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### Case Report

# Intracranial Hypertension and Papilledema: An Unusual Complication After the Adenoviral DNA Vector–Based Coronavirus Disease 2019 Vaccination in an Air Medical Transportation Pilot

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### A B S T R A C T

A 32-year-old male, Mil Mi-17 (air medical transport) helicopter pilot presented to the emergency department with a headache and visual blurring 12 days after the first dose of the Sputnik V vaccine. He had no past medical history; he successfully passed his last annual medical examination, and his vital signs were in the normal range. The significant findings were decreased visual acuity, papilledema, severe visual field narrowing, and increased nerve fiber layer thickness in both eyes. The aviation medical examiner suspended him from flight duties and referred him for a complete neuro-ophthalmic investigation. The patient underwent a lumbar puncture; his cerebrospinal fluid pressure was 39 cm H<sub>2</sub>O, and his cerebrospinal fluid biochemical analysis and blood tests were normal. He refused ventriculoperitoneal shunt surgery and received methylprednisolone with acetazolamide. After 10 days, the patient reported a significant improvement. One month later, his visual acuity and visual field were better, papilledema resolved, and disc pallor appeared. Three months later, he needed no medical treatment; he had normal visual acuity and near-normal visual fields. Based on the aviation medical regulations and the importance of flight safety in air medical transportation operations, he cannot return to flight duties until full neuro-ophthalmic recovery is confirmed.

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Coronavirus disease 2019 (COVID-19) mostly affects the respiratory system, ranging from mild flulike symptoms to severe acute respiratory syndrome. However, several extrapulmonary multisystemic involvements (eg, neurologic, hematologic, cardiac, and gastrointestinal) have been reported.<sup>1,2</sup>

Many countries produced different types of COVID-19 vaccines for immunoprophylaxis. Recombinant adenoviruses are used widely as vaccine vectors because 1) they can accommodate largely genetic payloads, 2) they are unable to replicate, and 3) they stimulate the immune system for sufficient responses. Sputnik V (Gam-COVID-Vac), a common adenoviral DNA vector-based COVID-19 vaccine, is used based on the heterologous recombination of adenovirus 26 and adenovirus 5 as vectors for expression of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein. At first, Sputnik V was approved by many countries; it uses 2 varying serotypes, which are given 3 weeks apart. Research showed that the recipients generated robust antibody responses to the spike protein, which included neutralizing antibodies,

the proportion of the total immunoglobulin that inhibits the virus binding to its receptor. They also showed evidence of T-cell responses consistent with an immune response that should not quickly wane.<sup>3-5</sup> However, the development of the Sputnik V vaccine has been criticized for unseemly haste, cutting corners, and a lack of transparency. Its adenoviral load is beyond the limit value, resulting in a dilemma of usage in many countries because of the possible side effects.<sup>4-7</sup> We present the first reported case of unusual intracranial hypertension (IH) and papilledema after receiving the first dose of the Sputnik V vaccine in an air medical helicopter pilot.

### Case Report

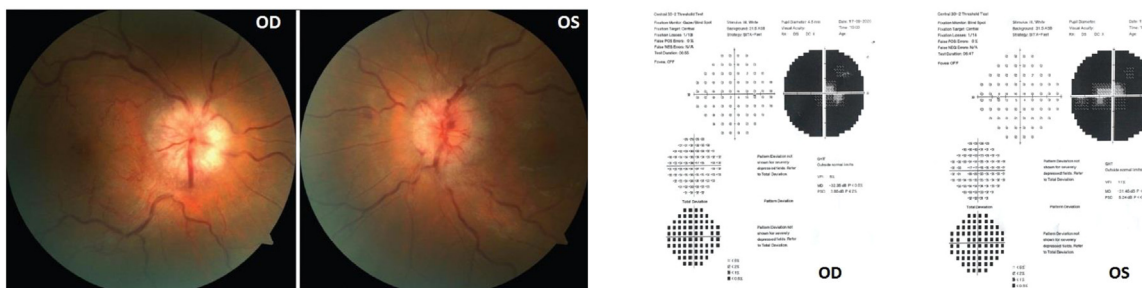
The patient was a 32-year-old white male, Iranian Red Crescent Society pilot flying with a Mil Mi-17 air medical transport helicopter. His total flight time was 1,520 hours, and he successfully passed his last annual medical examination 239 days ago and had no past medical history. After receiving the first dose of the Sputnik V COVID-19 vaccine, the aviation medical examiner (AME) suspended him from flying for 48 hours based on the Federal Aviation Administration regulations. One day later, he returned to the AME with the complaint of gradual onset of

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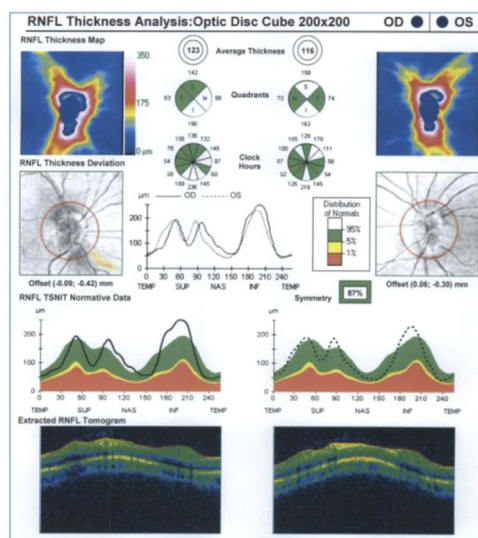
mild headache, dizziness, and weakness. The AME extended the grounding time for 2 weeks, prescribed naproxen 500 mg 3 times a day, and advised him to return if needed. The symptoms gradually intensified and became intolerable on the 12th day. The patient presented to the emergency ward with severe bilateral frontal and retro-orbital throbbing daily headaches, dizziness, nausea, generalized weakness, and visual blurring. He denied tobacco or medication use and had a body mass index of 22.5 kg/m<sup>2</sup>. His vital signs included an oral temperature of 37.1° C, blood pressure of 115/75 mm Hg, heart rate of 76 beats/min, respiratory rate of 14 breaths/min, and blood oxygen saturation of 98% in room air. The nasopharyngeal SARS-CoV-2 reverse transcription polymerase chain reaction test and chest computed tomography (CT) scan were inconclusive for COVID-19 pneumonia. The AME suspended him from flying duties temporarily and referred him for a complete neuro-ophthalmic investigation. Extraocular muscle examinations, confrontation fields, color vision test, and slit-lamp examination were normal. No focal deficit, ataxia, or pupil light response abnormalities were found on the neurologic examination. Best-corrected Snellen visual acuity of 6 of 12; edematous, crowded, and elevated optic discs without vessel obscuration, hyperemia, hemorrhage, or drusen on dilated fundus examination (modified Frisén scale II); severe visual field narrowing in Humphrey visual field testing; and increased nerve fiber layer thickness in optic nerve coherence tomography (OCT) were significant findings in both eyes (Fig. 1).

B-scan ultrasonography was negative for optic nerve head drusen. Brain magnetic resonance imaging revealed no space-occupying lesion (mass or hemorrhage), and magnetic resonance venography was also normal. He underwent a lumbar puncture, and cerebrospinal fluid (CSF) pressure was 39 cm H<sub>2</sub>O on entry and 19 cm H<sub>2</sub>O on exit. CSF biochemical analysis demonstrated clear and colorless fluid with 14 mg/dL protein, 59 mg/dL glucose, and negative microbial cultures. There were old erythrocytes (610/mm<sup>3</sup>), new erythrocytes (9230/mm<sup>3</sup>), and white blood cells (46/mm<sup>3</sup>) with 100% polymorphonuclear leukocytes. CSF aquaporin-4 antibodies, oligoclonal bands, and the SARS-CoV-2 reverse transcription polymerase chain reaction test were negative. Blood tests were in normal ranges, and negative serum anti-Neuromyelitis Optica (NMO) (cell-based assay method) was obtained. After ruling out any other causatives or predisposing factors, according to our findings, idiopathic intracranial hypertension (IIH) and bilateral low-grade papilledema (modified Frisén scale II) following the Sputnik V COVID-19 vaccination were considered for him. The physicians recommended the imminent ventriculoperitoneal shunt surgery to decrease CSF pressure effectively, but he refused surgical treatment. His medical treatment included intravenous methylprednisolone 500 mg daily for 5 days (pulse therapy) and oral acetazolamide 250 mg 3 times a day (TDS) for 10 days. After 10 days of treatment, the patient reported a significant improvement in symptoms and was discharged. At the first follow-up session 1 month later, his visual acuities were 6 of 7.5 in both



A

B



C

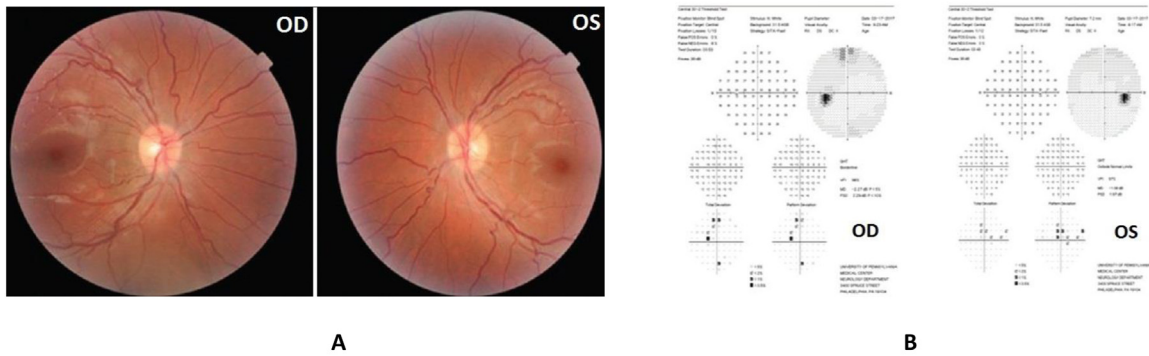
**Figure 1.** On admission, (A) there was a bilateral edematous, crowded, and elevated optic disc on dilated fundus examination (modified Frisén scale II); (B) the Humphrey visual field demonstrated severe bilateral visual field narrowing; and (C) OCT indicated bilateral increased retinal nerve fiber layer thickness.

eyes, the visual field was better, papilledema resolved, and disc pallor appeared. His CSF pressure was 28 cm H<sub>2</sub>O on entry, and cell analysis revealed 195 new erythrocytes with no old erythrocytes or leukocytes. The oral acetazolamide dose was increased to 500 mg twice a day because intracranial pressure (ICP) was still high. At the second follow-up session 3 months after treatment, he needed no medical treatment because of visual acuities of 6 of 6 in both eyes and near-normal visual fields (Fig. 2).

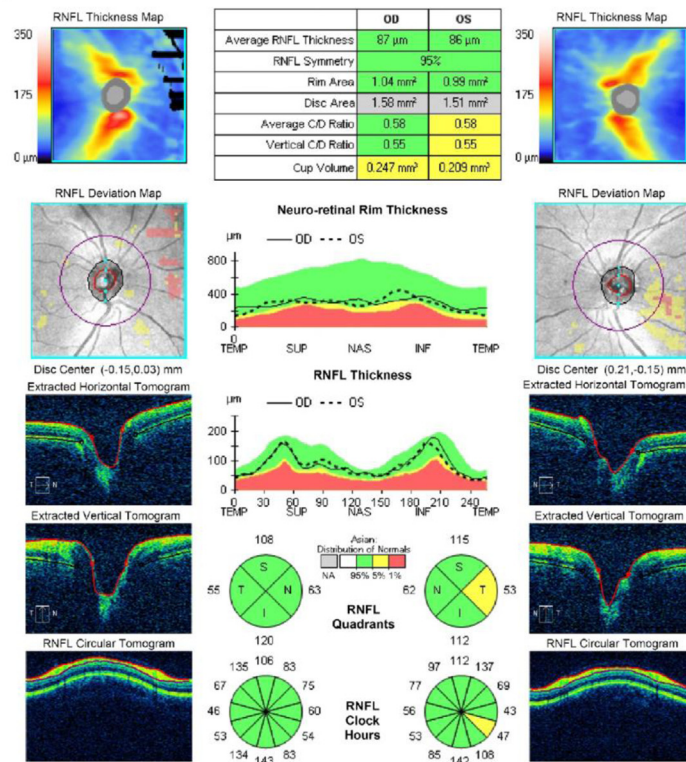
Based on the Federal Aviation Administration regulations (title 14/ chapter I/subchapter D/part 67/subpart B/section 67.103) and the importance of flight safety in air medical transportation operations, the Air Medical Council (AMC) suspended him from flight duties until complete recovery and the absence of any possible complications confirmed by the AME.

**Discussion**

IH has many causes, including IIH, intracranial space-occupying lesions (tumor, hemorrhage, foreign body, and so on), cerebral venous sinus thrombosis, increased CSF production (obesity), reduced CSF absorption (COVID-19 infection), medical and psychological conditions (renal failure, obstructive sleep apnea syndrome, Addison disease, severe anemia, and depression), and medications (vitamin A, oral contraceptive pills, tetracycline, and so on). Obesity (body mass index > 30 kg/m<sup>2</sup>), CSF dysregulation, glucagon-like peptide 1, glucocorticoid metabolism, hormonal dysregulation, venous hypertension, and SARS-CoV-2 infection (intracranial venous thrombosis) are the risk factors for IH. IIH is a neurologic disorder characterized by increased intracranial pressure without evidence of intracranial space-occupying lesions (tumor, hemorrhage, foreign



**ONH and RNFL OU Analysis: Optic Disc Cube 200x200** OD OS



C

**Figure 2.** Three months after the initiation of treatment, (A) there was a persistent resolution of papilledema with mild gliosis of both optic nerves on dilated fundus examination; (B) the Humphrey visual field demonstrated mild enlargement of both blind spots and nonspecific depression; and (C) OCT indicated normal retinal nerve fiber layer thickness.



**Table 1**  
Modified Dandy Criteria for Idiopathic Intracranial Hypertension Diagnosis

Symptoms of raised intracranial pressure:
1. Throbbing intense daily headaches
2. Pulsatile unilateral or bilateral tinnitus
3. Nausea
4. Dizziness
5. Transient visual obscurations as “graying” or “blacking out” of vision in 1 or both eyes and lasting seconds
6. Unilateral or bilateral sixth nerve palsy as horizontal diplopia
7. Cognitive impairment
8. Papilledema
Normal neurologic examination (with the exception of sixth nerve palsy)
Normal brain imaging (computed tomographic scan, magnetic resonance imaging, computed tomography or magnetic resonance venography)
Raised lumbar puncture opening pressure (> 25 cm H <sub>2</sub> O) with normal cerebrospinal fluid
Alert and awake patient

body, and so on) or any other underlying disease. IIH is a rare condition; however, increasing numbers of patients are being reported. Previously, the incidence in the general population was reported to be between 0.5 and 1.0 per 100,000. Women of childbearing age and who have a body mass index > 30 kg/m<sup>2</sup> have a higher risk of IIH development than men. IIH is more common in the United Kingdom, Italy, Israel, and the United States, but Asia has a lower incidence. IIH has a spectrum of manifestations; the most common are presented in Table 1.<sup>8–11</sup>

Papilledema is a neuro-ophthalmologic emergency requiring eminent identification, investigations, and rapid multidisciplinary management.<sup>12</sup> Papilledema in dilated fundus examination confirms IIH diagnosis. The guidelines recommend that papilledema must be confirmed by an experienced specialist. Fundus photography is a sensitive method for the detection of papilledema, especially by nonexpert physicians. However, OCT, OCT angiography, and fundus fluorescence angiography are helpful too. Because of diagnostic and management importance, the assessment of visual acuity, color vision, pupil assessment, dilated fundus examination, formal visual fields, and blood pressure (for excluding malignant hypertension) are necessary for patients with IIH. Neuroimaging (CT scan, magnetic resonance imaging, or CT/magnetic resonance venography) is necessary to exclude secondary causes of elevated ICP and to identify structural alterations associated with raised ICP, especially before lumbar puncture. If neuroimaging is normal, the patient undergoes a lumbar puncture in the left lateral recumbent position to assess CSF constituents (which should be normal in IIH) and check the opening pressure.<sup>8–11</sup>

The IIH guideline suggests 3 principles for management: 1) addressing the underlying modifiable risk factor (weight loss), 2) protecting the vision through regular assessment and escalation of treatment when sight is threatened, and 3) reducing the headache morbidity through active management. It also gives consensus recommendations for attention to comorbid conditions, pregnancy, managing headache in the shunted patient and IIH without papilledema, and the timely follow-up of patients reflecting the status of their optic nerve head and visual field assessment.

Based on the patient's clinical condition, the management of IIH may be medical, surgical, or hybrid. Oral acetazolamide, a carbonic

anhydrase inhibitor, is usually prescribed 250 or 500 mg 2 or 3 times a day, up to a maximum dose of 1,500 mg. Paresthesia, dysgeusia, vomiting, diarrhea, malaise, fatigue, and depression are the possible side effects of acetazolamide. Topiramate is a migraine prophylactic with mild carbonic anhydrase inhibitor activity and additional appetite suppressant action. Common side effects include reduced appetite, paresthesia, and cognitive and concentration impairment.

Surgical shunting is definitive management and has disadvantages of invasion and infection risk, which may require revisions in up to one third of patients. Adjustable valves (antigravity or antisiphon devices) can reduce the risk of low-pressure headaches in the long-term. Optic nerve sheath fenestration surgery is another option. Disadvantages of this surgical approach include persistently raised ICP, risk of vision loss, and diplopia. If surgery is delayed or canceled, the lumbar drain can be inserted to protect vision in the intervening period. Weight loss is an effective method for improving headache and papilledema and reducing ICP in obese patients. Bariatric surgery is the most effective method for sustained weight loss, which results in 15% to 30% weight loss over 15 to 20 years depending on the surgical procedure. Gastric bypass (Roux-en-Y) surgery is an effective method for reducing weight, which can result in a concomitant reduction in ICP and reduction or resolution of papilledema, headache, and tinnitus. Gastric sleeve surgery has also been reported to be useful.

The course of the disease is variable, and visual monitoring is essential for patients with active disease. If there is a deteriorating visual function, more steps in management may be required. Imaging the fundus (color fundus photography) is useful for longitudinal assessment. OCT is increasingly being used to objectively monitor changes in the retinal nerve fiber layer and the optic nerve head disc volume to track papilledema.

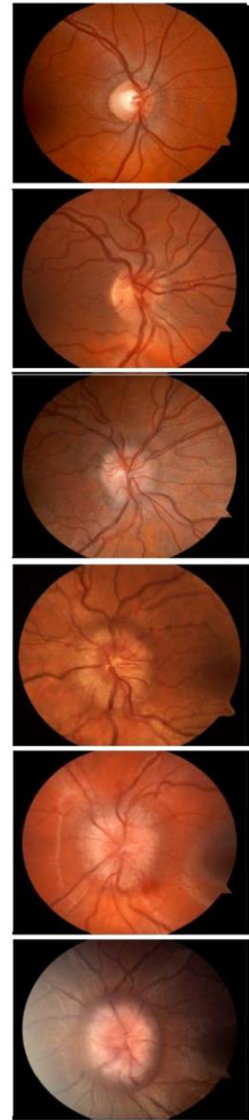
The severity of papilledema (as graded using the modified Freson scale) is a predictor of final visual outcome rather than cotton wool spots or retinal hemorrhages as previously thought (Fig. 3).<sup>8–10,13</sup> Weight gain and lack of exercise promote the development of headaches, sleep disturbances, depression, and recurrent episodes of IIH in the future.<sup>10,11</sup>

The Mil Mi-17 is a Russian medium twin-turbine transport helicopter that uses a powerful engine with 5 blades, giving it a high lifting capacity and good performance in “hot and high” conditions. This helicopter retains the outstanding performance characteristics of its predecessors and can fly in tropical, maritime, and desert conditions. The large cabin of the helicopter offers a floor area of 12.5 m<sup>2</sup> and an effective space of 23 m<sup>3</sup>. The standard portside door and ramp at the rear allow for the quick ingress and egress of troops and cargo. The Mil Mi-17 can be fitted with an extended starboard sliding door, rappelling and parachute equipment, searchlight, Forward-Looking InfraRed (FLIR) system, and emergency flotation system. This helicopter has a crew of 3, including the pilot, copilot, and flight engineer. The Mil Mi-17 can carry 24 passengers or even small vehicles. This helicopter is 1 of the most prolific utility helicopters ever built and is well suited for regional military or commercial transport needs.

Based on the Federal Aviation Administration regulations (title 14/ chapter I/subchapter D/part 67/subpart B/section 67.103) and the importance of flight safety in air medical transportation operations, these pilots must have intact visual function, and pilots with any ophthalmologic impairment may be a potential safety hazard. The complete recovery and absence of any possible complications of aviators with a history of COVID-19 or vaccination must be considered by the AMC according to the policy memo regrading AME evaluations of airmen and air traffic control specialists with a history of COVID-19 or vaccination.<sup>14</sup>

The IIH and bilateral low-grade papilledema in a healthy and physically fit male pilot with no medical history (except for receiving the first dose of the Sputnik V vaccine 12 days ago) and presentations of several extrapulmonary complications after COVID-19 pneumonia or COVID-19 vaccines in the literature indicated that the Sputnik V

- STAGE 0: Normal optic disc or not a normal disc but with no C-shaped halo
- A. Prominence of the retinal nerve fiber layer at the nasal, superior, and inferior poles in inverse proportion to disc diameter
- B. Radial nerve fiber layer striations, without tortuosity
- STAGE I: Minimal degree of edema
- A. C-shaped halo that is subtle and grayish with a temporal gap; obscures underlying retinal details\*
- B. Disruption of normal radial nerve fiber layer (NFL) arrangement striations
- C. Temporal disc margin normal
- STAGE II: Low degree of edema
- A. Circumferential halo\*
- B. Elevation: nasal border
- C. No major vessel obscuration
- STAGE III: Moderate degree of edema
- A. Obscuration of 1 or more segments of major blood vessels leaving disc\*
- B. Circumferential halo
- C. Elevation: all borders
- D. Halo: irregular outer fringe with finger-like extensions
- STAGE IV: Marked degree of edema
- A. Total obscuration of a segment of a major blood vessel on the disc\*
- B. Elevation: whole nerve head, including the cup
- C. Border obscuration: complete
- D. Halo: complete
- STAGE V: Severe degree of edema
- A. Partial obscuration of all vessels on disc and total obscuration of at least 1 vessel on disc\*



**Figure 3.** The modified Frisén scale of papilledema.<sup>10</sup>

vaccine may be the leading cause for the neuro-ophthalmic abnormalities in the presented case. However, this is a primary clinical suspicion that must be confirmed after complete investigations.

## Conclusions

Unprecedented strategies have been instigated globally to deal with the COVID-19 pandemic. This resulted in much of the world's population being subjected to lockdown from the end of 2019. So far, COVID-19 and its vaccines have caused different complications to service recipients, especially neurologic complications. There were many reports of IH and papilledema associated with COVID-19 infection in the literature. Air medical transportation pilots are involved with operational and medical stressors; therefore, pilots' health becomes a prominent factor in in-flight safety.<sup>1–4,8,13</sup> We reported the first case of papilledema and IH after adenoviral DNA vector-based COVID vaccination after ruling out the other possible causative or predisposing factors. However, confirmation of IH as a complication of adenoviral DNA vector-based COVID vaccines needs more accurate investigations in the future. The authors recommend that 1) all air medical

transportation pilots must be aware that they will not be allowed to fly if they have any post-COVID-19 vaccine complications, 2) the AMC must suspend these aviators from flight duties until complete recovery and the absence of any possible complications confirmed by the AME, 3) these aviators must be medically assessed for possible complications regularly in short intervals, and 4) this case is an aviation safety concern that needs more accurate investigations and revision of the current regulations in the future.

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