

Chloroquine and Hydroxychloroquine: A Closer Look on Skeletal Muscle

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ABSTRACT

Chloroquine (CQ) and Hydroxychloroquine (HCQ), antimalarial agents and widely used in the treatment of autoimmune diseases are considered safe nonetheless, they can provoke side effects, including myopathy. Literature data regarding the prevalence and incidence of this toxic myopathy are scarce and main symptoms encompass Proximal Muscle Weakness (PMW) and normal or slightly elevated creatine kinase (CK) levels. So, definitive diagnosis requires muscle biopsy, showing autophagic vacuoles and curvilinear bodies. The results from a literature review, revealed PMW in 87.2% and respiratory distress in 12.5% of patients; dysphagia, cervical and axial weakness in 8.9%, 17.8%, and 1.8%, respectively. Elevated CK levels in 60.7%, EMG with myopathic pattern in 54% and vacuolar myopathy in 53.7% associated to “curvilinear bodies” in 86.8%. The recovery after discontinuation of therapy occurred in 85.4%. Clinicians should be aware about this possible condition. Even with normal CK levels, muscle biopsy must be the gold-standard tool to diagnose and differentiate patients with this condition from other neuromuscular disorders.

Keywords: lupus; Chloroquine; Hydroxychloroquine; Myopathy; Muscle biopsy; Toxicity

INTRODUCTION

The Coronavirus Disease (COVID-19) pandemic (due to severe acute respiratory syndrome coronavirus 2) was identified in Wuhan, China before 2020. A couple of months later, the infection spread to many other countries, and the world was assaulted by the deadly COVID-19 pandemic, the most challenging situation that we have faced in a century.

Since then, emerging therapies and even repurposing existing drugs came to light as a possible therapeutic approach for this new disease, including Chloroquine (CQ) and Hydroxychloroquine (HCQ) [1], formerly known as disease-modifying antirheumatic drugs of several autoimmune diseases such as Lupus Erythematosus (LE), rheumatoid arthritis, antiphospholipid syndrome, primary Sjögren's syndrome, and sarcoidosis [2].

LITERATURE REVIEW

It is worth noting that the first reuse of these antimalarial drugs was incidental during the Second World War, when soldiers receiving malaria prophylaxis (Quinacrine and CQ)

demonstrated improvements in cutaneous rashes and arthritis. Some years later, in 1951, the efficacy of Mepacrine (Quinacrine) for LE was evidenced in 18 cases, with significant improvement in most of them [3].

Over the past few decades, these two compounds have also attracted attention as potential antiviral agents. The proposed mechanism of action involves elevating the pH of the cell membrane to make virus entrance into cells difficult, in addition to operating in the final stages of virus replication [4].

Although the widespread acceptabilities of CQ and HCQ are well attested and considered safe even during pregnancy [5], they can provoke side effects, some of which are mild, such as gastrointestinal and cutaneous manifestations, and do not delay the continuation of treatment. Meanwhile, other side effects are considered serious and need drug discontinuation, such as neuromuscular, cardiac, and mainly retinal manifestations [6].

Skeletal muscle is a highly flexible tissue and one of the three significant muscle tissues in the human body. As it is highly sensitive to many substances, prompt recognition of a possible toxic myopathy is important, as they may be reversible on

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removal of the harmful agent, with greater chances of recovery [7].

The course of antimalarial drugs involved in muscle toxicity, besides being complex, are not entirely explained. Both CQ and HCQ belong to a class of drugs known as 4-aminoquinolines (containing an amino group attached to a quinoline ring), in addition to having a flat aromatic core structure. They are classified as weak bases because of the presence of a basic side chain, which contributes to the accumulation of these drugs in several intracellular compartments, as mentioned previously [6,8].

Relating to its role, at the molecular level, they interfere with lysosomal activity and autophagy; a break in the integrity of the plasma membrane causes instability and alters signaling pathways and transcriptional activity. On the other hand, at the cellular level, both direct and indirect mechanisms, of these drugs inhibit immune activation by reducing Toll-like receptor signaling and cytokine production as well as reducing CD154 a protein that is primarily expressed on activated T cells [8]. These drugs also inhibit lysosomal proteinase and cathepsin B, which are responsible for intracellular proteolysis. Nevertheless, correlating the combination of both mechanisms of action with their efficacy in several autoimmune and infectious disorders is difficult.

In particular, with regard to skeletal muscle, elevated intralysosomal pH and consequent lysosomal disarrangement and autophagic dysfunction, will result in vacuolar changes in skeletal muscle [9].

Another point that may contribute to antimalarial toxicity is the large volume of distribution of CQ in the human body, reaching an elimination half-life in 20–60 days and exhibiting a propensity to concentrate in metabolically active tissues such as those of the muscle, skin, heart, liver, and brain than in blood. Based on this, the usual recommended dose of 500 mg twice per day may provoke dangerous thresholds with prolonged treatment in relation to a fatal dose of CQ (500 mg) in adults [6,8].

Concerning the prevalence and incidence of these adverse neuromuscular effects, there are several reports of CQ- and HCQ-induced myopathies, most of them being case reports [10-38]. Only two articles presenting large studies of the incidence and prevalence of antimalarial-induced myopathies [10,11]. In this regard, the prevalence rate of antimalarial-induced myopathies is estimated in 12.6% [2].

In one of the large prospective series of patients receiving CQ and HCQ, muscle biopsy was performed if the patients exhibited elevated muscle enzyme levels. Their conclusion was that muscle enzyme elevation preceded the development of clinical weakness [11]. It is curious to note in this cohort, that lactate dehydrogenase (LDH) was the most sensitive enzyme in comparison to creatine kinase (CK) and aldolase for detecting muscle damage. This series of cases evaluated all patients with rheumatic diseases who were taking antimalarial drugs over a period of 3 years. A total of 119 patients were included, 15 of whom were detected with CQ- or HCQ-induced myopathy. The annual incidence was 1.2%, with a prevalence of 6.7% [11].

Avina-Zubieta selected 214 patients from a retrospective review of 4405 patients who initiated antimalarial therapy for different rheumatic disorders [10]. Of them, only three patients presented with CQ-induced myopathy from a total of 303 patient-years with an estimated incidence of 1 in 100 patient-years. All patients improved within 2 months after the drug was stopped [10].

Therefore, one of the reasons for the scarcity of data is that toxic myopathies associated with CQ and HCQ are often unrecognized, making the diagnosis quite challenging. In addition, underlying diseases and associated medications may mask the symptoms of possible deleterious effects on skeletal, cardiac, and smooth muscles. Further, classic symptoms and/or morphological abnormalities in muscle are not always present.

CQ- and HCQ-induced myopathies may develop from months (at least six) to some years after drug intake, with symptoms characterized by proximal muscle weakness associated with normal or slightly elevated CK levels [12]. Dysphagia or diaphragmatic muscle involvement, cardiomyopathy, and secondary respiratory failure have also been reported [12,29,30]. In addition to these unspecific signs, definitive diagnosis requires muscle biopsy [11], and typical findings are autophagic vacuoles on optic microscopy and curvilinear bodies observed on electron microscopy [2].

In 2020, Carvalho published a narrative review of 28 publications on antimalarial myopathies from January 1963 to April 2020, including 56 patients presenting with CQ- or HCQ-induced myopathy after using these drugs for different autoimmune disorders [39]. The results of the compilation revealed proximal muscle weakness as the predominant symptom (87.2%) associated with respiratory distress in 12.5% of all patients. Dysphagia, cervical weakness, and axial weakness were also observed less frequently: 8.9%, 17.8%, and 1.8%, respectively. In relation to laboratory examinations, CK levels were elevated in 60.7% of patients, and electromyography demonstrated the predominance of a myopathic pattern (54%), followed by a mixed pattern in 16% and neurogenic in only one patient (2%) [39].

Based on two previous large series studies, specifically in relation to morphological findings, similar numbers of cases of vacuolar myopathy were identified among patients using CQ and HCQ, although the proportions of CQ-users and HCQ-users were different: 58.9% and 41%, respectively [10,11]. In this report, no case of myopathy associated with anti-malarial drug has been reported before 6 months of continued intake [11].

Morphological findings of muscle biopsy were described for half of all reported patients based on a literature review [10-38]. In total, 53.7% of patients exhibited a vacuolar pattern while 46.3% presented with non-specific findings on optical microscopy, 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. In contrast, when muscle samples were processed for electron microscopy, the typical ultra-structural finding of “curvilinear bodies” (tightly packed, short, curved linear bodies due to phospholipid accumulation in the cytoplasm) [40] was

observed in 86.8% of patients [39]. It is important to underline that these structures are only observed in two conditions: neuronal ceroid lipofuscinosis and myopathy secondary to HCQ or CQ [40].

The vacuolar changes found in muscle are considered the most typical aspect in antimalarial myopathies; however, the absence of these vacuoles in some cases does not exclude the diagnosis [10]. On the other hand, 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 [41].

Regarding outcomes, prompt recovery is usual. Improvement after discontinuation of therapy occurred in 85.4% of cases, and seven deaths (12.7%) were reported [11,12,27,31,39]. Apparently, five of the deaths were not related to antimalarial drugs (dose or treatment duration) but to underlying disease complications, and the other two deaths occurred due to cardiac complications, but detailed data were not provided [11,27]. Despite major drug interactions of CQ and HCQ with other medications leading to a greater risk of arrhythmia, the effects of pro-arrhythmic and antiarrhythmic drugs are poorly characterized [42].

Also, in regard to the two large series reports [10,11], they revealed no typical clinical symptoms or specific changes in morphological findings, highlighting the challenge of early diagnosis of toxic myopathies. Casado and colleagues proposed serial muscle enzyme screening of patients receiving antimalarial drugs to identify patients at risk, since all 15 patients with myopathy presented with mildly to moderately increased levels of CK or LDH [11]. In contrast, Kalajian and Callen did not find an association between elevated serum muscle enzyme levels and underlying CQ-or HCQ-induced myopathy in patients [42].

DISCUSSION

Although the myopathic side effects of HCQ are mild in most patients, clinicians should be aware of possible myotoxicity when treating patients with antimalarial agents. Whether or not elevated CK levels are associated with myopathy, muscle biopsy must be the gold-standard tool to diagnose and differentiate patients with this condition from other neuromuscular disorders.

Moreover, although the incidence of CQ- and HCQ-induced myopathies is low and described only with long-term use, the prescription of these drugs even for short periods requires attention, as the prolonged elimination half-lives of these drugs can be harmful.

CONCLUSION

Many drugs have the potential to cause muscle damage, including commonly prescribed medications such as antimalarial drugs for autoimmune diseases. A detailed medical history including current and previous medications should be obtained from patients, as discontinuing the administration of toxic agents usually leads to an improvement or complete recovery in muscle function inasmuch as, satellite cells are

intimately linked to the processes of muscular recovery in muscle cells owing to their notable capacity to regenerate.

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