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CASE REPORT

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Treatment of COVID-19 Vaccine Resistant Migraine Attack with CGRP Monoclonal Antibody: A Case Report

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ABSTRACT

Many researches have shown that coronavirus infection can lead to neurological symptoms. The most common symptom is headache. Calcitonin gene-related peptide (CGRP), which has an important role in the pathophysiology of migraine, may have an active role in persistent headaches after COVID, due to the structural similarity between the CGRP receptor and the SARS-CoV-2 spike protein. In this case report, the effect of the anti-CGRP monoclonal antibody on the migraine attack occurring after COVID-19 m-RNA vaccine will be discussed. A 55-year-old female patient who is followed up with a diagnosis of chronic migraine, had severe and throbbing headache that started after the COVID-19 m-RNA vaccine. After galcanezumab (CGRP monoclonal antibody – CGRP mAb) was started in the patient whose complaints did not regress despite the adjustment of the current drug doses, clinically significant improvement was observed in her complaints after the first dose and it was planned to continue with 120 mg CGRP mAb per month in her follow-ups.

Keywords: CGRP monoclonal antibody, coronavirus, galcanezumab, migraine

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INTRODUCTION

COVID-19 is a disease caused by the virus that entered our lives in December 2019 and named as "Severe acute respiratory failure syndrome corona virus-SARS-CoV-2" by the World Health Organization. COVID-19, which was declared a pandemic by the World Health Organization in March 2020, can occur in forms ranging from mild to severe and with many organ involvement and symptoms (1). Studies have also shown that coronavirus infections can cause neurological involvement (2). The most common neurological symptom is headache (3). Usually, pain in the form of pressure is felt in the frontal area bilaterally. According to the ICDH-3 (the International Classification of Headache Disorders, 3rd edition) criteria, 25% of headaches are compatible with migraine and 50% with tension-type headache (4). Although the average duration of headache was 2 weeks, 20% of the patients continued to have chronic persistent daily headache (5). The new onset of headache and the addition of symptoms such as insomnia and dizziness are also interesting (6).

In this case, we describe the effect of SARS-CoV-2 vaccine on the clinical features of headache and the results of prophylactic treatment with CGRP mAb galcanezumab in a 55-year-old female patient with chronic migraine who was evaluated for severe headache attacks after receiving a preventive vaccine for COVID-19.

Highlights

- **Headache is a common complaint after COVID-19 infection.**
- **The migraine-type headache in Covid cases is evaluated in favor of trigeminovascular system activation.**
- **Structural similarity of the Coronavirüs and the CGRP receptor may be the cause of migraine.**
- **The COVID-19 vaccine triggered resistant migraine attack is regressed with CGRP monoclonal antibody.**

CASE

A 55-year-old female patient applied to the Neurology Outpatient Clinic of our hospital. The patient's medical history was unremarkable, with recurrent headache attacks since the age of 10. There was no history of previous COVID-19 infection. The patient, who had moderate-to-severe, often unilateral, throbbing pain accompanied by nausea,

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triggered by psychogenic causes, did not report any aura or trigemino-autonomic symptoms. After receiving the COVID-19 m-RNA vaccine, the patient, who was diagnosed according to the ICHD-3 criteria, using topiramate and sertraline with the diagnosis of chronic migraine and whose headache was normally under control with these drugs, started to have complaints of pain with the same characteristics as the one she had previously experienced but was persistent and severe (Visual analogue scale (VAS): 9), and she complained of a throbbing headache that did not subside with the drugs.

The patient was started on galcanezumab (CGRP monoclonal antibody-CGRP mAb) because her complaints did not regress despite the adjustment of the current drug doses. After the first dose (2*120 mg/mL) of the patient who was keeping a pain diary, it was observed that there was a significant improvement in pain severity (VAS: 4) and persistent headache. No side effects related to galcanezumab treatment were observed. It was planned to continue the monthly 120 mg CGRP mAb treatment in the follow-ups.

DISCUSSION

The mechanisms by which SARS-Cov-2 affects the nervous system are not yet fully understood. According to studies, viral infection by neuronal retrograde transport (via the olfactory nerve) directly affects the peripheral and central nervous systems and causes neurological symptoms in the early period.

The relationship between headache and anosmia also supports the direct invasion of the cranial nerves by the virus (7). In addition, the widespread inflammation caused by the virus in endothelial cells may also trigger trigeminovascular activation by causing vascular pathogenesis and headache (8).

Calcitonin gene-related peptide (CGRP) has an important role in the pathophysiology of migraine. It plays a role in trigeminal system activation, nociceptive transmission, vasodilation, inflammation, and peripheral-central sensitization. CGRP release from the trigeminal ganglion by C fibers activates CGRP receptors on satellite glial cells as well as on Aδ trigeminal afferents. This CGRP release leads to sensitization and exaggerated peripheral and central signaling by trigeminal Aδ fibers.

It is known that CGRP, which increases with the effect of interleukin (IL)-6 and tumor necrosis factor alpha (TNF-a), also has an effect on immunological conditions such as respiratory system and sepsis. IL-6 level is especially high during SARS-CoV-2 infection. Calcitonin gene-related peptide release causes COVID-19 symptoms such as cough, fever and pain. Calcitonin gene-related peptide may play a role in the progression towards a proinflammatory state by causing an increase in T cell response in favor of Th17 and IL-17 in some COVID-19 patients (9).

Moreover, CGRP receptors coexist with angiotensin converting enzyme and two receptors to which SARS-CoV-2 binds to enter cells in trigeminal ganglion neurons (10). In a previous study by our group, structural similarity was detected between the CGRP receptor and the SARS-CoV-2 spike protein (11). This mimicry, due to its similarities with CGRP and its receptors, can lead to a long-term reaction of antibodies in the body, hence persistent post-COVID headaches. It may also explain why a persistent headache occurs especially in COVID-19 rather than other viral systemic infections. The decrease in persistent severe headache of the patient treated with CGRP mAb also supports this situation. Another study showed the protein similarity between the spike protein of the CGRP receptor and the receptor activated modified protein 1 (RAMP1) (12). This similarity may explain the persistent and new-onset headaches seen after SARS-Cov-2 infection or vaccine. The decrease in complaints after treatment with CGRP mAb also supports this finding.

Other case studies in the literature also show that persistent and severe headaches after COVID-19 infection improved with CGRP mAb (13,14). However, as far as we know, our case is the first case to benefit from the use of CGRP mAb in the treatment of persistent headache after the SARS-Cov-2 vaccine.

Studies are underway to use a nasal spray high-affinity CGRP receptor antagonist for the treatment of pulmonary complications related to COVID-19 infection (15). This shows that the use of anti-CGRP monoclonal antibody during COVID-19 infection does not pose a risk, but may also contribute to clinical improvement. Detailed molecular and clinical studies are needed to prove this possibility.

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