COVID-Vaccination Induces RCVS Attacks: A Case Report

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Case Report

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Abstract

Background

To describe and discuss the association between COVID-19 vaccination and RCVS attacks in a patient with RCVS and whether targeting angiotensin 2 receptor could be a preventive option.

Case presentation

A 30-year-old male previously diagnosed with reversible cerebral vasoconstriction syndrome (RCVS), presented to the department of neurology with accumulation of RCVS attacks after receiving the first Pfizer COVID-19 vaccine. The neurologic exam, blood samples, electrocardiogram (ECG), and a computer tomography (CT) of the head were normal. The patient was treated with angiotensin-II receptor antagonist, Losartan, with a good response and was discharged with a prescription for Losartan lasting until three days after the second Pfizer COVID-19 vaccine. No further RCVS attacks were reported.

Conclusions

Our case suggests that COVID-19 vaccine induces RCVS attacks in susceptible individuals and targeting angiotensin 2 receptor could be a preventive option.

Background

Reversible cerebral vasoconstriction syndrome (RCVS) is an acute and self-limiting thunderclap headache, mimicking that of a ruptured aneurysm, caused by narrowing of cerebral vessels. Headache which could last anywhere between a few minutes and several days is the main manifestation of RCVS and often remains the only symptom. A single RCVS attack is possible, but usually patients have a mean of four attacks with 1–4 weeks of moderate headache between exacerbations. RCVS occurs in all age groups, but occurrences peak around 42 years and more often in women. Although the underlying molecular pathophysiology of RCVS is unknown, several vasoactive biochemical and immunologic factors including prostaglandins, catecholamines, nitric oxide, serotonin, and endothelin-1 are thought to be involved. To diagnose RCVS, a computer tomography (CT) or a magnetic resonance (MR) cerebral angiography is needed to show calibre irregularities affecting the anterior and posterior circulation bilaterally(1).

Case Presentation

A 30-year-old male, known with RCVS and bipolar disorder, presented to the department of neurology with three new RCVS-attacks after receiving the first Pfizer COVID-19 vaccine.

The patient was diagnosed with RCVS three years previously after a longer hospitalization with suspected subarachnoid haemorrhage. The CT-angiography in 2018 showed no haemorrhage but segmental cerebral vasoconstriction of the basilar artery. A week later the vasoconstriction could not be reidentified on a new CT-angiography. He started Nimodipine treatment and has been taking it since.

The present-day symptoms started 12 hours after vaccination with a thunderclap headache at night followed by a pressing headache characterized as 7 on the numerical rating scale (NRS). A new thunderclap headache arose the following evening during sexual intercourse and decreased to a moderate headache lasting 3 hours. The next morning a third episode of thunderclap headache began spontaneously followed by nausea, dizziness, and a pressing headache (NRS 4–5) localized to the right temporal lobe. The patient described the symptoms as identical to the symptoms of previous RCVS attacks but with much higher frequency than usual. On examination the patient had no dizziness, and displayed no visual, speaking, or motoric disturbances. He had a completely normal neurological exam, blood samples, ECG, and CTC. The patient was not previously infected by Covid-19.

To prevent further attacks of RCVS related to Pfizer COVID-19 vaccine, the patient was prescribed 50 mg Losartan one time daily until follow up at the Danish Headache Center two weeks later. Losartan treatment continued until three days after the second vaccine and the patient experienced no more RCVS attacks.

Discussion And Conclusions

Cerebrovascular complications arise in 0,5–5% of acute COVID-19 infections, including ischemic stroke, intracerebral haemorrhage, cerebral venous sinus thrombosis, and a few cases of RCVS(2). In a multicenter case series of ten patients with concurrent RCVS and COVID-19 infection, nine patients were diagnosed with COVID-19 within 30 days prior to the RCVS diagnosis. Three of those patients did not have a provoking illness or use of vasoactive agents (Arandela K. et al, 2021). Other case reports (Dakay Katarina et al., 2020 and Mansoor Tarab et. Al, 2021) describe two independent COVID-19 patients presenting with RCVS attacks confirmed on diagnostic cerebral angiogram (DCA). These findings suggested a possible association between COVID-19 infection and RCVS attacks(2–4)

Angiotensin-converting-enzyme 2 (ACE-2) is suspected to be a key component of the pathophysiological mechanism underlying COVID-19 vaccine induced RCVS. ACE-2 is a membrane protein that is expressed at several organs including the heart, lungs, blood vessels, and gastrointestinal tract. It is part of the renin-angiotensin-aldosterone system (RAAS), and its primary function is to downregulate the vasoconstrictive peptide angiotensin 2 to the vasodilative peptides angiotensin 1–7 (Fig. 1)(5).

Several studies have shown that COVID-19 spike protein interacts with ACE-2 to promote cellular entry and initiate infection. This leads to downregulation of ACE-2 and consequently higher levels of angiotensin 2 inducing vasoconstriction and possibly causing an RCVS attack (Fig. 2). The Pfizer COVID-19 vaccine works similarly by introducing the spike protein with two amino acid replacements that stabilize the spike protein at the prefusion state(6) which promotes cell signalling and elicits virus-

neutralizing antibodies(7). Therefore, it seems plausible that the RCVS attacks in the patient were induced by the Pfizer vaccine. The fact that Losartan, an angiotensin 2 inhibitor, prevented new attacks strengthens this theory.

Another explanation could be that Atacand (Candesartancilexetil), also an angiotensin II inhibitor, is used as prophylaxis in difficult-to-treat migraine patients(9). The mechanism of action in reducing migraine is yet unknown. Therefore, the supposed effect of Losartan on the prevention of RCVS could be due to the general prophylactic effect of angiotensin II inhibitors on headache rather than the RAAS-mediated vasoconstriction.

The lack of RCVS-attacks after the second COVID-19 vaccination could also be confounded by the statistical phenomenon “regression to the mean”. This refers to the tendency of results that are extreme by chance on preliminary tests to move closer to the average in subsequent measurements. This statistical phenomenon can lead to the false conclusion that the intervention caused the effect. However, the fact that there have been several examples of RCVS cases after COVID-19 infection, makes it seem unlikely that it was pure coincidence.

The prophylactic medication for RCVS patients (Nimodipine) causes vasodilation, much like Losartan. Why could Nimodipine alone not prevent RCVS attacks after COVID-19 vaccination? Nimodipine is a calcium channel antagonist characterized by its ability to cross the blood brain barrier. It blocks voltage-gated L-type calcium channels in vascular smooth muscle cells inhibiting calcium influx and subsequently inducing vasoconstriction(10). This is an entirely different mechanism of action. Targeting different receptors on cerebral arteries with the combination of Losartan and Nimodipine might have resulted in more effective vasodilation and consequently preventing more RCVS attacks.

In conclusion the present case report suggests a possible association between Pfizer COVID-19 vaccination and RCVS attacks in susceptible individuals and targeting angiotensin-2 receptor could be a preventive option. More cases are needed to establish whether there is a causal relationship.

Declarations

Consent to participate and consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editors-in-Chief of this journal.

Availability of data and material

Not applicable.

Competing interests

The authors declare that there is no conflict of interests.

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Author contributions

MAM (Mohammad Al-Mahdi Al-Karagholi) acquired the case story, contributed to the analysis and interpretation of the outcome. AML (Anne Marie Lund) has been involved in drafting the manuscript and contributed to the analysis. All authors read and approved the final manuscript.

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References

1. Calabrese LH, Dodick DW, Schwedt TJ, Singhal AB. Narrative Review: Reversible Cerebral Vasoconstriction Syndromes. *Ann Intern Med.* 2007 Jan 2;146(1):34.
2. Arandela K, Samudrala S, Abdalkader M, Anand P, Daneshmand A, Dasenbrock H, et al. Reversible Cerebral Vasoconstriction Syndrome in Patients with Coronavirus Disease: A Multicenter Case Series. *Journal of Stroke and Cerebrovascular Diseases.* 2021 Dec;30(12):106118.
3. Dakay K, Kaur G, Gulko E, Santarelli J, Bowers C, Mayer SA, et al. Reversible cerebral vasoconstriction syndrome and dissection in the setting of COVID-19 infection. *Journal of Stroke and Cerebrovascular Diseases.* 2020 Sep;29(9):105011.
4. Mansoor T, Alsarah AA, Mousavi H, Khader Elias J, Girotra T, Hussein O. COVID-19 Associated Reversible Cerebral Vasoconstriction Syndrome Successfully Treated with Nimodipine and Aspirin. *Journal of Stroke and Cerebrovascular Diseases.* 2021 Jul;30(7):105822.
5. Tikellis C, Thomas MC. Angiotensin-Converting Enzyme 2 (ACE2) Is a Key Modulator of the Renin Angiotensin System in Health and Disease. *International Journal of Peptides.* 2012 Mar 20;2012:1–8.
6. Xia X. Domains and Functions of Spike Protein in SARS-Cov-2 in the Context of Vaccine Design. *Viruses.* 2021 Jan 14;13(1):109.
7. Suzuki YJ, Gychka SG. SARS-CoV-2 Spike Protein Elicits Cell Signaling in Human Host Cells: Implications for Possible Consequences of COVID-19 Vaccines. *Vaccines.* 2021 Jan 11;9(1):36.
8. Datta PK, Liu F, Fischer T, Rappaport J, Qin X. SARS-CoV-2 pandemic and research gaps: Understanding SARS-CoV-2 interaction with the ACE2 receptor and implications for therapy. *Theranostics.* 2020;10(16):7448–64.
9. Messina R, Lastarria Perez CP, Filippi M, Goadsby PJ. Candesartan in migraine prevention: results from a retrospective real-world study. *J Neurol.* 2020 Nov;267(11):3243–7.

Figures

Figure 1

Effect of angiotensin 2 and angiotensin 1-7 on vasculature. *Angiotensin 2 binds to the G-protein coupled AT1-receptor, activating a downstream signalling pathway, leading to vasoconstriction, hypertopia, and inflammation of blood vessels. Angiotensin 1-7 bind to the G-protein coupled MAS-receptor which counter-regulates the effect of angiotensin 2.*

AT1: Angiotensin 2 Type 1, MAS: mitochondrial assembly.

Figure 2

The role of Pfizer Covid vaccine in downregulation of ACE-2. ACE-2 converts angiotensin 2 to angiotensin 1-7 as part of the RAAS system. The SARS-CoV-2 spike protein binds to the ACE-2 receptor to fuse with the cell and start RNA replication and transcription. This leads to downregulation of ACE-2, an increase in angiotensin 2, a decrease in angiotensin 1-7, and eventually vasoconstriction(6–8).