Neurological Sciences (2022) 43:767–770
https://doi.org/10.1007/s10072-021-05741-x

COVID-19

Status migrainosus: a potential adverse reaction to Comirnaty (BNT162b2, BioNtech/Pfizer) COVID-19 vaccine—a case report

Stefano Consoli[1] · Fedele Dono[1] · Giacomo Evangelista[1] · Maria D'Apolito[1] · Daniela Travaglini[2] · Marco Onofrj[1] · Laura Bonanni[2,3]

Received: 2 November 2021 / Accepted: 4 November 2021 / Published online: 22 November 2021

Abstract

Background Coronavirus disease-19 (COVID-19) due to acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is the largest emergency that humanity had to be dealing with in the last century. During the last months, different types of vaccines have been designed to contain the ongoing SARS-CoV-2 pandemic, with successful results in many countries. Comirnaty (Pfizer/BioNtech) COVID-19 vaccine is a lipid nanoparticle-formulated, nucleoside mRNA vaccine encoding the prefusion spike glycoprotein of SARS-CoV-2. Although vaccines have an undeniable efficacy, they can also present several neurological side effects, including headache. According to ICHD-3 Classification, status migrainosus (SMg) is described as a debilitating migraine attack lasting for more than 72 h. Symptoms of SMg can be very severe, preventing the normal daily activities of the individual.

Case presentation In the present report, we describe a case of SMg that lasted 11 days, time correlated with the second dose of COVID-19 vaccine (Pfizer/Comirnaty) in a 37-year-old woman with a history of migraine without aura.

Conclusions In patients with a history of migraine, COVID-19 vaccination could lead to a worsening of headache and, in rare cases, to the development of a SMg. This may be related to the inflammatory response that occurs after vaccination.

Keywords COVID-19 · Comirnaty BNT162b2 · Status migrainosus · Migraine without aura · Case report

Introduction

Since the first mass vaccination program started in early December 2020, about 31.6% of the worldwide population has completed the vaccination cycle and more than 5.5 billion doses of vaccine have been administered (updated to September 2021). In the countries with the highest rate of vaccination, there has been a clear reduction in the spread of the virus and consequently a reduction in the number of deaths and hospitalized patients. Although their undeniable efficacy, vaccines have also been related to several side effects which can be limited to the injection site (e.g., pain, redness, swelling) or presenting as systemic manifestations (e.g., fever, chills, tiredness). Neurological adverse effects have been described in several cases [1] and may include sleeping disorders, dizziness, paresthesia, and headache.

According to literature, headache is one of the most frequent side effects due to coronavirus disease-19 (COVID-19) vaccines [2]. In the population vaccinated with Comirnaty (Pfizer/BioNtech) vaccine, both migraine and tension-type headaches have been described. In most cases, headache can be moderate-severe in intensity and last few days, generally resolving spontaneously or responding to common analgesic medications.

According to International Classification of Headache Disorders (ICHD-3), status migrainosus (SMg) is a severe condition characterized by migraine attacks, moderate-severe in intensity, lasting for more than 72 h [3]. SMg can be a very debilitating condition, precluding the normal daily activities of the affected individual and, in some cases, leading to systemic manifestation such as severe dehydration

✉ Fedele Dono
fedele.dono@unich.it

✉ Laura Bonanni
l.bonanni@unich.it

[1] Department of Neuroscience, Imaging and Clinical Science, "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy

[2] Department of Neurology, Headache Center, "SS Annunziata" Hospital, Chieti, Italy

[3] Department of Medicine and Aging Sciences, "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy

and electrolyte imbalance in case of associated nausea and vomiting.

Though the pathophysiology of SMg is largely unknown, some risk factors including psychiatric comorbidities (i.e., depression and anxiety) and daily-life stressors have been identified [4]. Treatment of SMg is challenging and lacks international consensus.

In the present report, we describe a case of SMg following with the administration of the second dose of Comirnaty (BNT162b2, BioNtech/Pfizer) COVID-19 vaccine in a patient with a history of migraine without aura.

Case presentation

A 37-year-old woman referred to our Headache Center complaining of persisting fluctuating moderate (VAS 5/10) to severe (VAS 8/10) right pulsating headache, associated with photophobia/phonophobia and nausea, started about 4 days before. The patient reported poor responsiveness to analgesic treatment with non-steroidal anti-inflammatory drugs (NSAIDs). During those days, she was unable either to perform her normal daily activities or work because of the debilitating condition. According to the patient, symptoms started the day after taking the second booster of Comirnaty (Pfizer/BioNtech) COVID-19 vaccine.

Patient past medical history revealed a diagnosis of migraine without aura with low-frequency attacks (3–4 attacks per month) usually responsive to orally administered Ibuprofen 400 mg.

The current headache was described by the patient as having the same localization as her usual headache but worse in severity and intensity.

The patient neurological examination was normal. A magnetic resonance image (MRI) scan of the brain, performed 3 days after the symptoms' onset, showed a large (maximum diameter 14 mm), rounded cystic degeneration, involving the epiphysis with no contrast enhancement (Fig. 1A-E). The patient performed also an MR angiography (MRA) scan, which was normal (Fig. 1F). These findings were already reported in a previous brain MRI examination performed 4 years before. Laboratory results (which included serum electrolytes and inflammatory markers and blood counts) were unremarkable. The patient did not show any depressive symptoms or sleep disturbance and morning somnolence according to Beck's Depression Inventory scale (BDI) [5], Pittsburgh Scale (PTS) [6] and Epworth Sleepiness Scale (ESS) [6] (Supp.Table 1-3). According to ICHD-3 beta diagnostic criteria, a diagnosis of SMg was made. Due to an unspecified family history of heart disease, we considered unsafe to start therapy with triptans or ergots. Calcitonin gene-related peptide (CGRP) antagonists and ditans were not available in Italy at the time of the visit. Thus, a steroid therapy with intravenous hydrocortisone 1 g for 3 days was suggested but refused by the patients due to fear of steroid side effects.

After 4 days, the patient referred a little improvement of her condition with ibuprofen 400 mg administration even though a moderate (VAS 4-5/10) migraine persisted. At day 11, the patient described a full recovery (Fig. 2).

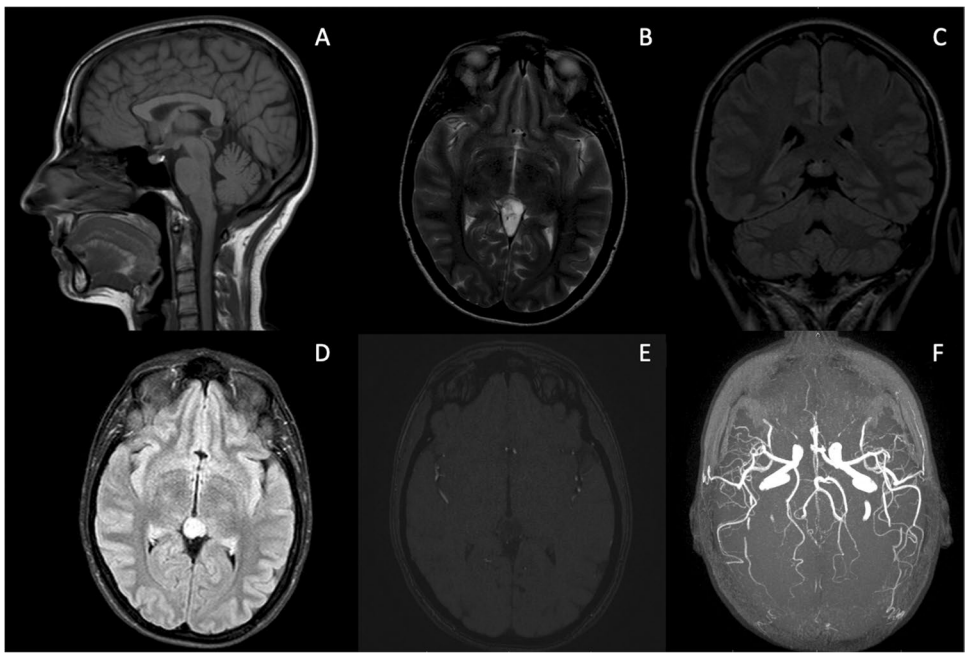

Fig. 1 Magnetic resonance image (MRI) scan of the brain at 3 days after symptoms onset. Sagittal T1 (**A**), axial T2 (**B**), coronal T2 fluid attenuated inversion recovery sequence (FLAIR) (**C**), axial T2 FLAIR (**D**), axial T1 with contrast (**E**) MRI scans showing a large, maximum diameter 14 mm, rounded cystic degeneration, involving the epiphysis with no contrast enhancement. MRI Angiography (**F**) scan was normal.

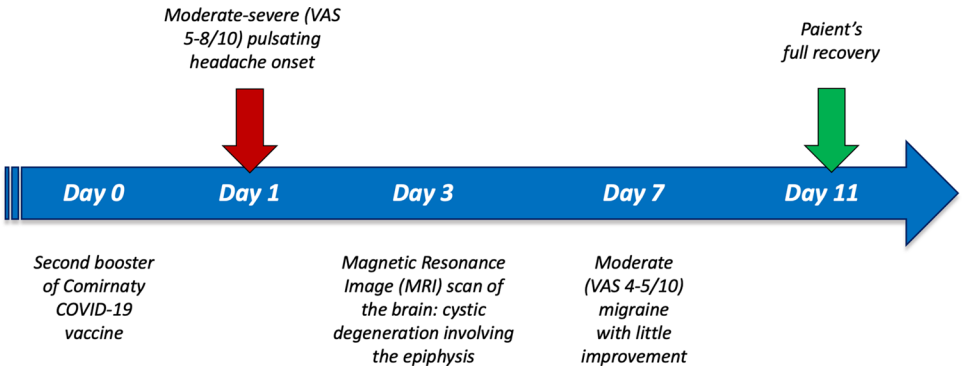

Fig. 2 Case report's timeline. The onset of status migrainosus (SMg) was the day after the second booster of Comirnaty COVID-19 vaccine. On day 11, the patient described a full recovery.

Discussion

COVID-19 vaccines' side effects are generally mild and spontaneously resolve in a few days. About 30% of vaccinated people have experienced headache as a side effect, even without a previous history of chronic headache [7]. A recent study [8] shows that in the Italian population, the risk of developing headache/migraine episodes after receiving Comirnaty (Pfizer/BioNtech) COVID-19 vaccine was 2.78-fold higher than the daily frequency of headache disorders. The headache intensity can be variable but is usually mild with spontaneous resolution within 1 to 3 days after vaccination.

The association between headache and COVID-19 vaccines could be explained by the immune response which takes place after the vaccination. In fact, the mRNA vaccines (as BNT162b2, BioNtech/Pfizer) encode the production of SARS-CoV-2 spike (s) protein, which generates significant neutralizing antibody titers and stimulate T cells (both CD4+ and CD8+) activation [9]. The inflammatory response that occurs could directly cause the development of headache by causing a release of inflammatory cytokines (i.e. *cytokine storm*) that could lead to the activation of trigeminal nociceptors. Indeed, people suffering from migraine have a central sensitization of trigeminal fibers innervating cerebral vessels which are more likely to respond to inflammatory stimuli, causing more severe and prolonged migraine attacks [10].

In the present report, we described a patient with SMg triggered by the second booster of Comirnaty (BNT162b2, BioNtech/Pfizer) COVID-19 vaccine. The diagnosis of post-Comirnaty (BNT162b2, BioNtech/Pfizer) vaccine SMg was made according to the close relationship between the onset of headache and the vaccination. Treatment of SMg is challenging, and no international guidelines have been proposed so far. Generally, patients are treated with intravenous (i.v.) specific headache medications which can include triptans, calcitonin gene-related peptide (CGRP) antagonists, ditans, or ergots. Sometimes, treatment strategies include the administration of parenteral dexamethasone [11]. However, SMg can be a self-limiting condition that does not deserve any treatment but can be highly disabling while it lasts. In our case, due to an unspecified family history of heart disease, we decided not to use triptans or ergots. In the following days, the patient presented a partial response to her usual acute symptomatic treatment with NSAID and complete remission after 11 days.

Conclusion

The present report shows that SMg can represent a rare side effect of Comirnaty (BNT162b2, BioNtech/Pfizer) COVID-19 vaccine in people suffering from migraine. The association between vaccine-induced inflammatory response and SMg can explain this peculiar association, though it should be further explored by experimental models.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10072-021-05741-x.

Author contribution FD and SC contributed to the conception and design of the study. FD, SC, GE, MDA, DT, MO, and LB wrote the manuscript and supervised all the data. All authors contributed to manuscript revisions, read, and approved the submitted version.

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

Declarations

Ethical publication statement Written informed consent was obtained from the patient for publication of this case report and any accompanying images. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The paper is exempt from ethical committee approval because it is not necessary for the publication of the case report.

Conflict of interest The authors declare no competing interests.

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