Hydroxychloroquine neuromyotoxicity: a case with rapid course and complete recovery.

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Background

Hydroxychloroquine (HCQ), a 4-aminoquinoline, with addition of a hydroxyl group initially used as antimalarial agent, is now mainly utilized for the long-term management of rheumatological disorders such as rheumatoid arthritis (RA) and lupus erythematosus (SLE). Its toxicity against retina, heart, skin, nervous system and muscle has very well know [1]. HCQ myopathy may onset from months (at least 6) to years after drug intake with symptoms characterized by aspecific mild to moderate proximal muscle weakness with normal CK levels or slightly elevated. Proximal muscle strength usually slowly recovers after drug discontinuation and may be incomplete [1,2,3,4,5].
We report a case of severe neuromyopathy with a very early diagnosis, rapid and complete recovery followed two weeks after HCQ discontinuation.

Case Report

A 63 year-old italian woman referred to us for a severe and generalized weakness, with more evident involvement of lower limbs, progressing from three weeks, gait disturbance and falls. The patient, with a hystory of reumathoid artritis, has been treated with hydroxychloroquine (HCQ) for the last 2 months (from September to November 2013, 200 mg twice a day). The previous 4 years she assumed Salazopyrin. Family history was negative for neuromuscular disorders. On admission the patient complained tingling of distal lower and upper limbs and diffuse muscle wasting, waddling gait, possible with unilateral support. Muscle strength evaluated in proximal and distal muscles of upper and lower limbs (graded according to the Medical Research Council scale-MRC), showed severe muscle weakness mainly at the girdles (2/5 vs 1/5 at upper limbs and 4/5 vs 2/5 at lower limbs, in distal and proximal district, respectively). Serum Creatinine kinase (CK), lactate and aldolase levels were normal. **Deltoid muscle biopsy** revealed in fiber sizes variation with rare regeneration. Ultrastructural analysis detected diffuse agglomerates of lipofuscin-like membrane-bound electrondense material (fig 1) .
Nerve conduction study (NCS) showed slight sensory polineuropathy. **Electromyography** was compatible with myopathy,
Suspecting an iatrogenic myopathy, HCQ was discontinued and replaced with Salazopyrin. Two months (February 2014) later a rapid improvement of all symptoms, especially recovery of muscle strength in all districts, with evidence only of a mild weakness to the upper right limb that completely disappeared in June 2014 (MRC in proximal and distal district in all four limbs was 5/5,with NCS and EMG fully recovered) .

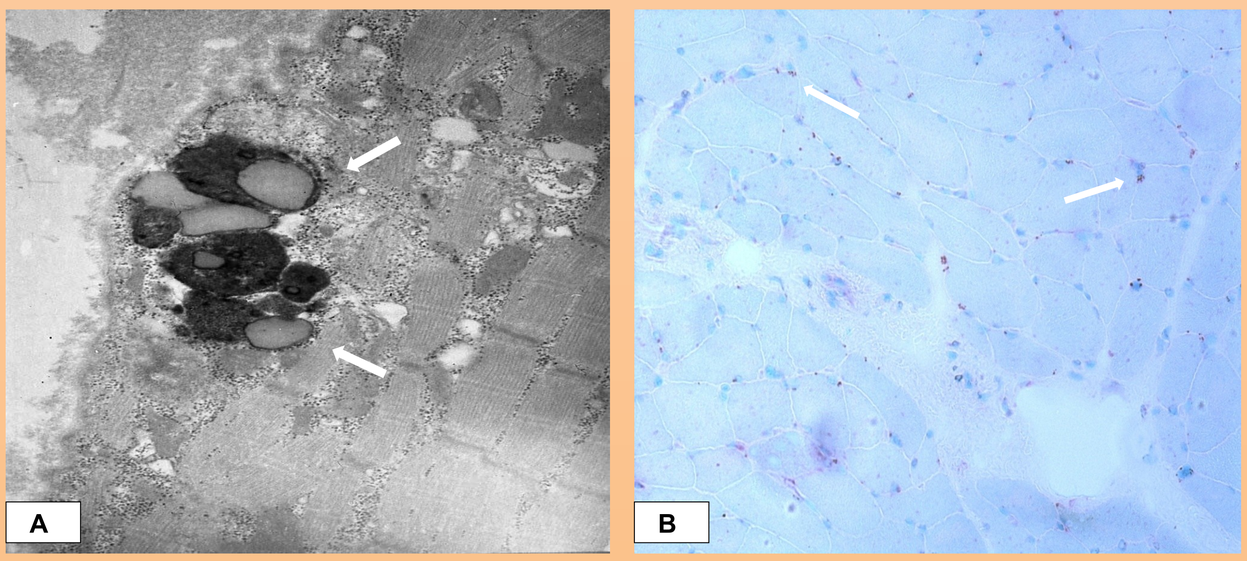

Figure 1: Muscle Biopsy from deltoid. 1A: transmission electron microscopy (TEM x 6000). White arrow indicate the electron-dense deposits. 1B: Acid phosphatase. In red indicated inclusions of lipofuscin-like material.

Conclusions

Despite the absence in our patient of the typical vacuolar myopathy at muscle biopsy and the atypical presence of a mild peripheral sensory motor neuropathy, rarely described, the rapid improvement of all symptoms within six months after drug discontinuation, suggests a diagnosis of HCQ neuromyopathy. An early diagnosis and immediate drug discontinuation enabled us to avoid more severe multisystem involvement

Discussion

Antimalarial drugs have substantial lysosomal affinity with promiment development of autophagic vacuoles in several tissues [5] and long term administration may result in accumulation of intracellular deposits. HCQ myopathy is relatively unrecognized and may be undiagnosed. In literature were described cases (assuming HCQ for at least 6 months) with typical lipid deposits at muscle biopsy (curvilinear or myeloid bodies or both)[4]. Disorder has variable correlation with treatment duration and dosage, heterogeneous symptomatology (mild to moderate proximal muscle weakness) and not constant elevation of serum muscle enzyme activity. [2,3,4].
In our case, the diffuse subsarcolemmal accumulation of lipofuscin-like material may indicate a metabolic muscle impairment, possible related to HCQ. Infact HCQ-induced autophagy by reducing lysosomal acidity is the main pathogenetic mechanism [5]. We didn't found myeloid and curvilinear bodies as described [3,4] probably in relationship to the early diagnosis. In many cases the diagnosis of HCQ myopathy is often difficult and delayed since musculoskeletal manifestations of rheumatic deseases might hide myopathic symptoms .

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