Chloroquine myopathy

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Chloroquine (7-chloro-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 opacities (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 spondylitis. 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 tinnitus 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 trapezius, 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.
Erb's point. Angel m./sec., conduction velocity electrode 47 in H terminal latency in the mean to the latency terminal was 59 (1959), particularly in velocity in some appearances there was deltoids and mum duration in some portion of there though was some in the activity. At Motor brevis. abductor pollicis brevis Electromyograph (b) activity. In the right reflex motor technique measured (a) Electromyograph (b) and (c) Electromyograph innervation motor units, were decreased in right the left deltoid according to 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
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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.
(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 active 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>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Sex</th>
<th>Primary Disease</th>
<th>Daily Chloroquine Dose (mg.)</th>
<th>Duration of Therapy before Start of Muscle Disorder</th>
<th>Duration of Muscle Disorder till Diagnosed</th>
<th>Distribution of Muscle Involvement</th>
<th>Clinical Evidence of Neuropathy</th>
<th>Other Evidence of Chloroquine Toxicity</th>
<th>Therapy from Chloroquine Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humphrey (1963)</td>
<td>33</td>
<td>F</td>
<td>Systemic lupus erythematosus</td>
<td>500</td>
<td>3 years</td>
<td>2 years</td>
<td>Jaw, face, neck, trunk, symmetrical limb weakness mainly proximal</td>
<td>Nil</td>
<td>Retinopathy, keratitis, blanching of hair</td>
<td>Prednisone</td>
</tr>
<tr>
<td>Wishnant (1963)</td>
<td>1</td>
<td>F</td>
<td>Disoid lupus erythematosus</td>
<td>250-750</td>
<td>4½ years</td>
<td>1 year</td>
<td>Maximal distally in limbs</td>
<td>Nil</td>
<td>Corneal abnormality</td>
<td>Amodiaquin for 4 months</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>F</td>
<td>Disoid lupus erythematosus</td>
<td>500</td>
<td>11 months</td>
<td>2⅓ years</td>
<td>Proximal weakness of limbs</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>M</td>
<td>Arthritis of knee</td>
<td>250</td>
<td>6 months or less</td>
<td>nearly 1 year</td>
<td>Proximal limb involvement</td>
<td>Nil</td>
<td>Mild corneal oedema</td>
<td>Nil</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>F</td>
<td>Disoid lupus erythematosus</td>
<td>750</td>
<td>3 years</td>
<td>4 years</td>
<td>Thighs and legs</td>
<td>Nil</td>
<td>Corneal oedema and retinopathy</td>
<td>Nil</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>F</td>
<td>Rheumatoid arthritis</td>
<td>250</td>
<td>some weeks to weeks</td>
<td>Legs</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>M</td>
<td>Parapnoiasia</td>
<td>390</td>
<td>6 months</td>
<td>virtually nil</td>
<td>Legs and deltoid</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>F</td>
<td>Lichen planus</td>
<td>?</td>
<td>4 months</td>
<td>2 months</td>
<td>Proximal leg weakness</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Begg (1964)</td>
<td>28</td>
<td>M</td>
<td>Rheumatoid arthritis</td>
<td>250-500</td>
<td>11 months</td>
<td>4 months</td>
<td>Legs diffusely</td>
<td>C.S.F. protein raised</td>
<td>Nil</td>
<td>A.C.T.H. 4 weeks of prednisone therapy</td>
</tr>
<tr>
<td>Garcia (1964)</td>
<td>57</td>
<td>F</td>
<td>Glomerulo-nephritis</td>
<td>300</td>
<td>6 months</td>
<td>1⅓ years</td>
<td>Diplopia, proximal involvement in arms, diffuse in legs</td>
<td>Parasthesiae in feet and hands, sensory changes</td>
<td>Retinopathy, corneal oedema and mild corneal oedema</td>
<td>—</td>
</tr>
<tr>
<td>Present case</td>
<td>54</td>
<td>F</td>
<td>Lumbar spondylosis</td>
<td>240-750</td>
<td>some weeks</td>
<td>about 6 months</td>
<td>Neck, proximal muscles of arms and legs, diplopia</td>
<td>—</td>
<td>Corneal changes</td>
<td>Nil</td>
</tr>
</tbody>
</table>

**TABLE I
SUMMARY OF CERTAIN FEATURES IN 11 CASES OF CHLOROQUINE MYOPATHY**
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TABLE I—continued

<table>
<thead>
<tr>
<th>Result of Chloroquine Withdrawal</th>
<th>Muscle Biopsy</th>
<th>Serum Enzymes</th>
<th>E.M.G.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SGOT</td>
<td>SGPT</td>
</tr>
<tr>
<td>Improved in 3 months, full recovery in 15 months</td>
<td>Vacular myopathy with glycogen in vacuoles</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>Marked improvement in 8 months</td>
<td>Vacular myopathy</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>Recovery in 3 months</td>
<td>Rare degenerating fibres</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Marked improvement in 3 months</td>
<td>Vacular myopathy</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Recovered in 6 months</td>
<td>Normal</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>Good recovery in 2 months</td>
<td>Rare</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Recovering in 3 months</td>
<td>Scattered degenerating fibres</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Recovery</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Normal in 7 months</td>
<td>Lymphorrhages and occasional degenerating fibres</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Recovery began in 2 months and progressed</td>
<td>Vacular myopathy with glycogen excess</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>Reasonably full recovery in 4 months</td>
<td>Vacular myopathy with glycogen in vacuoles</td>
<td>†</td>
<td>†</td>
</tr>
</tbody>
</table>

+ = 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 ery-
thematosus, 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
vacular 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
vacular 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 vacua-
lar 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 progamine-insensitive myasthenia
occurring in six of 42 patients with systemic lupus
erthematous 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 neumopathy
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 arcridines will inhibit adenosine triphos-
phatase 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 neuromy-
opathy 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 dis-
order 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 myo-
pathy due to chloroquine are described, and the
available literature on the subject is reviewed.

The characteristic lesion in muscle produced by
chloroquine is a vacular myopathy. A similar
myopathy has been described in systemic lupus
erthematous, and it is difficult to know whether
certain of the reported instances of vacular myo-
pathy 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 vacular changes in muscle have been ac-
companied by glycogen accumulations, it seems
possible that chloroquine may injure muscle by
inhibiting enzymes involved in glycogen metabolism.

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