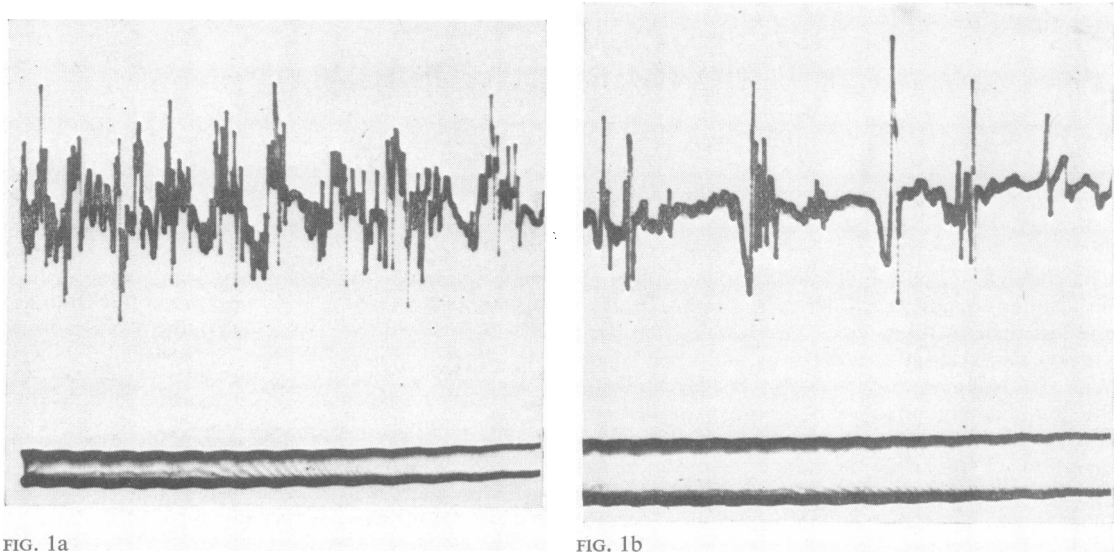

FIG. 1a FIG. 1b

FIG. 1. *(a) Electromyograph on maximum voluntary innervation of the left tibialis anterior showing reduction in amplitude of all motor units and a number of polyphasic units.*
(b) Electromyograph on partial voluntary innervation of the left deltoid showing a number of polyphasic units.
In both (a) and (b) the time trace covers 300 msec. and its peak to peak amplitude is 300 microvolts.

ELECTROMYOGRAPHY At electromyography insertion activity was normal in the muscles sampled. There was no spontaneous activity. The interference pattern on maximum voluntary contraction was normal in the right abductor pollicis brevis and left extensor digitorum brevis. Motor units were of decreased amplitude and duration in the right biceps brachii, and in right and left deltoids and quadriceps. There was an increased proportion of polyphasic units in the left deltoid and both tibialis anterior muscles (Fig. 1). In the left quadriceps there was some loss of motor units, and in the right quadriceps some long duration units (up to 10 msec.). The appearances suggested a primary muscle disorder, though there was some suggestion of denervation, particularly in the quadriceps.

In the right forearm the maximum motor conduction velocity in the median nerve, measured with a coaxial needle electrode in the abductor pollicis brevis, according to the technique described by Thomas, Sears, and Gilliatt (1959), was 59 m./sec. (normal range 52-67 m./sec.). The terminal latency was normal (4 msec.). Spindle afferent mean conduction velocity in the right median nerve in the forearm, measured with H reflex latencies according to the principles described by Angel and Alston (1964), was 47 m./sec. The maximum motor conduction velocity in the left lateral popliteal nerve, measured to a needle electrode in the extensor digitorum brevis, was 43 m./sec. (normal range 36-64 m./sec., Thomas *et al.*, 1959), with a terminal latency of 5 msec. The spindle afferent mean conduction velocity in this nerve, measured by differences in H reflex latencies, was 46 m./sec. (normal range 33-51 m./sec., Angel and Alston, 1964). With stimulation at Erb's point the latency to a coaxial needle electrode in the right biceps 28 cm. away was 5·2 msec. (normal value at 28 cm. is 5·0 + S.D. 0·5 msec., Gassel, 1964). The latency from Erb's point to a needle electrode in the right deltoid 18 cm. away was 5 msec. (at 18·5 cm. the normal value is 4·4 + S.D. 0·35 msec., Gassel, 1964).

The measurements of nerve conduction provided no evidence of peripheral nerve involvement, and the electromyographic diagnosis was that of myopathy.

MUSCLE HISTOLOGY The left quadriceps muscle was biopsied. Muscle fibres showed no gross variation in diameter. In haematoxylin and eosin preparations many randomly scattered muscle fibres contained clear vacuoles of various sizes. In places long segments of expanded fibres consisted of clear spaces interlaced by eosinophilic strands, some of which contained centrally placed nuclei. In transverse sections many muscle fibres appeared a little swollen, and the myofibrils were a little more widely separated from each other than usual. In P.A.S.-stained material fine granules were seen in the majority of muscle fibres, with more coarse P.A.S.-positive deposits in the vacuolated areas. This P.A.S.-stained material was absent in a control section preincubated with diastase. This suggests that the P.A.S.-positive deposits were glycogen (Pearse, 1960). No inflammatory cells were seen and the intramuscular blood vessels, nerves, and connective tissue appeared normal. The appearance was that of a vacuolar myopathy (Fig. 2).

Chloroquine therapy was ceased immediately after the initial consultation. There was little improvement for about two months but the patient then became aware of a progressive return of strength in her upper and lower limbs. Over four months she regained the 3 kg. weight she

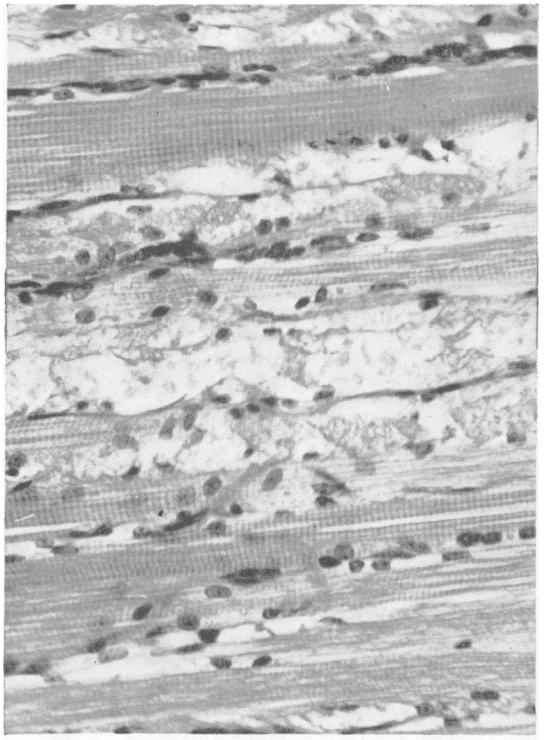

FIG. 2a

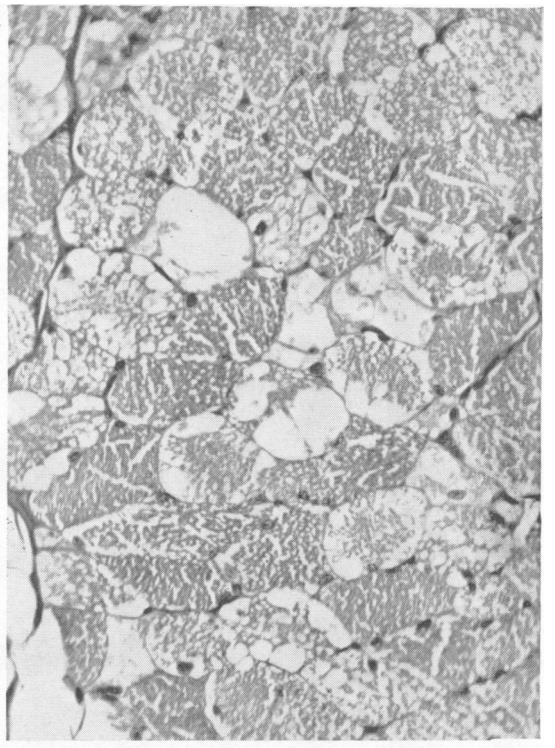

FIG. 2b

FIG. 2. *Muscle from quadriceps in longitudinal section (a) showing relatively normal fibres with well-preserved cross striation, varying degrees of vacuolation separating bundles of myofibrils in some fibres, and near the centre of the field fibres in which the vacuolation has progressed till the fibre consists only of irregular eosinophilic strands and granules. In the transverse section (b) vacuolation of varying degree affects many of the muscle fibres, and almost completely replaces the sarcoplasm in a few. Haematoxylin and eosin* × *400.*

had lost. The sensory symptoms in her left arm and the diplopia ceased.

When seen four months after the chloroquine had been stopped, the patient considered that she still had a little residual weakness, though she was able to carry out reasonably full activity. The muscle wasting had completely disappeared, the muscle tone was normal, and there was virtually full power in all muscle groups. Tendon reflexes were more active than previously. Dynamometer readings of handgrip power (mean of three readings) had increased from 31 to 51 lb. in the right hand, and from 37 to 40 lb. in the left. Measurements of serum glutamate-oxaloacetate and glutamate-pyruvate transaminases (respectively 23 and 6 Karmen units) had fallen to within the normal range.

DISCUSSION

In this patient the clinical, biochemical, electromyographic, and histological findings all suggested the diagnosis of a myopathy. The relation of the onset of symptoms to the exhibition of chloroquine, the recovery after this drug was stopped, and the reversible corneal changes, all implicated the chloroquine as the cause of the myopathy. Further, the clinical pattern of the disorder and the muscle biopsy appearances were entirely consistent with the descriptions of other reported instances of chloroquine neuromyopathy.

We have been able to trace 10 previous descriptions of the condition. Whisnant, Espinosa, Kierland and Lambert, (1963) described in detail four cases of their own, and mentioned in outline a further three patients of whom they had been told. Single cases have been recorded by Humphrey and Rewcastle (1963), (described again by Rewcastle and Humphrey, 1965)), Begg and Simpson (1964), and Garcin, Rondot, and Fardeau (1964). The salient features of these 10 cases are summarized in Table I, where they may be compared with the findings in the present case.

With the exception of one case of Whisnant *et al.*

TABLE I

SUMMARY OF CERTAIN FEATURES IN 11 CASES OF CHLOROQUINE MYOPATHY

Author	*Age*	*Sex*	*Primary Disease*	*Daily Chloroquine Dose (mg.)*	*Duration of Therapy before Start of Muscle Disorder*	*Duration of Muscle Disorder till Diagnosed*	*Distribution of Muscle Involvement*	*Clinical Evidence of Neuropathy*	*Other Evidence of Chloroquine Toxicity*	*Therapy apart from Chloroquine Withdrawal*
Humphrey (1963)	33	F	Systemic lupus erythematosus	500	3 years	2 years	Jaw, face, neck, trunk. Symmetrical limb weakness mainly proximal	Nil	Retinopathy, keratitis, blanching of hair	Prednisone
Wishnant (1963)										
1	44	F	Discoid lupus erythematosus	250-750	4⅓ years	1 year	Maximal distally in limbs	Nil	Corneal abnormality	Amodiaquin for 4 months
2	47	F	Discoid lupus erythematosus	500	11 months	2½ years	Proximal weakness of limbs	Nil	Nil	Nil
3	51	M	Arthritis of knee	250	6 months or less	nearly 1 year	Proximal limb involvement	Nil	Mild corneal oedema	Nil
4	55	F	Discoid lupus erythematosus	750	3 years	4 years	Thighs and legs	Nil	Corneal oedema and retinopathy	Nil
5	47	F	Rheumatoid arthritis	250	some weeks	weeks	Legs	—	—	—
6	38	M	Para-psoriasis	390	6 months	virtually nil	Legs and deltoid	—	—	—
7	62	F	Lichen planus	?	4 months	2 months	Proximal leg weakness	—	—	—
Begg (1964)	28	M	Rheumatoid arthritis	250-500	11 months	4 months	Legs diffusely	C.S.F. protein raised	Nil	A.C.T.H. after 4 weeks of no therapy
Garcin (1964)	57	F	Glomerulo-nephritis	300	6 months	1½ years	Diplopia, proximal involvement in arms, diffuse in legs	Paraesthesiae in feet and hands, sensory changes	Retinopathy, corneal changes	Nil
Present case	54	F	Lumbar spondylosis	240-750	some weeks	about 6 months	Neck: proximal muscles of arms and legs, diplopia	Paraesthesiae in one arm only	Corneal changes	Nil

(1963), the general clinical picture has been that of a proximal myopathy, with overall, a tendency for the lower limbs to be affected earlier, and more severely, than the upper. In three instances there was some clinical reason for suspecting involvement of neural structures. In six of the 11 cases there has been evidence of the ocular toxicity of chloroquine. The drug had been taken for intervals of between a few weeks and over four years before symptoms appeared; the amounts of chloroquine ingested before the onset of symptoms varied between approximately 45 and 1,100 g. On the whole, patients on the higher doses of the drug seemed to develop symptoms more slowly than those on lower dosage. This could be interpreted as suggesting that individual susceptibility was a more important aetiological factor than was cumulative toxicity.

While the disorder was still active serum enzyme measurements have usually shown raised values of the glutamate-oxaloacetate and glutamate-pyruvate transaminases; other serum enzymes have not been measured in sufficient patients for any pattern to be obvious. Electromyography has been performed in eight patients. In seven there was evidence of primary muscle disease, but in three instances there was appreciable, and in a further two minimal, evidence of actual motor unit fall-out. Moreover five patients exhibited fibrillation. Thus the electromyogram provided some suggestion of lower motor neurone involvement as well as of myopathy in several patients. Motor nerve conduction velocities were measured in six patients, and were reduced in only one. In another the lateral popliteal velocity was at the lower limit of normal and the authors

TABLE I—continued

SUMMARY OF CERTAIN FEATURES IN 11 CASES OF CHLOROQUINE MYOPATHY

Result of Chloroquine Withdrawal	*Muscle Biopsy*	*Serum Enzymes*					*E.M.G.*				
		SGOT	*SGPT*	*Aldolase*	*Lactate Dehydro-genase*	*Creatine Kinase*	*Fibrilla-tion*	*Decreased Unit Size*	*Loss of Units*	*Motor Nerve Conduction*	*Afferent Conduc-tion*
Improved in 3 months, full recovery in 15 months	Vacuolar myopathy with glycogen in vacuoles	↑	↑	—	—	—	+	+	O	—	—
Marked improvement in 8 months	Vacuolar myopathy	↑	—	—	—	—	+	+	O	N	—
Recovery in 3 months	Rare degenerating fibres	N	—	—	—	—	+	+	+	N	—
Marked improvement in 3 months	Vacuolar myopathy	N	—	—	—	—	+	O	+	N	N
Recovered in 6 months	Normal	↑	—	—	—	—	O	+	+	Slowed in arms and legs	N
Good recovery in 2 months	Rare	—	—	—	—	—	—	—	—	—	—
Recovering in 3 months	Scattered degenerating fibres	—	—	—	—	—	—	—	—	—	—
Recovery		—	—	—	—	—	—	—	—	—	—
Normal in 7 months	Lymphorrhages and occasional degenerating fibre	N	N	—	—	—	+	+	Very little	N (lower limits)	—
Recovery began in 2 months and progressed	Vacuolar myopathy with glycogen excess	↑	↑	N	—	←	—	+	—	—	—
Reasonably full recovery in 4 months	Vacuolar myopathy with glycogen in vacuoles	↑	↑	N	N	N	O	+	Little	N	N

+ = present N = normal ↑ = increased O = absent

(Begg and Simpson, 1964) considered this suggestive of a peripheral neuropathy. Afferent conduction velocities, when measured, have been normal. From the electrical studies it appears possible that chloroquine may induce abnormalities in either the central or the peripheral segments of the lower motor neurone though the dominant changes are primarily in muscle.

Muscle biopsies have been normal in one patient, showed mild degenerative changes in five, and in the remaining five revealed a vacuolar myopathy. Histochemical tests were used on three of these five latter biopsy specimens and in each showed that the vacuoles in the muscle contained glycogen. All the published illustrations of the vacuolar myopathy look remarkably similar. Vacuolation of muscle is also said to occur in systemic lupus erythematosus (Pearson and Yamazaki, 1958; Levy, 1962; Lang, Smith, and Green, 1965), in familial periodic paralysis (Adams, 1964), in dermatomyositis (Pearson and Rose, 1960), in carcinoma, rheumatoid arthritis, and during steroid therapy (Adams, Denny-Brown, and Pearson, 1962), in trauma (Garcin *et al.*, 1964), and in some forms of glycogen storage disease (Adams, 1964). Unfortunately Pearson and Yamazaki (1958) and Levy (1962) did not mention whether their patients had received chloroquine when they described the vacuolar myopathy of systemic lupus. The patient described by Lang *et al.* (1965) as having a vacuolar myopathy due to systemic lupus erythematosus had received chloroquine for four and a half years before the myopathy was diagnosed.

Of the five cases of vacuolar myopathy attributed

to chloroquine therapy, one (Humphrey and Rewcastle, 1963) had systemic lupus erythematosus, one (Whisnant *et al.*, 1963) had discoid lupus, and a third (Garcin *et al.*, 1964) had an unexplained glomerulonephritis, though L.E. cell tests were negative and there was no evidence of lupus at renal biopsy. In these three patients it could be suggested that the myopathy was due to lupus erythematosus, and not to the chloroquine, but in each the myopathy improved when chloroquine was withdrawn, though Humphrey and Rewcastle (1963) gave prednisone to their patient. Although there may be some little doubt about the aetiological role of chloroquine in these three instances, in the remaining two examples of chloroquine-induced vacuolar myopathy the drug had been given for arthritis of one knee (Whisnant *et al.*, 1963), and for relatively mild low back pain associated with spinal osteoarthritis (the present case). It therefore seems highly likely that chloroquine can indeed induce a vacuolar myopathy, and it is possible that some or all of the muscle vacuolation seen in systemic lupus erythematosus is due to chloroquine and not to the primary disease (Merwin, 1965).

The way in which chloroquine produces a vacuolar myopathy is uncertain. It seems that a factor of individual susceptibility must be involved, because of the lack of relationship between the dose of the drug and length of administration before the onset of the myopathy, and because for some years large amounts of chloroquine were administered, *e.g.*, in cases of dermatitis, without neuromuscular side effects being noted (Goldman and Preston, 1957). However, Lane (1951) did comment on weakness occurring during chloroquine therapy and Dubois (1956) had described a prostigmine-insensitive myasthenia occurring in six of 42 patients with systemic lupus erythematosus receiving chloroquine and recovering within a few days of ceasing the therapy. In rats chloroquine may produce focal necrosis and fibrosis of muscle (Fitzhugh, Nelson, and Holland, 1948). At least in those cases of chloroquine neuromyopathy which have shown muscle vacuolation and glycogen accumulations, it seems reasonable to postulate that the chloroquine has inhibited an enzyme, or enzymes, involved in glycogen breakdown in muscle. In this connexion Goldman and Preston (1957) cite a personal communication from Rothman (1955) that chloroquine interferes with hexokinase and the yellow enzymes (flavine adenine nucleotides). Kaldor (1960) has shown that mepacrine (atebrin) and other acridines will inhibit adenosine triphosphatase under certain ionic conditions in the test medium. The molecule of chloroquine is structurally similar to part of that of mepacrine. Inhibition of one or more of the glycolytic enzymes by chloroquine could explain the toxicity of this drug to both nerve and muscle, and perhaps to other tissues. Similar inhibition might also explain the toxicity of other quinoline derivatives, *e.g.*, the polyneuritis reported with Nivaquin (Bureau, Barrière, Litoux, and Bureau, 1963).

With the widespread use of quinoline derivatives, it seems likely that further instances of neuromyopathy will occur from time to time. Because it is rare, there is some risk that the aetiology of this potentially reversible disorder will not be recognized, particularly when it occurs during the treatment of a disease which may itself affect nerve and muscle. It is also possible that chloroquine may produce a subclinical disturbance of muscle much more often than an overt myopathy, and this inapparent disorder may explain part of the vague ill health and lassitude that occurs in certain diseases for which chloroquine is used as therapy. Once again modern chemotherapeutics may prove a two-edged sword.

SUMMARY

Since 1963 there have been several suggestions that myopathy may arise from chloroquine ingestion. The clinical, electromyographical, and histological findings in a further instance of a reversible myopathy due to chloroquine are described, and the available literature on the subject is reviewed.

The characteristic lesion in muscle produced by chloroquine is a vacuolar myopathy. A similar myopathy has been described in systemic lupus erythematosus, and it is difficult to know whether certain of the reported instances of vacuolar myopathy have been due to lupus or to chloroquine. In the instance here reported, and in certain others, there was every probability that the myopathy was due to chloroquine.

As the vacuolar changes in muscle have been accompanied by glycogen accumulations, it seems possible that chloroquine may injure muscle by inhibiting enzymes involved in glycogen metabolism.

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