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Nasser Mikhail *

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Review Article

Does COVID-19 vaccine cause pituitary apoplexy?

Nasser Mikhail [1*], Soma Wali [2]

[1] Endocrinology Division, Olive View-UCLA Medical Center, David-Geffen UCLA Medical School, CA, USA

[2] Department of Medicine, Olive View-UCLA Medical Center, David-Geffen UCLA Medical School, CA, USA

***Corresponding Author:** Nasser Mikhail, Endocrinology Division, Olive View-UCLA Medical Center, David-Geffen UCLA Medical School, CA, USA

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Abstract

Background: Few cases of pituitary apoplexy were described after exposure to the vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Main objective: To summarize cases of pituitary apoplexy related to severe coronavirus disease 2019 (COVID-19) vaccination.

Keywords: covid-19; vaccination; pituitary apoplexy; mechanisms; treatment

Introduction

Pituitary apoplexy is defined as is acute infarction and/or hemorrhage of pituitary gland usually on top of a pre-existing undiagnosed pituitary adenoma, or very rarely occurring without presence of pituitary tumors [1]. Pituitary apoplexy is a rare disease with a prevalence of approximately 6.2 cases per 100,000 subjects [1]. Main symptoms of pituitary apoplexy include abrupt onset of severe headache, ophthalmoplegia and hypopituitarism [1]. COVID-19 infection was shown to be a multisystem disease and the pituitary gland is not spared [2]. In fact, in a paper published in November 2022, Aghdam et al [3]. summarized 14 COVID-19 infected patients having pituitary apoplexy. Whether COVID-19 infection was the direct cause of pituitary apoplexy was unclear. After the widespread use of vaccination against COVID-19, 5 cases of pituitary apoplexy were reported shortly after vaccination [4-8]. (suumarized in table 1). In addition, few cases of hypophysitis (without apoplexy) were reported after COVID-19 vaccination [9-10]. The main purpose of this article is to review characteristics of pituitary apoplexy taking place shortly following COVID-19 vaccination to alert physicians to this possible rare and serious complication of the vaccine.

Methods: Pubmed search up to June 2, 2023. Search terms were COVID-19, vaccine, apoplexy. Case reports, observational studies, and reviews were included.

Description of cases

Review of literature revealed only 5 patients, 4 women and one man, with pituitary apoplexy possibly caused by COVID-19 vaccination (table 1). Their age ranged from 24 to 50 years. Astrazeneca vaccine was implicated in 3 cases, Moderna mRNA vaccine in one patient. In the first patient reported by Jaggi and Jabbour [4]. the type of vaccine was not mentioned. Yet, since the latter case was reported in the USA, the implicated vaccine is most likely a mRNA vaccine pertaining to either Moderna or Pfizer. The time duration between vaccine administration and onset of pituitary apoplexy was 1-5 days. In the patient of Roncati et al [7]. the authors did not mention a specific duration. Interestingly, onset of symptoms of pituitary apoplexy occurred after the first vaccination in one case [5]. in 2 patients after the second vaccine dose [4-6]. one patient after third dose [8]. and in one patient after both the first and second dose [7]. (table 1). Patients presented with classic symptoms of pituitary apoplexy, mainly sudden onset of severe headache, and ophthalmoplegia [4-8]. Three of the 5 cases had gradual recovery with conservative approach, whereas 2 patients had transsphenoidal resection of pituitary lesion (table 1). No mortality was reported.

Possible mechanisms of COVID-19 induced pituitary apoplexy

The mechanisms whereby COVID-19 vaccine might cause pituitary apoplexy are unknown. While Aleverti et al [8]. demonstrated SARS-CoV-2 proteins located next to capillaries in pathology specimen of pituitary gland after its surgical resection, the clinical significance of this finding is unclear. A possible mechanism might be that the COVID-19 vaccine could induce thrombosis of pituitary vessels leading to pituitary infarction or hemorrhage. In fact, several cases of thrombotic thrombocytopenia were reported 5-16 days after vaccination with ChAdOx1 nCoV-19, adenoviral vector Astra-Zeneca vaccine and m-RNA vaccines [11-14]. The latter cases resembled heparin-induced thrombocytopenia, but without previous exposure to heparin [11-14]. The authors called this rare adverse effect "vaccine-induced immune thrombotic thrombocytopenia (VITT)" [11-14]. In the latter condition, thrombosis occurred in unusual sites such as cerebral venous sinuses [11-14]. However, in none of the 5 cases of pituitary apoplexy described herein, thrombocytopenia was reported. In addition, there was no laboratory evidence of thrombosis as reflected by normal plasma levels of D-dimers in the 2 cases reported by Zainordin et al [6]. and Roncati et al [7].

Implication of COVID-19 in triggering pituitary apoplexy: strength of evidence

There are several pieces of evidence to justify the direct implication of COVID-19 vaccination in triggering pituitary apoplexy. First, the close time duration between vaccination and occurrence of pituitary apoplexy, which ranged from 1 to 5 days after receipt of the vaccine (table 1). Second, in terms of epidemiology, the patients' characteristics were distinct from those with non-vaccine related pituitary apoplexy. Thus, classic pituitary apoplexy usually occurs more frequently in the fifth and sixth decade, with a male to female ratio between 1.1:1 and 2.3: 1.0 [1]. In contrast, cases described herein were mainly young women aged 28-50 years. Moreover, vast majority of pituitary apoplexy in general developed on top of a pre-existing pituitary adenoma [1]. Meanwhile, pituitary adenoma was demonstrated in only 2 of the 5 cases reported in relation to COVID-19 vaccine. Third, while no mechanisms were identified, pituitary apoplexy could be a rare thrombotic adverse effect of the COVID-19 vaccine similar to the cases reported with Astra Zeneca, Moderna and Pfizer-BioNtech vaccines [11-14].

On the other hand, it cannot be excluded that the occurrence of apoplexy after the vaccine might be simply a coincidence. In addition, coagulopathy, reflected by thrombocytopenia and elevated D-dimers was not demonstrated in any of the 5 cases of pituitary apoplexy [4-8].

Summary and clinical implications

Five cases of pituitary apoplexy possibly triggered by vaccination against COVID-19 were described. The development of pituitary apoplexy shortly within 1-5 days after vaccination coupled with the distinct epidemiology of this vaccine-related pituitary apoplexy suggest a possible causal relationship. The underlying mechanisms of pituitary apoplexy induced by COVID-19 vaccination are unclear. While the number of cases is still very limited, it is likely to be under-reported. Nevertheless, physicians should be aware of this possible rare adverse effect of COVID-19 vaccine. Thus, any patient who receives a COVID-19 vaccine and develops a few days later sudden onset of severe headache with or without ophthalmoplegia should get magnetic resonant imaging (MRI) of pituitary gland to rule out pituitary apoplexy. Moreover, it is essential to report suspected cases to the vaccine manufacturer and health authorities (e.g, Federal Drug Administration in the USA) to better define the relationship between pituitary apoplexy and COVID-19 vaccine.

Reference, country	Age Years)/gender	Type of Covid-19 vaccination	Timing of apoplexy symptoms in relation to COVID-19 vaccine	Clinical presentation	MRI and laboratory findings	Course and treatment/comments
1.Jaggi & Jabbour [4], USA	44/man	Not reported	3 days after second dose	Fever, hypotension, blurred vision	4.7 cm sellar and suprasellar mass with compression of optic chiasm	ETR. Pathology showed focal hemorrhage of pituitary gland
2.Pinar-Gutierrez et al [5], Spain	37/woman	Astra-Zeneca	5 days after first dose	Frontal headache	Bleeding in 10 mm pituitary adenoma	Symptoms resolved in 2-3 weeks without treatment or residual hormone defect
3.Zainordin et al [6], Malaysia	24/woman	AstraZeneca	1 day after second dose	Severe frontal headache	Hypophysitis was diagnosed Normal platelet and coagulation profile	Headache improved 3 weeks after dexamethasone. Pituitary mass decreased by 50% after 1 month,
4.Roncati & Manenti [7], Italy	28/woman	AstraZeneca	Headache occurred after the first and worsened after second dose.	Fever and tension headache, amenorrhea	Hemorrhage in sella 69 days after second vaccination. Normal platelet and D-dimer	Gradual recovery
5.Aliberti et al [8], Italy	50/woman	Moderna mRNA	1 day after the third dose	Vomiting, diplopia, headache	Bleeding in pituitary adenoma extending to left cavernous sinus and optic chiasm	TSR on the 6th day after presentation. SARS-CoV-2 proteins located next to capillaries in pathology specimen.

Table 1: Cases of pituitary apoplexy following COVID-19 vaccination

Results

Literature search revealed 5 cases of pituitary apoplexy possibly triggered by administration of COVID-19 vaccine. Four of the 5 subjects were women aged 28-50 years-old, and the fifth patient was a 44 years-old man. Astra-Zeneca vaccine was the implicated vaccine in 3 of 5 patients, Moderna mRNA in one subject, and in one subject type of vaccine was not mentioned. Classic symptoms of pituitary apoplexy started 1-5 days after vaccination. Two patients had pre-existing undiagnosed pituitary tumor.

Overall, patients' characteristics were not typical of pituitary apoplexy occurring in the general population. Two patients underwent transsphenoidal resection (TSR) of pituitary gland, and the remaining 3 patients recovered with conservative treatment. No abnormalities in blood coagulation were demonstrated in any patient as reflected by normal number of blood platelets and plasma levels of D-dimers.

Conclusions

Physicians should be aware of pituitary apoplexy as a possible rare complication occurring within few days after COVID-19 vaccination to avoid delay of diagnosis of this serious condition.

Conflict of interest

The authors do not have any conflict of interest to declare.

Abbreviations: ETR: endoscopic transsphenoidal resection of pituitary gland, TSR: transsphenoidal resection, SARS-CoV-2: severe acute respiratory syndrome coronavirus disease

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