



Side Effects of Chloroquine and Hydroxychloroquine on Skeletal Muscle: a Narrative Review

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Accepted: 29 September 2020 / Published online: 31 October 2020
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Abstract

Purpose of Review Concerning adverse neuromuscular effects, there are quite a few reports about the incidence and prevalence of chloroquine (CQ) and hydroxychloroquine (HCQ) myopathy. Given the above, I decided to explore the relationships of these drugs with skeletal muscle in an attempt to clarify how they affect the muscle now and in the future, as millions of people are using CQ and HCQ.

Recent Findings The literature review identified 28 publications about CQ/HCQ myopathy, totaling 56 patients, from 1963 to 2020. A compilation of all patients was carried out by computing demographic features, clinical aspects, laboratory exams, and clinical evolution. All articles but two represented a large series about incidence and prevalence of the myopathy. Fifty-nine percent used QC, mean daily dose was 393 mg per day, and mean duration of treatment was 37 months. The predominant underlying diseases were rheumatoid arthritis (42.8%) and lupus erythematosus (26.8%). Respiratory distress was present in 12.5% in patients with proximal muscle weakness (87.2%). Dysphagia and cervical and axial weakness were observed in a smaller percentage. Creatine kinase was elevated in 60.7%, and EMG showed a myopathic pattern in 54%. Muscle biopsy showed a vacuolar pattern in 53.7%, and curvilinear bodies (CB) were the predominant ultrastructural finding (86.8%). After drug withdrawal, 85.4% of patients improved, and 12.7% died from other causes than myopathy.

Summary CQ and HCQ myopathy has been known for a long time, but the incidence is low, being described only with long-term use. The use of these drugs for a short period has not been reported, although a prolonged elimination half-life of these drugs actually exists.

Keywords Chloroquine · Hydroxychloroquine · Myopathy · Myotoxicity

Introduction

The world faces the deadly COVID-19 pandemic, the most challenging situation in a century that we have confronted. Currently, emerging therapies and repurposing of old drugs have been considered therapeutic strategies, including chloroquine (CQ) and hydroxychloroquine (HCQ) [1, 2], both drugs showing activity against COVID-19 in vitro [3]; however, the level of preclinical and clinical data is not strong and must be approved by a higher level of evidence [4, 5].

Specifically, at the beginning of 1943, the incidental repurposing of antimalarial drugs (quinacrine and CQ) was demonstrated after a crucial improvement of cutaneous rashes and arthritis in soldiers on malaria prophylaxis. Sometime later, in 1951, the first trial showed the efficacy of mepacrine in lupus erythematosus from 18 cases. However, nine of the results were very dramatic, and the other nine showed good-to-slight improvement [6].

CQ and HCQ are disease-modifying anti-rheumatic drugs (DMARDs) that suppress the clinical progression of several autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis, antiphospholipid syndrome, primary Sjögren's syndrome, and sarcoidosis) [7].

Over the past few decades, these two compounds have also drawn attention as potential antiviral agents [8].

The suggested mechanism of action is raising the pH of the cell membrane, thus making it difficult for the virus to enter cells and interfering in the final stages of virus replication [3]. Also, they have an immunomodulatory effect and block the

This article is part of the Topical Collection on *Clinical Pharmacology*

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cascade of events that lead to acute respiratory distress syndrome [9]. Regardless of promising experimental studies, clinical trials have shown controversial effects [10, 11].

Peripheral nervous system manifestations caused by COVID-19 are rare, with the most common ones being hypogeusia (5.6%) and hyposmia (5.1%), while skeletal muscle complaints were reported in 10.3% of patients; however, electromyography, muscle MRI, or histopathologic findings were not mentioned [12]. Two recently published studies of COVID-19 in China reported myalgia or fatigue in 44–70% of hospitalized patients and increased creatine kinase (CK) in up to 33% of admitted patients [13, 14]. Additionally, a third of patients infected with other coronavirus infections manifested with myalgias and elevated CKs [15] and rhabdomyolysis [16]. So, it is possible that coronavirus infections may cause a viral myositis [17].

Although the good tolerability of CQ and HCQ is well-proven and considered safe even during pregnancy [18], they can cause side effects, some of which are classified as “non-serious” and do not impede the continuation of treatment. In contrast, others are considered “serious” and require drug suspension, which, unfortunately, does not always lead to their complete resolution. The first group is represented by gastrointestinal and cutaneous manifestations, while retinal, neuromuscular, and cardiac toxicities are part of the second group [19].

Concerning adverse neuromuscular effects, there are quite a few reports about the incidence and prevalence of CQ and HCQ myopathy. Given the above, I decided to explore the relationships of these drugs with skeletal muscle in an attempt to clarify how they affect the muscle now and in the future, as millions of people are using CQ and HCQ.

The review of the literature using PubMed let me identify 28 publications about antimalarial myopathy (only case reports or case series), totaling 56 patients, from 1963 to April 2020 [20–41]. A compilation of data from these studies was carried out and analyzed in a general context by computing demographic features (age, gender, previous diagnosis, duration of CQ/HCQ treatment), clinical aspects (muscle weakness, respiratory distress), laboratory tests (creatinine kinase (CK) levels, morphological and ultrastructural findings from skeletal muscle biopsy, electromyography), and clinical evolution (improvement or death). Mean and median values were obtained for age, daily dose, treatment duration, and CK values, and percentage values in relation to gender, underlying disease, the drug used, clinical symptoms, CK elevation rates, respiratory distress, EMG features, muscle biopsy findings, and evolution were also analyzed.

Results

Two articles presented large studies of the incidence and prevalence of antimalarial myopathy, the others being case reports. These findings are detailed in Table 1 and Table 2.

A previous and elegant study [26] selected 214 patients from a retrospective review of 4405 patients who initiated antimalarial therapy from January 1987 to April 1993 due to different rheumatic disorders. From these, only three patients presented with CQ myopathy from a total of 303 patient-years with an estimated incidence of 1 in 100 patient-years [26]. After 10 years, the second series of patients was published as a prospective study, which evaluated over 3 years all patients with rheumatic diseases who were taking antimalarial drugs. A total of 119 patients were included, 15 being detected with CQ or HCQ myopathy. The annual incidence was 1.2%, with a prevalence of 6.7% [31].

The mean age of affected patients was 59 years (median 59, varying from 28 to 89 years), with a clear predominance of females (73.2%). The preference for the use of CQ or HCQ was not explained in those previous reports: 58.9% used CQ and 41% used HCQ. The median daily dose was 400 mg per day (mean 393 mg), and the mean duration of treatment was 37 months (median 24 months). The underlying diseases treated with these drugs were rheumatoid arthritis, 42.8%; systemic and discoid lupus erythematosus (SLE/DLE), 26.8%; other rheumatic disorders (progressive systemic sclerosis (PSS), connective tissue disorder, psoriatic arthritis, polymyositis/calculinosis/Raynaud’s phenomenon, esophageal dysmotility/sclerodactyly/telangiectasia, Sjögren’s syndrome/primary biliary cirrhosis, PSS/ interstitial lung disorder), 17.8%; and a miscellaneous group (chronic graft-versus-host disease, shoulder pain, lumbar spondylosis, knee arthritis, morphea, polymyalgia rheumatica), 12.6% (Table 1).

Respiratory distress was present in 12.5% of patients as an initial symptom and associated with proximal muscle weakness (87.2%). Dysphagia, cervical weakness, and axial weakness were also observed in smaller percentages: 8.9%, 17.8%, and 1.8%, respectively.

In laboratory tests, 34 (60.7%) patients underwent measurement of CK level that was elevated in 60.7% (mean value, 339.5 IU; median value, 613 IU; ref. value < 130 to 170 IU). EMG was performed for 50 patients with a predominance of a myopathic pattern (54%), followed by a neuromyopathic pattern in 16% and neurogenic in only one (2%).

Muscle biopsy, analyzed by optical microscopy (OM), was performed in 54 (96.4%) patients showing a vacuolar pattern in 53.7% and non-specific findings in 46.2% (Fig. 1). A total of 38 (67.8%) muscle samples were processed for electron microscopy (EM); the predominant ultrastructural finding was the presence of CB in 38 (86.8%) patients, while myeloid bodies and non-specific findings were present only in three cases (8.0%). From 16 patients with a non-specific finding by OM, 15 (93.7%) demonstrated the presence of CB and myeloid bodies on ultrastructural examination. After withdrawing the drug (CQ or HCQ), 85.4% showed an improvement, and 12.7% died (Table 2 and Table 3).

Table 1 Compilation of all patients' data

	N	G	Age	Underlying disease	Drug	Dur treat (M)	DD (mg)	CK (IU/l)
Whisnant et al., 1963 [19]	1	F	44	DLE	CQ	48	625	
	2	F	47	DLE	CQ	11	500	
	3	M	51	Knee arthritis	CQ	6	250	
	4	F	55	DLE	CQ	36	750	
Begg et al., 1964 [20]	5	M	28	RA	CQ	12	500	
Ebringer and Coville, 1967 [21]	6	F	49	Pain shoulder	CQ	42	250	231
Rewcastle et al., 1965 [22]	7	M	33	SLE	CQ	60	500	ND
Hicklin et al., 1965 [23]	8	F	72	RA	CQ	24	400	nl
Eddie et al., 1966 [24]	9	M	54	Lumbar spondylosis	CQ	7	240	nl
Chapman et al., 1969 [25]	10	F	64	Non-specific papular rash	CQ	66	400	2230
Gerard et al., 1973 [26]	11	F	57	DLE	CQ	36	700	170
Mastaglia et al., 1977 [27]	12	F	55	SLE/thymoma	CQ	5	450	nl
Parodia et al., 1985 [28]	13	F	28	SLE	CQ	24	500	206
Estes et al., 1987 [29]	14	F	58	DLE	CQ	72	500	617
	15	F	47	SLE	CQ	24	500	
	16	F	54	RA	HCQ	24	200	
	17	M	67	RA	HCQ	36	200	110
	18	F	69	RA	HCQ	7	400	235
	19	M	59	SLE	HCQ	24	400	NA
Seguin et al., 1995 [30]	20	F	61	RA	HCQ	60	600	nl
Avina-Zubieta et al., 1995 [31]	21	M	40	RA	CQ	12	250	nl
	22	M	71	RA	CQ	12	250	nl
	23	F	49	RA	CQ	12	250	nl
Richards, 1998 [32]	24	F	65	SLE	HCQ	6	400	nl
Nucci et al., 1996 [33]	25	F	59	RA	CQ	10	250	nl
Stein et al., 2000 [34]	26	F	72	RA	HCQ	24	400	336
Bolanos-Meade, 2005 [35]	27	M	51	Chronic graft-versus-host disease	HCQ	2	800	nl
Casado et al., 2006 [36]	28	M	68	RA	CQ	31	250	NA
	29	F	73	RA	CQ	23	250	1497
	30	F	77	RA	CQ	26	250	NA
	31	M	77	Psoriatic arthritis	HCQ	74	400	NA
	32	F	78	RA	CQ	28	250	NA
	33	F	28	SLE	HCQ	12	400	207
	34	F	74	RA	CQ	62	250	NA
	35	M	57	RA	CQ	76	250	276.3
	36	F	65	RA	CQ	26	250	NA
	37	F	61	RA	CQ	104	250	NA
	38	F	59	RA	CQ	70	250	255.5
	39	M	39	Pol R	CQ	11	250	NA
	40	F	53	SS	CQ	6	250	NA
	41	F	64	SS	CQ	68	250	319.7
	42	F	62	RA	CQ	30	250	NA
Mateen et al., 2007 [37]	43	M	89	Morphea	HCQ	216	400	557
Siddiqui et al., 2007 [38]	44	F	88	RA	HCQ	60	600	nl

Table 1 (continued)

	MW	F	EMG	MB	EM	HCQ	Dysp/dys	FW	CW/AW	RD	Improv/death
Abdel-Hamid et al., 2008 [39]	45	F	56	SLE/SS/autoimmune hepatitis/cirrhosis	HCQ	6	400	146			
Lonesky et al., 2009 [40]	46	F	64	PSS/ILD	HCQ	48	400	nl			
Posada et al., 2010 [41]	47	F	66	RA	HCQ	144	200	343			
Kwon et al., 2010 [42]	48	F	59	DEL	HCQ	7	500	218			
Vinciguerra et al., 2015 [43]	49	F	70	CTD	HCQ	60	400	609			
Takizawa et al., 2018 [44]	50	F	63	RA	HCQ	2	400	nl			
Khosa et al., 2018 [45]	51	F	59	SLE	HCQ	8	300	437			
	52	F	52	SLE/PM	HCQ	NA		NA			
	53	F	76	PM/CREST/SS/PBC	HCQ	NA		NA			
	54	M	59	SLE	HCQ	NA		1683			
	55	F	62	NA	HCQ	NA		NA			
Shukla et al., 2019 [46]	56	F	65	CTD	HCQ	36	200	1203			
Whisnant et al., 1963 [19]	Y			VM	ND	No	No	Y	No	No	Y
	Y			No VM	ND	No	No	No	No	No	Y
	Y			No VM	ND	No	No	No	No	No	Y
	Y			No VM	ND	No	No	No	No	No	Y
Begg et al., 1964 [20]	Y, P limbs		Neurop	No SF	ND	No	No	Y	No	No	Y
Ebringer and Coville, 1967 [21]	Y, P limbs			VM	ND	No	No	Y	Y	No	Y
Rewcastle et al., 1965 [22]	Y, P limbs		Myop	VM	Coiled material electron-dense membrane (CB?)	Y	Y/Y			No	Y
Hicklin et al., 1965 [23]	Y, P limbs		Neurop	VM	ND	No	Y			No	Y
Eddie et al., 1966 [24]	Y, P limbs		Neurop	VM	ND	No	No			No	Y
Chapman et al., 1969 [25]	Y, P limbs		Myop	VM	ND	Y	No			No	Y
Gerard et al., 1973 [26]	Y, P L limbs		Neurop	VM	Membrane vermicular structure shape (CB?)	No	No			No	Y
Mastaglia et al., 1977 [27]	Y, P limbs		Myopathic	VM	CB	No	No	Y	No	No	Y
Parodia et al., 1985 [28]	Y, P limbs		Myop	VM	ND	No	No	No	No	No	Y
Estes et al., 1987 [29]	Y, P limbs		Neurop	NSF	CB	No	No	No	No	No	Y
	Y, P limbs		Myop	VM	CB	No	Y			No	Y
	Y, P L limbs		Myop	No SF	CB	No	No	No	No	No	Y
	Y, PL limbs		Myop	No SF	CB	No	No	No	No	No	Y
	Y, P limbs		Myop	No SF	CB	No	No	No	No	No	no
	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA
Seguin et al., 1995 [30]	Y, P limbs		Myop	VM	CB	No	No	Y	No	Y	Y
Avina-Zubieta et al., 1995 [31]	Y, P L limbs		ND	No SF	ND	No	No	No	No	No	Y
	Y, P L limbs		Myop	VM	ND	No	No	No	No	No	Y
	Y, P limbs		ND	No SF	ND	No	No	No	No	No	Y
Richards, 1998 [32]	Y		Myop	No SF	No CB	No	No	No	No	Y	Death
Nucci et al., 1996 [33]	Y, P limbs		Myop	VM	CB	No	No	No	No	No	Y
Stein et al., 2000 [34]	Y, P limbs		Neurop	VM	CB	Y	No	No	No	No	Y
Bolanos-Meade, 2005 [35]	Y		Myop	VM	CB	Y	No	No	Y	Y	Y
Casado et al., 2006 [36]	Y		Myop	VM	CB/MB	No	No	No	No	No	Death

Table 1 (continued)

	Y	Myop	VM	MB	No	No	No	No	Y
	Y	Myop	VM	CB/MB	No	No	No	No	Y
	Y	Myop	No SF	CB/MB	No	No	No	No	Death
	Y	Myop	No SF	CB/MB	No	No	No	No	Death
	nl	nl	No SF	CB	No	No	No	No	Y
	Y	Neurop	No SF	CB	No	No	No	No	Y
	nl	nl	No SF	CB/MB	No	No	No	No	Y
	nl	nl	No SF	MB	No	No	No	No	Y
	nl	nl	No SF	CB/MB	No	No	No	No	Y
	Y	Myop	No SF	CB/MB	No	No	No	No	Y
	nl	nl	No SF	CB/MB	No	No	No	No	Y
	nl	nl	No SF	CB/MB	No	No	No	No	Y
	nl	nl	No SF	CB	No	No	No	No	Y
	nl	nl	No SF	CB	No	No	No	No	Y
	Y	Myop	No SF	CB	No	No	No	No	Y
Mateen et al., 2007 [37]	Y, P U L	Myop	VM	ND	Y	No	No	No	Y
Siddiqui et al., 2007 [38]	Y, P limbs	Myop	VM	CB	No	No	No	Y	Death
Abdel-Hamid et al., 2008 [39]	Y, P limbs	Myop, myotonia	VM	CB	No	No	Y	Y	Death
Lonesky et al., 2009 [40]	Y, P limbs	Fib, myotonia	VM	CB	Y	No	No	No	Death
Posada et al., 2010 [41]	Y, P limbs/Y	Myotonia	VM	CB	No	No	No	No	Y
Kwon et al., 2010 [42]	Y, P limbs	Myop	VM	CB	No	No	No	No	Y
Vinciguerra et al., 2015 [43]	Y, P/D limbs	Myop	VM	CB	No	No	No	Y	Y
Takizawa et al., 2015 [43]	Y, P limbs	Myop	NSF	ND	No	No	No	No	Y
Takizawa et al., 2018 [44]	Y, P limbs	ND	ND	Lipofuscin-like material	No	No	No	No	Y
Khosa et al., 2018 [45]	Y	NA	VM	ND	No	No	No	No	Y
	Y	SM neurop	nl	No CB	No	No	No	No	Y
	Y, P L limbs	Neurop	VM	No CB	No	No	No	No	Y
	Y, P L limbs/Y	NA	VM	CB	No	No	No	No	Y
Shukla et al., 2019 [46]	Y, P/D limbs	Myop	VM	CB	No	No	No	No	Y
	Y, P/D limbs	Myop	VM	No CB	No	No	Y	No	Y

N, number of patients; G, gender; CM, comorbidity; RD, respiratory distress; MW, muscle weakness; FW, facial weakness; CW, cervical weakness; CK, creatine kinase (ref. value < 200 IU); EMG, electromyogram; MB, muscle biopsy; EM, electron microscopy; Myop, myopathic; Neuro, neuromyop; M, months; VM, vacuolar myopathy; SF, specific findings; L, lower; P, proximal; RA, rheumatoid arthritis; SS, Sjögren syndrome; DLE, discoid lupus erythematosus; SLE, systemic lupus erythematosus; PSS, progressive systemic sclerosis; ILD, interstitial lung disease; CTD, connective tissue disease; ND, not done; NA, not available; Dysp, dysphagia; Dys, dysarthria; Y, yes; CB curvilinear bodies; MB, myeloid bodies; nl, normal

Table 2 Data compilation of CQ and HCQ myopathy based in the literature review from 1963 to April/2020

Data	Values	<i>n</i>
Age (year)	59(M) 59 (Med) 28–89	56
G (F)%	73.2	56
Underlying disease (%)		
RA	42.8	56
SLE	26.8	
ORD	17.8	
Misc	12.6	
Drug %		
CQ	58.9	56
HQC	41	
DD(mg/d)	393(M) 400(Med)	56
DT(m)	37(QC) 24(HCQ)	56
PW/CW/Dys (%)	87.2/17.8/8.9	56
Elevated CK %/M/Med	60.7/613/339	34
RD %	12.5	56
EMG %		
Myop	54	50
Neuromyo	16	
N	2	
Muscle biopsy %		
Vacuolar	53.7	54
NSF	46.2	
MB (EM) %		
CB	86.8	38
MB	8	
Impr/death (%)	85.4/12.7	55

M, mean; *Med*, median; *y*, year; *G*, gender; *F*, female; *CQ*, chloroquine; *HCQ*, hydroxychloroquine; *DD*, daily dose; *DT*, duration treatment; *m*, months; *PW*, proximal weakness; *CW*, cervical weakness; *Dys*, dysphagia; *OM*, optic microscopy; *EM*, electron microscopy; *RA*, rheumatoid arthritis; *SLE*, systemic lupus erythematosus; *ORD*, other rheumatic diseases; *Misc*, miscellaneous; *CQ*, chloroquine; *HQC* *ORD*, other rheumatic disorders; *CK*, creatine kinase; *RD*, respiratory distress; *Myop*, myopathic; *Neuromyo*, neuromyopathic; *N*, neuropathy; *NSF*, no specific findings; *CB*, curvilinear bodies; *MB*, myeloid bodies; *Impr*, improvement

Discussion

The muscle toxicity of CQ and HCQ is often unrecognized and is likely to be more common than described in the literature since the diagnosis of muscle toxicity attributable to these drugs is quite challenging. This is mainly because the underlying diseases and associated medications mask the symptoms of possible harmful effects on skeletal, cardiac, and smooth muscle, and also because of a lack of classic symptoms and/or morphological abnormalities of muscle. CQ has a large

volume of distribution in the human body with an elimination half-life of 20–60 days and a tendency to accumulate in metabolically active tissues like the brain, muscle, skin, heart, and liver than in blood [9, 13]. Based on that, the recommended dose of 500 mg twice per day can approach dangerous thresholds with prolonged treatment compared with a lethal dose of chloroquine (5 g) in adults.

The pathways of antimalarial drugs involved in muscle toxicity, besides being complex, are far from being fully explained, and available data are scanty with no long-term monitoring of experimental models or detailed molecular analysis. Even now, it is difficult to relate the composite action mechanisms of these drugs to their efficacy in different autoimmune and infectious disorders.

HCQ and CQ belong to a class of drugs known as 4-aminoquinolines (containing an amino group attached to a quinoline ring). They are most notable for their roles as antimalarial drugs [9, 13]. Both drugs have a flat aromatic core structure. They are classified as weak bases due to the presence of a basic side chain, which contributes to the accumulation of these drugs in intracellular compartments, especially lysosomal organelles. Their amphiphilic properties elevate intralysosomal pH causing specific lysosomal disarrangement and autophagic dysfunctions, which result in vacuolar changes in muscle. They also specifically inhibit the lysosomal proteinase, cathepsin B, responsible for intracellular proteolysis [42].

The rimmed vacuolar changes found in muscle have been considered the most representative aspect in muscle biopsies of patients with myopathy induced by antimalarials; however, the absence of these vacuoles in some cases does not exclude the diagnosis [25]. This study demonstrated by OM the absence of vacuoles in half the sample (53.7%), which could be partially explained by the interval between the interruption of therapy and timing of the muscle biopsy beyond the technical difficulties in interpreting the biopsies. On the other side, their presence has also been described in other neuromuscular disorders, such as sporadic and familial inclusion body myositis, myofibrillary myopathy, oculopharyngeal muscular dystrophy, and some other myopathies [43–46].

Considering the high percentage of CB (86.8%) found on ultrastructural exam makes us think that EM is more sensitive for the diagnosis of CQ or HCQ induced myopathy than OM. Also, two previous reports [17, 21] observed the presence of coiled- and vermicular-shaped material very similar to CB on EM. So, considering both cases, the percentage of CB would increase to 92% of cases. By contrast, the literature described CB as a rare finding on muscle tissue seen in some but not all patients who have received treatment with antimalarials [29, 37]. CB has been described for the first time in different tissues, including muscle, of patients with late infantile and juvenile forms of Batten disease. They appear as tightly packed, short, curved linear bodies under an electron microscope [47–50].

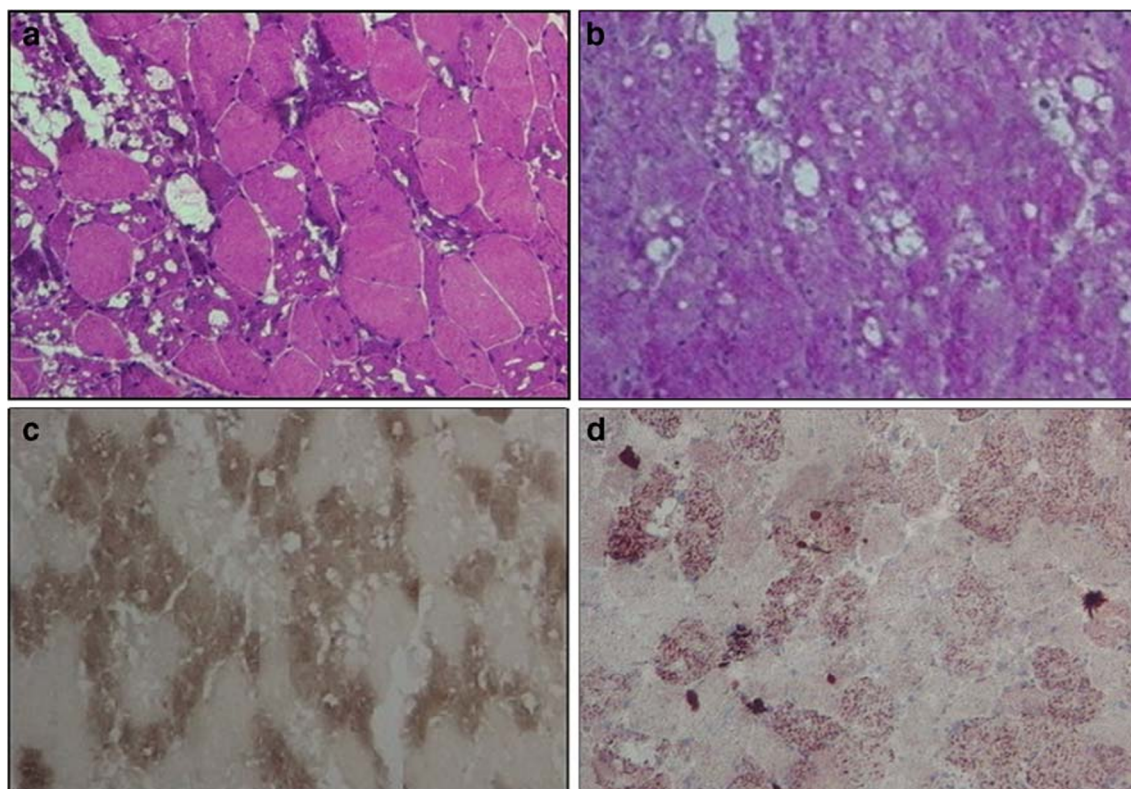


Fig. 1 Muscle biopsy findings from patient with dermatomyositis after chloroquine use for 6 months. **a** H&E: fiber-size variation and multiple intracytoplasmic vacuoles. **b** PAS: vacuoles without glycogen. **c** ATPase

4.35: presence of vacuoles in type 1 and 2 fibers. **d** Oil Red O: vacuoles without lipides (personal archive from author)

Another relevant aspect is that the consequences of using CQ and HCQ are not restricted to the peripheral organelles of the cell and seem to involve other pathways. Nrf2 is a basic leucine zipper (bZIP) protein that regulates the expression of antioxidant proteins that protect against oxidative damage triggered by injury and inflammation [51]. In vacuolar muscle disorders, such as autophagic vacuolar myopathy induced by CQ/HCQ, Nrf2 is persistently activated with negative consequences on organ functions. The chronic activation of Nrf2 in skeletal muscle results in changes in cellular redox potential, a response that contributes to muscle pathologies [52–54].

Looking at some of the results, I was initially surprised not to find seemingly typical clinical symptoms and biopsy changes in this compilation. A study conducted by Casado and colleagues suggested serial muscle enzyme screening of patients on these therapies as a way to identify patients at risk. All 15 patients with myopathy presented increased levels, mild to moderate, of CK or lactic dehydrogenase. By contrast, Kalajian and Callen [55] did not find an association between elevated serum muscle enzymes and underlying antimalarial-induced myopathy in patients taking CQ or HCQ.

Table 3 Data from patients that evolved with death

Patient	Gender	Age	Underlying disease	Drug	Dur treat (M)	DD (mg/d)	RD	Cause of death
25	F	59	RA	CQ	10	250	No	Cardiac insufficiency and broncopneumonia
29	M	68	RA	CQ	31	250	No	Myocardial infarction
31	M	77	Psoriatic arthritis	HQC	74	400	No	Sepsis
32	F	78	RA	CQ	28	250	No	Heart failure
44	F	88	RA	HQC	60	600	Y	Obstructive airway disease
45	F	56	SLE/SS/autoimmune hepatitis	HQC	6	400	Y	Gallstones and sepsis
46	F	64	PSS/ILD	HQC	48	400	Y	Pulmonary fibrosis/Nocardia/Aspergillus

CQ, chloroquine; HQC, hydroxychloroquine; Dur treat (M), duration of treatment; DD, daily dose; RD, respiratory distress; M, months; m/d, milligrams per day; Y, yes

In this review, seven asymptomatic patients with mildly elevated muscle enzymes (CK or DHL) and normal EMG presented curvilinear and myeloid bodies on EM as a unique finding. The isolated presence of this specific ultrastructural finding in skeletal muscle may not always signify a muscle disorder. However, it could be a muscular accumulation of CQ/HCQ or their metabolites, as demonstrated by Kumamoto et al., who observed dense membranous structures (CB) in soleus muscle fibers by EM in CQ-treated rats [31, 56].

Experimental studies have suggested that the absolute tissue levels of CQ are 2.5 times higher than those of HCQ. Thus, the depositing of the drug in several tissues with subsequent enzyme inactivation, which is the proposed mechanism for toxicity, might be more likely to occur with CQ [26]. Nevertheless, we did not observe crucial differences between compounds in terms of symptoms, morphological analyses, or clinical evolution. The number of patients using CQ or HCQ, 58.9% and 41%, respectively, was not very different; specifically, in relation to morphological findings, we identified almost the same number of cases with vacuolar myopathy in the group using CQ [15] and HCQ [17].

Concerning outcomes, prompt recovery was usual. Improvement after discontinuation of therapy occurred in 85.4% of cases, and seven deaths (12.7%) were reported. Apparently, five of the deaths were not related to the antimalarial drug (dose, treatment duration), but as a result of underlying disease complications, and the other two deaths occurred due to cardiac complications. Despite major drug interactions of CQ and HCQ with other medications leading to a greater risk of arrhythmia, there were no reports of this as being the cause of death (Table 3).

Conclusions

CQ and HCQ myopathy has been known for a long time, but the reports are sporadic, and the incidence is low, being described only with long-term use. The use of these drugs even for a short period requires attention as a prolonged elimination half-life of these drugs can be harmful.

Data Availability Statement We declare that the supplementary material is available as a supplementary table.

Compliance with Ethical Standards

Conflict of Interest The author declares no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Ethical Publication Statement We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines and according to the Declaration of Helsinki.

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