Hydroxychloroquine and Myasthenia Gravis-Can One Take This Risk?

We read with interest the article on neuromuscular manifestations of COVID-19 published in the Journal by Benny *et al*.[1] We wish to highlight the fact that the currently used medication for this condition, Hydroxychloroquine (HCQ), may be associated with complications.

COVID-19 has emerged as a pandemic and has been associated with mild to moderate symptoms in the majority of the patients. However, around 10-15% of patients develop severe disease and need intensive care. During this COVID-19 pandemic, medical health workers are at high risk of infection and are likely to take HCQ as prophylaxis as well as co-medication for treatment. This recommendation is based on some studies in-vitro in Vero E6 cell lines and initial studies in France which showed it to be effective in clearing the virus.[2] Further studies have not shown any efficacy in improving clinical outcomes.[3] However, currently, it is being used around the world including the ICMR advisory for healthcare workers.

Chloroquine has been used for several decades for the treatment and prophylaxis of malaria in endemic areas. HCQ and chloroquine are being used widely in the management of rheumatoid arthritis, lupus nephritis as well other systemic rheumatic diseases such as sarcoidosis, Sjogren's syndrome etc., Chloroquine, a precursor of HCQ, has been associated with proximal myopathy, neuropathy as well as drug-induced myasthenia which have been described in case series.[4]

With the onslaught of COVID-19 pandemic, the drug is being used widely in a high number of patients and it is possible that several neuromuscular manifestations are missed given the overwhelming systemic manifestations. In the early case series describing the clinical feature of COVID-19 from Wuhan, there has been no mention of the neuromuscular features. Likewise, in the large series from France of more than a thousand patients who were administered HCQ, no observations of weakness have been explicitly made.

Recently we witnessed a 32 year-old lady who was a follow-up case of anti-AChR antibody (anti-acetylecholine receptor antibody) positive myasthenia gravis, who was stable on pyridostigmine (SOS) without any disease-modifying drug for the last 4 years. On the line of duty, she was posted in the intensive care unit. She had taken HCQ as prophylaxis for 3 weeks prior to presentation (1st dose 800 mg on first day, second dose 400 mg after 1 week, and the same dose in 3rd week). After the 3rd week, she noticed shortness of breath at night which worsened over the next few days to longer durations overnight. She consulted the neurologist (VG). HCQ was stopped and she was treated with pyridostigmine (180 mg/day) which reduced the symptoms, but she continued to be symptomatic and was required to be admitted. She had tachycardia and tachypnoea during this period though her blood gas analysis was normal. Suspecting an impending crisis, she was treated with intravenous immunoglobin for 5 days, with which she improved significantly.

In a recent review on Duchenne and Becker's muscular dystrophy, a recommendation that HCQ is not to be used in this condition has been made. There have been certain reports of drug-induced myasthenia associated with the use of chloroquine.[5-11] In these case reports, it had been seen that these patients had been on chloroquine for few weeks to years before the onset of myasthenic symptoms. Some of them had antibodies against the Acetyl choline receptor.[5,7,8] Myasthenic symptoms resolved in most of these cases with withdrawal of the drug. In 2 of the cases,[7,11] rechallenge with chloroquine led to recurrence of symptoms and muscle biopsy in one case, had revealed a vacuolar myopathy.[7]

Most of these cases were associated with chloroquine administration for the treatment of rheumatologic conditions. However, Varan *et al*. reported an association with HCQ also.[5]

In another series of 17 patients of SLE and associated Myasthenia studied retrospectively,[4] it was found that, in 8 patients, myasthenia occurred after initiation of HCQ for the treatment of SLE. In this series of 8 patients, only one of them was presumed to be due to HCQ and this patient had rapid development of myasthenic symptoms and was not associated with antibodies against AChR. This patient had resolution of symptoms following withdrawal of the drug, however rechallenge with HCQ was not done.

On reviewing these case series and case reports, few findings are worthy of comment. Most of these patients[5,7,10] had ocular symptoms like ptosis and diplopia which resolved after stopping chloroquine. In other patients, the case description had not mentioned what symptoms of myasthenia had occurred following chloroquine. Among the reviewed cases, only one had persistent symptoms.[10]

Since the number of patients who are diagnosed with COVID-19 so far has been close to 3 million, and the pandemic is still ongoing, it is possible that several thousands of patients are treated with HCQ. Moreover, in India, HCQ has been advocated as prophylactic therapy in healthcare workers. In this situation, it is imperative that those who consume the drug are kept closely under watch and monitored for symptoms of myasthenia in addition to well known adverse effects such as cardiac QTc prolongation, retinopathy, hemolysis in those with Glucose-6 phosphate dehydrogenase deficiency. In most cases, cessation of the drug is essential if the patient develops weakness as the role of HCQ in treatment of COVID-19 is not clear.

The other important area of concern is the administration of HCQ in patients with known myasthenia in case he/she gets COVID-19. The recent advisory by the International MG/COVID-19 working group doesn't give any recommendation regarding HCQ.

In a series of 8 patients, it was seen that only one patient who had myasthenia and was given HCQ had aggravation of symptoms, and that this aggravation did not respond to withdrawal of the drug.[4] From the literature, it was seen that of 32 patients with myasthenia and SLE, only 3 had been prescribed HCQ and none of them had aggravation of myasthenia. So of these 11 cases, one had aggravation of myasthenic symptoms, which amounts to 9% of cases. So in cases with known myasthenia, it is worthwhile to avoid intake of HCQ for the management of COVID-19.

In these challenging times of COVID-19, we also have to take up the challenge of managing patients with COVID-19 along with diagnosing and appropriately managing drug-induced complications. Awareness of this entity amongst neurologists and specifically looking for it amongst patients and healthcare workers taking HCQ is of paramount importance.

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Conflicts of interest

There are no conflicts of interest.

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