Myasthenia gravis associated with anti-MuSK antibodies developed after SARS-CoV-2 infection.

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ABSTRACT

Introduction

Since the onset of the novel coronavirus pandemic, several neurological complications secondary to SARS-CoV-2 infection have been reported, affecting central nervous system, peripheral nervous system and neuromuscular junction.

Case Report

We present the case of a 77-year-old man who developed bulbar myasthenia gravis (MG) eight weeks after SARS-CoV-2 infection. The search for serum antibodies against the acetylcholine receptor, the muscle-specific tyrosine kinase (MuSK), and the low-density lipoprotein receptor-related protein 4 antibodies, performed by radioimmunoassay (RIA), resulted negative, while anti-MuSK antibodies were detected by cell-based assay (CBA). The patient was treated with pyridostigmine (60 mg four times a day) with unsatisfactory clinical response, followed by immunosuppressive therapy (azathioprine 1.5 mg/kg/day) with improvement of MG symptoms after two months of treatment.

Discussion

Several viral diseases have been described as associated with the onset of MG, although the underlying mechanisms are not yet fully understood. Similarly, a growing number of scientific reports suggest a correlation between SARS-CoV-2 infection and autoimmune diseases. The interest of our case lies in the timing of the MG onset (after two months from infection), together with the unusual late onset of anti-MuSK MG. These elements suggest that coronavirus infection may act as a trigger of the disease. We confirm the importance of CBA in the serological diagnosis of RIA-negative MG.

Introduction

Some cases of myasthenia gravis (MG) associated to anti- acetylcholine receptor autoantibodies (AChR) upon SARS-CoV-2 infection have been reported (range of age: 21-65)[1,2,3]. Moreover, cases of SARS-CoV-2 infections are reported in patients already diagnosed with anti-muscle-specific tyrosine kinase (MuSK)-MG[4]. In this report we describe an anti-MuSK MG case with onset eight weeks after SARS-CoV-2 infection.

Case Report

We describe the case of a 77-year-old man without relevant past medical history, who was diagnosed with SARS-CoV-2 infection in March 2020. He presented with bilateral interstitial pneumonia, dyspnea and fever. His clinical conditions slowly improved and the oropharyngeal swab turned negative after 42 days from diagnosis. Eight weeks after the onset of SARS-CoV-2 infection, the patient complained of chewing difficulty, dysphonia, diplopia, and eyelid ptosis, worsened by muscular activity, suggestive for MG. No weakness of limbs or respiratory muscles was evident. The diagnosis of MG was confirmed by the electrophysiological study (repetitive nerve stimulation and single fiber electromyography). Chest CT scan was negative for thymic changes. Radioimmunoassay (RIA) for anti-AChR, and anti-MuSK antibodies was performed twice (at disease onset and after one month) and resulted negative, as well as the low-density lipoprotein receptor-related protein 4 (LRP4) antibodies tested by immunohistochemistry. Therefore, patient serum was tested by cell-based assay (CBA)[5] around 3 months after disease onset, and resulted positive for anti-MuSK antibodies (Fig. 1). As the response to pyridostigmine (60 mg four times a day) was unsatisfactory, immunosuppressive therapy with azathioprine was started, reaching the final dosage of 1,5 mg/Kg b.w. /day, with improvement of chewing and eyelid ptosis after two months of treatment. No further increase of azathioprine dosage was needed. Steroids were avoided due to the history of severe arterial hypertension upon steroid administration. At the last visit performed in September 2020, patient's only complaint was mild chewing fatigability. Clinical features, electrophysiological findings, antibody positivity and the lack of response to pyridostigmine, were all consistent with the diagnosis of MuSK-MG[6] (grade IIb, according to MG Foundation of American Clinical Classification).

Discussion

MG is the most common autoantibody-mediated autoimmune disease of the neuromuscular junction (NMJ). RIA represents the gold-standard in the serological diagnosis of MG. Approximately

85% of MG patients have anti-AChR antibodies and around 40% of AChR antibody-negative have anti-MuSK antibodies[7]. More recently, antibodies directed against other proteins of the NMJ, as LRP4 antibodies, have been described in a low proportion of patients[7]. The use of the CBA technique, which has a higher sensitivity than RIA but retains the same specificity, has proven helpful in the serological diagnosis of RIA negative MG cases[7]. This patient was affected by mild MG symptoms that were easily managed with low-dose immunosuppression. This finding is in agreement with earlier observations that patients positive only on CBA have milder MG than RIA-positive cases[5].

It has long been known that infections can both precede the onset of MG and trigger disease deteriorations, as with other autoimmune disorders[8]. Specifically, there have been several reports about SARS-CoV-2 potential for inducing autoimmune diseases, including MG[9].–The mechanisms through which viral agents could trigger autoimmunity are not fully clarified. Increased release of type I interferons and other pro-inflammatory cytokines, T cell activation, molecular mimicry, and epitope spreading, may be involved[9]. The development of MG symptoms within two months after SARS-CoV-2 and the unusual late onset of MuSK-MG supports the hypothesis that the viral infection represented a trigger for MG, even though we cannot exclude that the viral infection unmasked a latent MG. In conclusion: post-SARS-CoV-2 infection MG may present in elderly people and may not be easily recognized in the post-infection period, because of co-morbidities and when patients are seronegative on the standard RIA. The prospective evaluation of patients with post-SARS-CoV-2 MG will provide valuable information about their long-term outcome, which could contribute to clarify the association between SARS-CoV-2 and increased risk for development of autoimmune conditions.

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All the plasmids used in this study were kind gifts from Professor Angela Vincent and Professor David Beeson, Nuffield Department of Clinical Neurosciences, University of Oxford.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Fig.1 legend

Cell-based assay results: IgG antibody binding (red) of patient serum (on the bottom) and healthy control serum (on the top) to human embryonic kidney 293-(HEK293) cells expressing enhanced green fluorescent protein (EGFP)-MuSK (green). For this study, HEK293 cells were transfected with complementary DNAs (cDNAs) expressing human AChR α, β, δ, and ε/γ subunits and rapsyn-EGFP in a ratio 2:1:1:1:1; full length MuSK–EGFP[5], and cDNAs expressing human LRP4 with a chaperone protein (low-density lipoprotein receptor–related protein–associated protein 1) to enhance cell surface expression. Serum was diluted 1:20 and scored 3 based on a score system from 0=negative to 4= strong labelling of almost all transfected cells, previously described[4].

MuSK: muscle-specific tyrosine kinase, EGFP: enhanced green fluorescent protein, HEK293: human embryonic kidney 293, AChR: acetylcholine receptor; LRP4: lipoprotein receptor-related protein 4.