Consider myotoxicity of anti-SARS-CoV-2 agents to explain relapses of myasthenia

Abstract:

Keywords: MELAS, stroke, stroke-like episode, mtDNA, respiratory chain, mitochondrial.

LETTER TO THE EDITOR

With interest we read the article by Rein, N. et al., (2020) about the management of three patients with seropositive myasthenia gravis, who got infected with SARS-CoV-2 (Rein, N. et al., 2020). Only one of these patients developed symptomatic SARS-CoV-2 infection (COVID-19) and received appropriate treatment (Rein, N. et al., 2020). This patient also experienced deterioration of myasthenic manifestations during the viral infection (Rein, N. et al., 2020). Interestingly, this relapse in this patient started already prior to the infection with SARS-CoV-2, suggesting that COVID-19 had no adverse effect on myasthenia (Rein, N. et al., 2020). In two of the myasthenia patients the SARS-CoV-2 infection remained asymptomatic and both did not experience a relapse of myasthenia, why they required neither a treatment for COVID-19 nor additional treatment for myasthenia (Rein, N. et al., 2020). We have the following comments and concerns.

Patient-1 was treated with an increase in prednisone and additionally received lopinavir, ritonavir, and chloroquine. Lopinavir is an anti-retroviral agent applied in the treatment of HIV-infected patients. Anti-retroviral agents generally inhibit the uptake of L-carnitine (Karahoda, R. et al., 2019). The myotoxic effect of anti-retroviral agents has been also attributed to suppression of the fatty acid oxidation and to impaired fatty acid handling and partitioning in myocytes (Richmond, S. R. et al., 2010). Particularly in combination with other myotoxic drugs, lopinavir may cause myopathy and rhabdomyolysis (Mah Ming, J. B., & Gill, M. J. 2003). Another side effect of the anti-retroviral treatment can be hyperthyroidism (Brown, J. D. et al., 2007). Hyperthyroidism on the other hand can cause hypokalemic thyrotoxic periodic paralysis, which may mimic deteriorations of myasthenia (Brown, J. D. et al., 2007). Thus, we should know if thyroidea-stimulating hormone levels were reduced or not in patient-1. Also, ritonavir may cause severe myopathy (Ali, M. S. et al., 2019).

Chloroquine commonly prescribed for inflammatory arthritis, can be myotoxic as well. Chloroquine myopathy manifests clinically as proximal muscle weakness and can be associated with neuropathy and cardiomyopathy (Stein, M. et al., 2000). Muscle biopsy consistently reveals curvilinear bodies and muscle fiber atrophy with vacuolar changes (Stein, M. et al., 2000). In rare cases, chloroquine may cause vacuolar myopathy (Mair, D. et al., 2020). Potential predisposing factors include Caucasian race and comorbid renal failure (Stein, M. et al., 2000). Resolution of chloroquine myopathy is slow after discontinuation of therapy and may be incomplete (Stein, M. et al., 2000).

It is unusual that patient with a long-term course of myasthenia receive steroids as a long-lasting therapy. From prednisone it is well-known that it triggers the development of a mitochondrial myopathy, and thus should be given for years but only...
as a bridging therapy until immunosuppressants exhibit their anti-myasthenic effect. Steroids should be given in long-term myasthenia patients only during acute exacerbations or for myasthenic crises.

The authors regard ptosis, respiratory insufficiency, and proximal limb muscle weakness in patient-1 as clinical manifestations of myasthenia triggered by the SARS-CoV-2 infection. We should know if the decremental response, jitter, and titers of acetyl-choline-receptor antibodies truly increased during the SARS-CoV-2 infection. If these parameters did not worsen, worsening of muscle manifestations can be rather attributed to myotoxic side effects of the anti-SARS-CoV-2 treatment than to myasthenia.

Particularly the combination of various myotoxic drugs (anti-retro-viral agents, chloroquine, steroids) could lead to clinical manifestations of a myopathy. Renal or liver insufficiency may predispose for the occurrence of these myotoxic effects. In this respect we should know which other drugs the three included patients were regularly taking and if patient-1 had any indications for renal or liver failure. We should know the entire medication to assess if the clinical manifestations in patient-1 were due to myasthenia or due to myotoxic side effects of any drugs.

Concerning the deterioration of muscle manifestations in patient-1 it should be considered that SARS-CoV-2 itself may cause myopathy (Román, G. C. et al., 2020), manifesting as myopathy, creatine-kinase elevation, rhabdomyolysis, or muscle weakness (Chan, K. H. et al., 2020). Deterioration of muscle manifestations in patient-1 prior to SARS-CoV-2 may, nonetheless, being attributed to the infection, which may have gone subclinical in its early stages.

Overall, the study about three cases with myasthenia and SARS-CoV-2 infection reported by Rein et al., has some shortcomings, which should be addressed before drawing final conclusions. All drugs the three patients were taking before and during the infection need to be mentioned, an explanation for the chronic use of prednisone should be provided, and myopathy due to the myotoxic effect of anti-SARS-CoV-2 medication should be considered as cause of the deterioration of muscle manifestations in patient-1

REFERENCES