
# Cerebral venous sinus thrombosis after 3rd dose of Pfizer vaccine: An interplay of factors

**Abstract**

The mRNA vaccines developed to combat the SARS-CoV-2 pandemic, including COMIRNATY® by Pfizer, have been regarded as generally safe. They have often been favoured over others such as AstraZeneca, which has been linked with thrombosis in the younger population. Here, we highlight the case of a young woman presenting with Cerebral Venous Sinus Thrombosis (CVST) post vaccination with COMIRNATY®.

A 36-year-old woman presented to the eye emergency department with a 2-week history of severe headaches, photophobia and diplopia, starting approximately one week following her third dose of COMIRNATY®. Despite two previous visits to emergency departments with normal CT head results, the symptoms persisted. Notably, she tested positive for COVID-19 after her vaccination, but without any symptoms suggestive of infection.

The patient's medical history included migraines without aura, and she was on Ethinylestradiol/Levonorgestrel, which was switched to Desogestrel on her initial presentation.

Neurological examination demonstrated right oculomotor palsy and horizontal binocular diplopia worse on right gaze. Fundoscopy demonstrated bilateral optic disc swelling confirmed on ocular coherence tomography. CT intracerebral venogram revealed changes consistent with right transverse sinus thrombosis. Treatment with low molecular weight heparin was initiated, with ongoing anticoagulation on discharge. Thrombophilia screens were negative on follow-up.

To our knowledge, there is no other case of CVST following vaccination with a dose of COMIRNATY® in the literature. Analysis of thrombus risk post-vaccination has focused primarily on vaccines other than COMIRNATY®. While a causal link with vaccination remains speculative, due to presence of possible viral infection and hormonal medication use, the temporal relationship warrants further exploration.

**Keywords: COMIRNATY® covid-19 Cerebral Venous Sinus Thrombosis (CVST)**

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## Introduction

### ▪ COVID-19 and vaccines

The emergence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has had a profound global impact since it was declared a worldwide pandemic in March 2020. The infection can affect multiple body systems, such as the cardiovascular system, including causing a state of hypercoagulability [1]. Various mechanisms by which this may occur have been suggested, such as renin-angiotensin-aldosterone system dysregulation, endothelial damage and a dysregulated immune response among others [2].

Vaccines have been an encouraging approach to controlling the pandemic, demonstrating notable efficacy and generally tolerable adverse reactions. The majority of these reactions manifest within a week, though occasional delays may occur. While the general profile of adverse reactions post vaccination remains favourable, instances of severe side effects, such as thromboembolic events, myocarditis and pericarditis have been identified, although at a low incidence. Hence, adverse drug reactions post COVID-19 vaccinations should be identified and addressed in a timely manner [3].

### ▪ Cerebral venous sinus thrombosis

Cerebral Venous Sinus Thrombosis (CVST) is a rare but potentially life-threatening condition, accounting for 1-4% of cerebral venous thrombosis cases [4]. In general, the main risk factor for developing CVST is facial infections; however pregnancy, oral contraceptives and/or HRT also pose significantly increased risk. As with venous thromboses in general, thrombophilia and various other genetic disorders such as Factor V Leiden mutation also increase the risk of developing the condition [5].

Regarding COVID-19 vaccination-related CVST, the incidence is relatively low, predominantly associated with adenovirus vector vaccines (such as AstraZeneca and Johnson & Johnson) with various studies having shown an incidence ranging from 0.5 - 0.8 in 1.000.000 cases to 1 in 100.000, rendering it quite an unusual side effect but with significant mortality rates of up to 39.2% in some studies [6,7].

A smaller number of cases of CVST have also been reported after Covid-19 vaccination with mRNA vaccines, such as the COMIRNATY® vaccine, produced by Pfizer. To our knowledge these have only been observed after the first or second dose of the vaccine. The case we present involves CVST occurring in a young woman after her third dose of vaccination with COMIRNATY®.

## Case Presentation

### ▪ History

We report the case of a 36-year-old woman who presented to the eye emergency department with a two-week history of progressively worsening headache associated with blurry vision. The headache was gradual in onset, rising to a severity of 9/10 on presentation, with the pain being felt over the frontal region, behind the eyes and radiating down her neck. It was sharp and consistent in nature. It worsened on movement, bending or straining. There was also associated photophobia. She reported no accompanying nausea, vomiting, fever, loss of consciousness, syncope, weakness, or loss of sensation.

The patient had received her first, second and booster doses of the COVID vaccinations at 10 months, 8 months and 3 weeks respectively prior to her initial presentation with headache. All doses were of the COMIRNATY® (Tozinameran), COVID-19 mRNA vaccine (nucleoside modified), produced by Pfizer-BioNTech and of 30 micrograms/0.3ml dose concentrate (for dispersion for injection).

Nine days prior to presenting at our hospital, the patient tested positive for COVID-19. Other than the headache and blurry vision described above, she was asymptomatic for COVID-19. She did not exhibit any of the typical symptoms for acute COVID-19 infections, such as cough, dyspnoea, nasal congestion or shortness of breath [8]. On admission to our hospital, multiple COVID-19 tests performed were negative for SARS-CoV-2 RNA.

Prior to arriving to our department, the patient had also presented to a different hospital (at 10 and 12 days prior to admission with us), both times with a headache. A CT scan on the latter of these presentations was performed primarily for exclusion of haemorrhage/mass lesion as a cause of the headache. None were visualised and the CT head reported by a consultant radiologist indicated no abnormal findings at the time.

The patient was taking Microgynon (Ethinylestradiol/Levonorgestrel) when she presented. She had been using this for 13 years without any complications. On her initial presentation she was advised to switch to Cerelle (Desogestrel) [9]. She did not take any other medications.

The patient's past medical history included migraines without aura since she was a teenager; however the presentation of this headache was notably different for her in terms of the character and duration of the headache. She had no other past medical history, no relevant family history, was fully independent, lived at home with her family and worked as a hostel manager. There was no history of smoking or using recreational drugs; she drank occasionally at social events.

### ▪ Examination and investigation findings

The patient's vital signs on presentation were within normal limits and can be found in TABLE 1.

**TABLE 1. Patient's vital signs on presentation.**

| | |
|---|---|
| **Blood pressure** | 137/78 mmHg |
| **Temperature** | 36.5$^0$ Celsius |
| **Heart rate** | 94 beats/min |
| **Respiratory rate** | 16/minute |
| **$SaO_2$** | 99% |
| **$FiO_2$** | 21% |

Ophthalmic examination demonstrated a third nerve palsy on the right. There was also intermittent decreased abduction in both eyes. Hess charts for the patient's eye movements can be found in FIGURE 1.

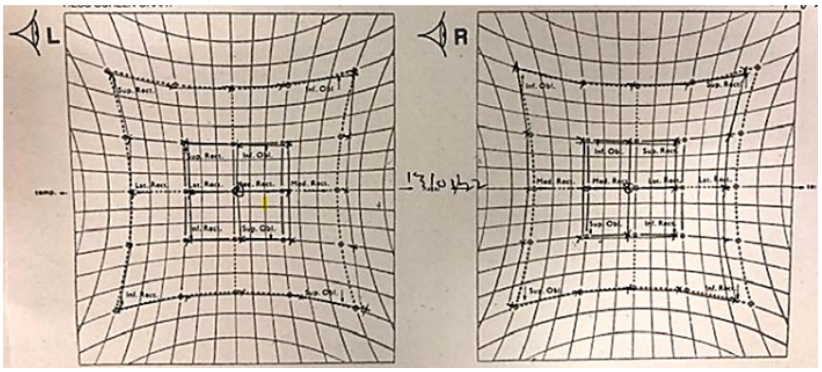


**FIGURE 1. Patient's Hess charts for Left (L) and Right (R) eyes demonstrating slight restriction of lateral rectus on chart for right eye.**

Visual acuity was 0.0 in the left and 0.1 in the right eye. Colour vision was intact bilaterally scoring 17/17 on Ischihara.
There was no relative afferent pupillary defect.
Visual field assessments were within normal limits.
Fundoscopy revealed bilateral papilloedema. Fundus photographic images can be seen in FIGURE 2, with Optos fundus images in FIGURE 3.

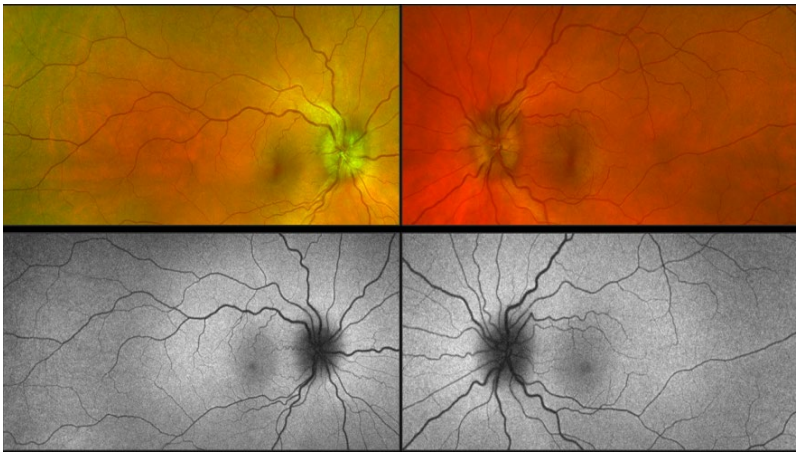

**FIGURE 2. Fundus photographic images demonstrating bilateral swollen discs**

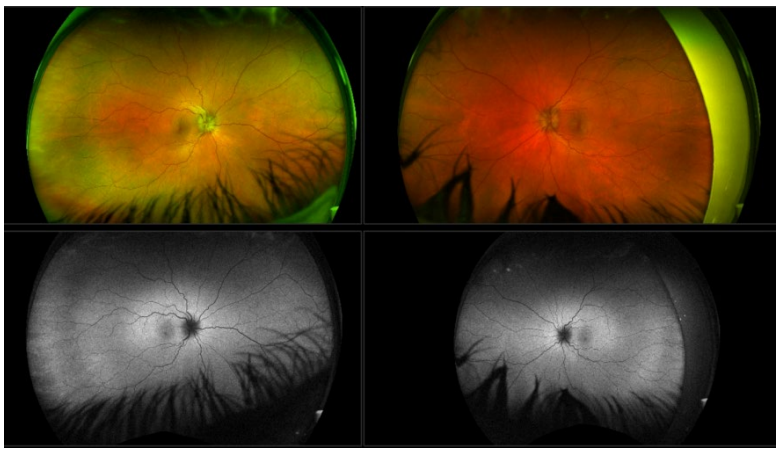

**FIGURE 3. Optos fundus images. Above: Optos fundus images (colour). Below; Red-free Optos fundus images.**

Ocular coherence tomography performed for additional evaluation is illustrated in FIGURE 4.

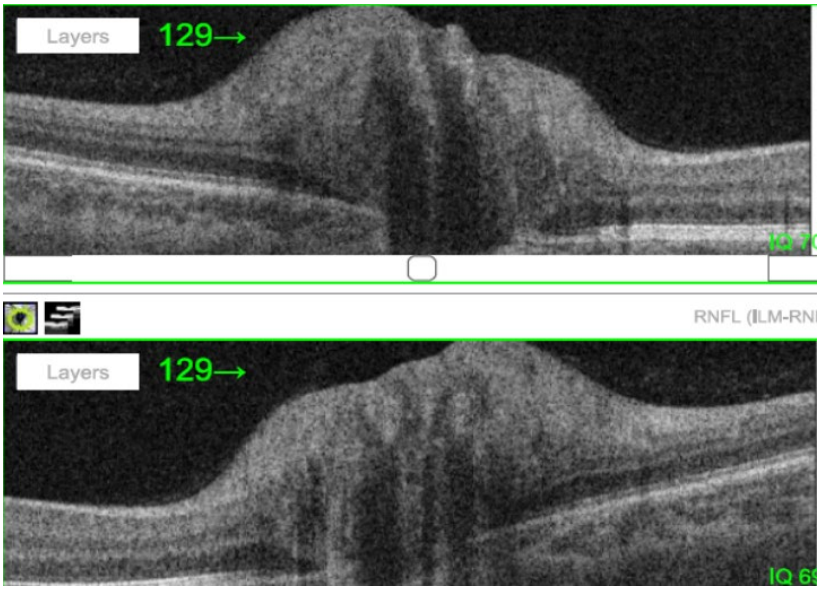


**FIGURE 4: OCT demonstrating bilateral swollen discs**

Ocular tonometry revealed bilateral pressures of 13 mmHg (using ICARE).
Neurological examination was normal other than the ophthalmic signs detailed above. The remaining cranial nerves were unaffected and peripherally tone, power, reflexes and sensation were intact.
Cardiac, respiratory and abdominal examinations were also unremarkable.
A CT head and CT intracerebral venogram was performed for further evaluation. This revealed low-attenuation within the right transverse sinus in keeping with central venous sinus thrombosis **(FIGURE 5).** There was also some eccentricity in the straight sinus. The sigmoid sinus and right internal jugular were patent.

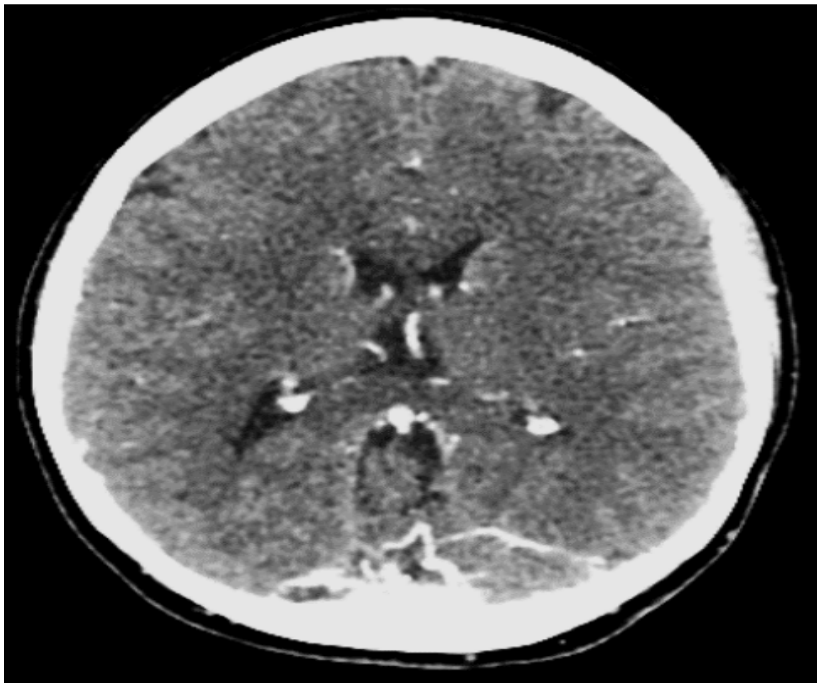

**FIGURE 5. CT intracerebral venogram demonstrating a right cerebral venous sinus thrombosis.**

Initial blood tests showed an APTT of 19.7 seconds and slightly raised lymphocytes of 4.14 x 109/L. The rest of the full blood count, urea and electrolytes, liver function tests, C-reactive protein and prothrombin time were within normal limits.

- **Management**

The patient's treatment for the CVST and subsequent multidisciplinary follow-up is summarized in **FIGURE 6.**

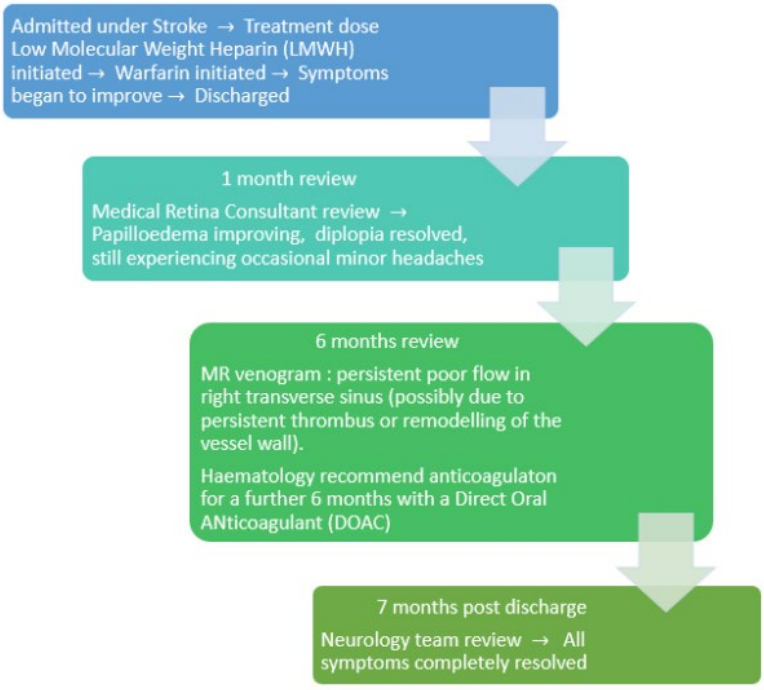


**FIGURE 6: Patient's treatment for CVST and follow-up.**

Outpatient investigations for Factor V Leiden, prothrombin gene variant and thrombophilia screen were all negative. FIGURE 7 demonstrates the appearance of her MR Venogram at 6 months post-discharge.

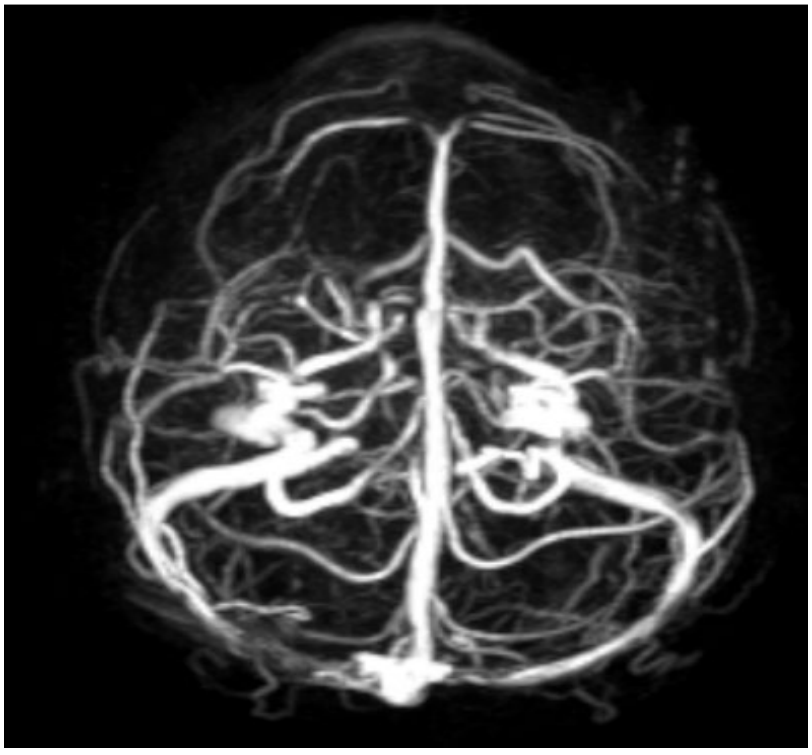

**FIGURE 7. MR Venogram at 6 months post-discharge demonstrating persistent poor flow signal in the proximal half of the right transverse sinus which may reflect some recanalisation, albiet incomplete.**

## Discussion

This case report highlights the multifaceted nature of thrombotic events in the context of COVID-19 and the need for continued research into vaccinations against SARS-CoV-2 as our understanding of the virus and the vaccination programs continue to improve.

A number of learning points can be derived from our case.

Firstly, it should be noted that vaccination for COVID-19 may reduce infectious symptoms such as cough, shortness of breath

and coryza [10]. Thus, the absence of these symptoms in our patient despite testing positive for COVID-19 may have contributed to her CVST being missed on her first 2 presentations.

COVID-19 itself as a pathogen causes coagulopathy due to vascular inflammation and large endothelial dysfunction. The virus triggers a pro-thrombotic immune response and high platelet reactivity. Hence a low threshold of suspicion for venous thromboembolism following COVID infection particularly is important [2].

Secondly, it is well established that hormonal contraceptives can represent a risk factor for thrombotic events [9]. While our patient was on a hormonal contraceptive for 13 years without prior reported adverse effects, we cannot ignore the potential role this might have had in her presentation.

Thirdly, we should consider the potential contribution of the patient's 3rd vaccination dose with COMIRNATY® towards the aetiology of her presentation. Regarding vaccines developed against the COVID-19 pandemic, it has been suggested that adenovirus vector vaccines, such as AstraZeneca and Johnson & Johnson, can cause platelet activation and clot formation inducing a prothrombotic cascade, similar to heparin-induced thrombocytopenia [11]. A number of CVST cases have been reported in relation to these [12].

A small number of CSVT cases have additionally been reported following administration of modified ribonucleic acid (mRNA) vaccines, such as Pfizer and Moderna, though the mechanisms behind these are poorly understood. One theory mentions SARS-CoV-2 spike protein induced APC activation, though this subject requires further research [13].

Due to the differences noted in the incidence of thrombotic events between adenovirus vector and mRNA vaccines the latter have been favoured, in particular for the vaccination of the younger population [14].

There are good indicators that a 3rd dose of mRNA vaccine further prevents hospitalisation for cases of COVID-19 in the general population who have already received their first two doses of the vaccine, with overall mild adverse effects [15]. Regarding serious side effects after the 3rd dose we could not find any prior reported cases of CVST as of yet.

This case report underlines the importance of keeping a wide differential in the emergency eye setting when it comes to patients presenting following vaccination. This is highlighted by the fact that the patient had a CVST, which was missed during two prior emergency department visits. There are multiple potential contributing factors to the development of the thrombus in this case. While it is likely that in her case an asymptomatic COVID-19 infection and her use of hormonal contraceptives played an important role, due to the temporal relationship to her vaccination, the part this might have potentially played in the aetiology of her thrombotic event cannot be ignored.

In conclusion, this case report serves as a contribution to the idea of the need for ongoing surveillance, individualized risk assessment, and a comprehensive approach to differential diagnosis in emergency settings, in particular for patients presenting after their third dose of COVID-19 vaccination.

## Conclusion

Thus, studying changes in the level of lipocalin-2 in the early stages of CKD, which has developed in the context of obesity, can serve as a marker of tubular apparatus damage. This is indicated by the average inverse correlation between Glomerular Filtration Rate (GFR) and the direct correlation between lipocalin and microalbuminuria. Additionally, in the early stages of CKD on the background of obesity, there is a disruption in lipid metabolism, characterized by increased levels of total cholesterol, triglycerides, low-density lipoprotein and decreased high-density lipoprotein levels.

Our study also found that in patients with early-stage CKD and obesity, urinary NGAL levels positively correlate with elevated triglyceride levels. Dyslipidemia that develops in the early stages of CKD and is associated with obesity likely increases the rate of progression of kidney tissue damage and is a risk factor for cardiovascular events.

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