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EDİTÖRE MEKTUP / LETTER TO THE EDITOR

COVID-19 vaccine induced myasthenia gravis: two cases

COVID-19 aşısıyla tetiklenen miyastenia gravis: iki olgu

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To the Editor,

Myasthenia gravis (MG) is an autoimmune disease characterized by exercise induced muscle weakness caused by antibodies against presynaptic acetylcholine receptors (AchR).[1] MG can be triggered by infections, major surgical procedures or vaccines. Currently our insight about effects of COVID-19 and SARS-CoV2 vaccines on MG is mostly limited to case reports and series. Hereby we present two patients with vaccine induced MG after SARS-CoV2 vaccines to discuss whether vaccines against SARS-CoV-2 are a risk factor for MG or it is only a temporal relationship.

Case-1 was a 71 years-old female who applied with bilateral fatigable eyelid weakness. She had the 3rd dose of Sinovac Biotech's SARS-CoV2 vaccine *(CoronaVac)*, which is a vector based inactivated vaccine whose one of the Phase-III studies was held in Turkey[2] and is the first vaccine approved for use in our country, three days before her symptoms' onset. Neurological examination revealed bilateral ptosis and horizontal conjugated gaze palsy. Sustained upgaze test (SUT) was positive. Repetitive nerve stimulation (RNS) test was normal but single fiber electromyography (SFEMG) from right orbicularis oculi muscle showed motor end plate dysfunction (minimum 34µs, maximum 68µs and average 52µs jitter and increased jitter in 3 muscle fibers individually). Anti-AchR was 6,84 nmol/L. Cranial imagings and malignancy screening were normal. The patient was started on 50 mg/day prednisolone and 180 mg/day prydostigmine because of her fatigability. One month later her neurological examination was completely normal except for her positive SUT. Prednisolone was tapered off, while pyridostigmine was continued.

Case-2 was a 29 years-old male who applied with fatigable diplopia and difficulty on speaking, chewing and swallowing. He had the 2nd dose of Pfizer-BioNTech SARS-CoV2 vaccine *(Comirnaty)* which is a nucleoside-modified mRNA vaccine also the first that had the full approval of Food and Drug Addministration (FDA)[3], 25 days before his initial complaits. Neurological examination revealed nasonated speech, palatal muscle weakness and diplopia in conjugated gaze due to his right external ophtalmoplegia. Muscle strengt was -4/5 at neck flexors and extensors, and -4/5 at proximal lower extremity muscle groups. Autoantibody test and tumor markers were normal. No thymic pathology was observed. RNS was normal but SFEMG showed motor end plate dysfunction with minimum 40µs, maximum 156µs and average 76µs jitter and increased jitter in 5 muscle fibers individually. Anti-MUSK antibody was positive (>12 U/mL). He was started on 5 days intravenous immunglobuline (IVIg) therapy. Despite the improvement, his findings were still present. He was added 60mg/day oral prednisolone and benefited. After a month, his disphagia worsened and required IVIg therapy. Thymectomy was planned as soon as his medical condition stabilized.

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COVID-19 pandemic made considerable changes in our medical approach to neuromuscular diseases. Multicentered studies revealed an increased risk of MG worsening[4]. Valuable data on COVID-19 flaired autoimmunity have been obtained through studies and many new onset MG cases after COVID-19 and SARS-CoV2 vaccines have been reported[5,6].

Vaccines are already known to be able to induce or exacerbate autoimmune diseases by shifting the balance in favor of the proinflammatory pathways. According to a study about vaccine sensitivity[7], an individual is more prone to have vaccine induced autoimmune disease if they previously had an autoimmune reaction after vaccination or have a family history of autoimmune diseases. However, due to the absence of predictive biomarkers, it is still not possible to say who is at risk.

Until today, vaccine induced MG cases were related to the traditional ones. mRNA vaccines increased speculations on the subject. They work on the basis of injecting mRNA particles, which encodes a viral protein, into the body in a lipid capsule. These particles are taken up by antigen presenting cells, then activated and results in viral antigen specific T cell production and costimulation. On the other hand, over producted Th17 cells, follicular Th cells, and dysfunctional Tregs may lead to autoantibody production and MG pathogenesis. The frequency and severity of inflammatory reactions with mRNA vaccines are higher than with conventional vaccines[6].

To date, only 4 mRNA vaccine induced MG cases have been reported[8]. Consequently, it can be clearly stated that the risk of developing MG after vaccination in healthy individuals is quite low and mRNA vaccines are quite safe for even frail MG patients, such that one study reported worsening after mRNA vaccination in only 0.4% of MG cases[9].

Since the number of SARS-CoV2 vaccine induced MG cases are so few, our knowledge about the prognosis is also insufficient. All previous cases had *Comirnaty* and developed MG in a few weeks after the 2nd dose. It is remarkable that only one patient had an early onset and only two patients had a history of comorbid diseases. Most of them initially showed mild symptoms but subsequently worsened. Some was scheduled to start immunotherapy after treated with IV pyridostigmine, IVIG and corticosteroids combined while the others had oral pyridostigmine alone.

On the other hand, neither of our patients had a history of COVID-19 and only Case-1 had a history of Hashimoto's thyroiditis which is known to frequently accompany MG. Prognosis and treatment needs of our patients seem to be similar to spontaneous MG therefore could mean that the prognosis might be related to the detected antibody even if it was triggered by vaccines. The fact that both patients developed antibody-positive MG after vaccination raised the debate over whether this was merely a temporal or a causal relationship.

By presenting these two MG cases we wanted to stand on the fact that this entity might be rare but can be difficult to manage. In this challenging period we are in, it should be emphasized in order to provide medical common sense that SARS-CoV2 vaccines do not increase the risk of developing MG in healthy individuals and the risk of MG due to COVID-19 is higher than the risk of MG due to vaccines.

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