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Intracranial hypertension and papilloedema; an unusual complication after the adenoviral DNA vector-based COVID-19 vaccination in an air medical transportation pilot

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## Article Title

Intracranial hypertension and papilloedema; an unusual complication after the adenoviral DNA vector-based COVID-19 vaccination in an air medical transportation pilot

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Conceptualization, Validation, Investigation, Resources, data curtain, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision and Funding acquisition.

**Ethics approval and consent to participate:**

The ethical approval of this study was issued with registration No#12201411 by the Ethics Committee of the Medical Faculty in Aja University of Medical Sciences. However, current article was merely a descriptive study (case report) without pre-designed prescription of the new therapeutic or pharmacological interventions on humans or animals (clinical trial study). Thus, IRB approval was not achieved.

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**Article Title:**

Intracranial hypertension and papilloedema; an unusual complication after the adenoviral DNA vector-based COVID-19 vaccination in an air medical transportation pilot

**Abstract**

A 32-year-old male Mil Mi-17 (air medical transport) helicopter pilot presented to the emergency with a headache and visual blurring twelve days after the first dose of the Sputnik V vaccine. He had no past medical history, successfully passed his last annual medical exam, and his vital signs were in the normal range. Significant findings were decreased visual acuity, papilloedema, severe visual field narrowing, and increased nerve fiber layer thickness in both eyes. The Aviation Medical Examiner (AME) suspended him from flight duties and referred him for a complete neuro-ophthalmic investigation. The patient underwent a lumbar puncture, cerebrospinal fluid (CSF) pressure was 39 cm H<sub>2</sub>O, and CSF biochemical analysis and blood test were normal. He refused ventriculoperitoneal shunt surgery and received methylprednisolone with acetazolamide. After ten days, the patient reported a significant improvement, and 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 due to 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 can't return to flight duties until his full neuro-ophthalmic recovery was confirmed.

**Keywords:** COVID-19, SARS-CoV-2, Papilloedema, Intracranial hypertension, Adenoviral vector-based vaccine, Sputnik V vaccine, Air medical transportation

### **Introduction:**

Coronavirus Disease 2019 (COVID-19) mostly affects the respiratory system ranging from mild flu-like symptoms to severe acute respiratory syndrome (SARS). However, several extra-respiratory multi-systemic involvements (such as neurologic, hematologic, cardiac, gastrointestinal, etc.) have been reported. [1, 2]

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. The Sputnik V (Gam-COVID-Vac), a common adenoviral DNA vector-based COVID-19 vaccine, is utilized based on the heterologous recombination of adenovirus 26 (Ad26) and adenovirus 5 (Ad5) as vectors for expression of the SARS-CoV-2 spike protein. At first, the Sputnik V is approved by many countries and used two 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

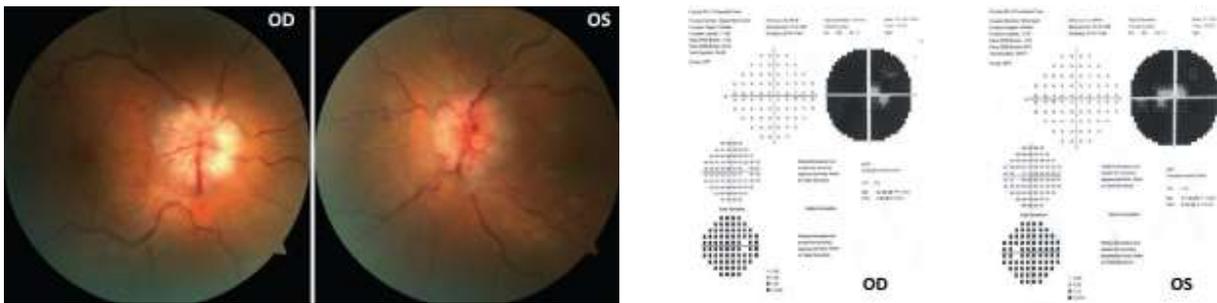
immunoglobulin that inhibits the virus binding to its receptor. They also showed evidence of T-cell responses, consistent with an immune response that should not quickly wane. [3-5] However, the development of the Sputnik V vaccine has been criticized for unseemly haste, corner-cutting, and a lack of transparency. Its adenoviral load is beyond the limit value and result in a dilemma of usage in many countries due to the possible side effects. [4-7]

Here we presented the first reported case of unusual intracranial hypertension and papilloedema after receiving the first dose of the Sputnik V vaccine in an air medical helicopter pilot.

### **Case Report:**

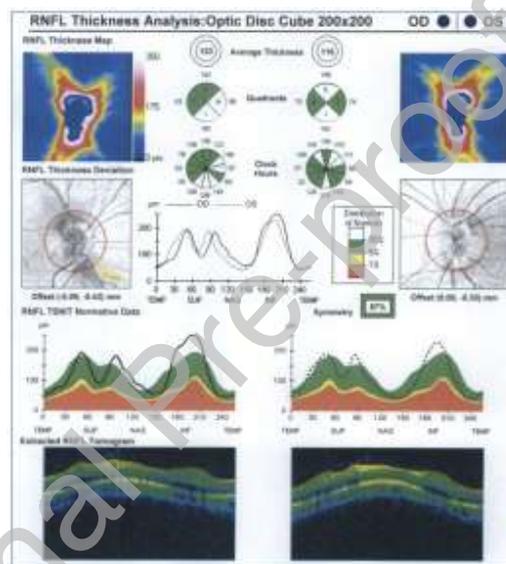
The patient was a 32-year-old Caucasian male Iranian Red Crescent Society pilot flying with a Mil Mi-17 air medical transport helicopter. He had a total flight of 1520 hours, successfully passed his last annual medical exam 239 days ago, and had no past medical history. After receiving the first dose 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 (FAA) regulations. One day later, he referred to the AME with the complaint of gradual onset of mild headache, dizziness, and weakness. The AME extended the grounding time for 2 weeks, prescribed Naproxen 500 mg three times a day, and advise to refer again if needed. The symptoms gradually intensified and became

intolerable on the twelfth 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>. The patient His vital signs included an oral temperature of 37.1°C, blood pressure of 115/75 mmHg, heart rate of 76 beats/minute, respiratory rate of 14 breaths/minute, and blood oxygen saturation of 98% in room air. Nasopharyngeal SARS-CoV-2 RT-PCR 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 neurological examination. The best-corrected Snellen visual acuity of 6/12, edematous, crowded, and elevated optic discs without vessel obscuration, hyperemia, hemorrhage, or drusen in dilated fundus examination (modified Frisén scale II), severe visual field narrowing in Humphrey visual field testing, and increased nerve fiber layer thickness in optic nerves coherence tomography (OCT) were significant findings in both eyes (Fig 1).



A

B



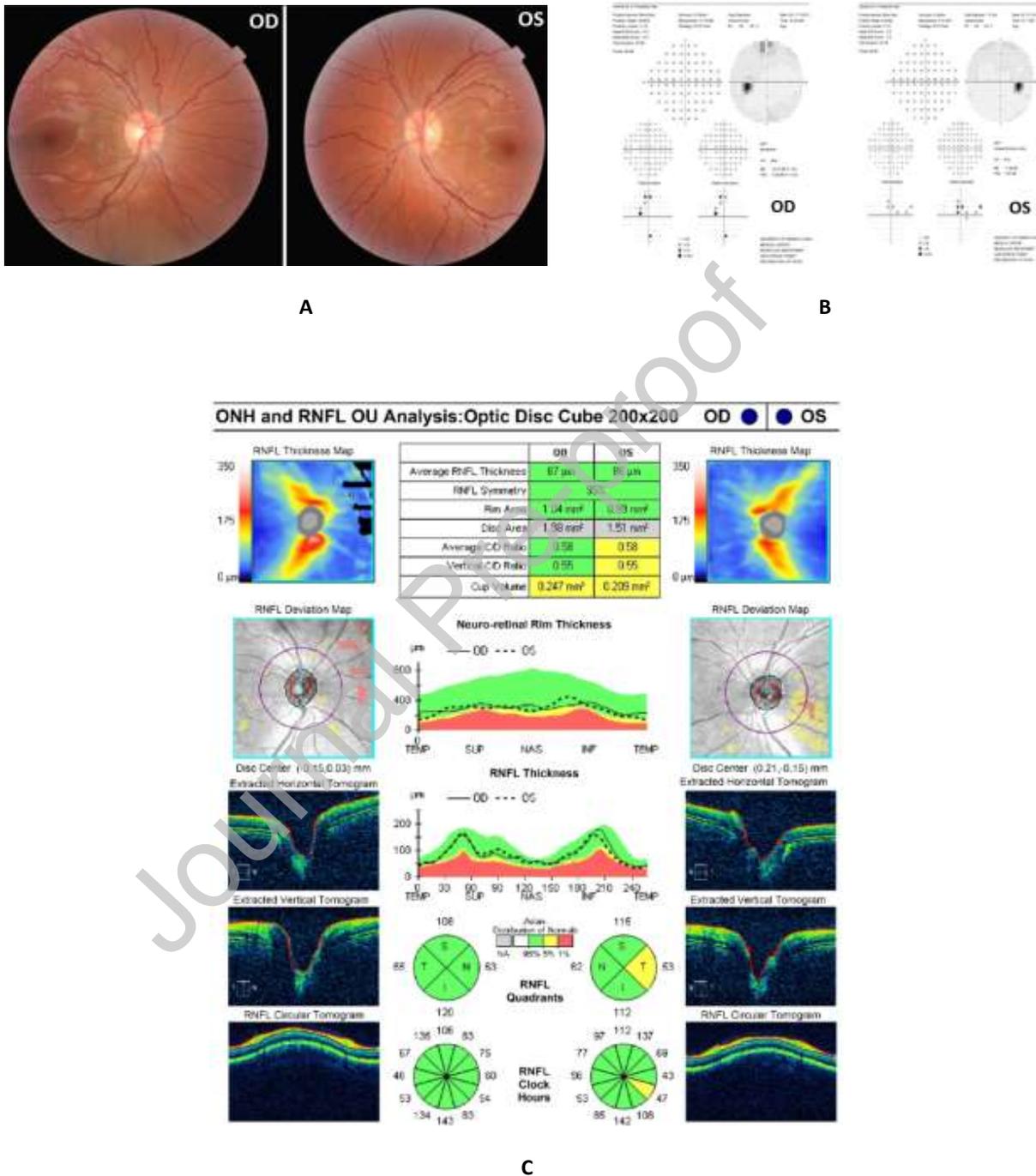
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**Figure 1:** On admission. A) There was a bilateral edematous, crowded, and elevated optic discs in dilated fundus examination (modified Frisén scale II), B) Humphrey visual field demonstrated severe bilateral visual field narrowing, and C) OCT indicated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

The B-scan ultrasonography was negative for optic nerve head drusen. Brain magnetic resonance imaging (MRI) revealed no space-occupying lesion (mass or hemorrhage), and MR venography was normal too. He underwent a lumbar puncture (LP), 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 of protein level, 59 mg/dL of 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 (WBCs; 46/mm<sup>3</sup>) with 100% polymorphonuclear leukocytes (PMNs). CSF aquaporin-4 antibodies, oligoclonal bands, and SARS-CoV-2 RT-PCR test were negative. Blood tests were in normal ranges, and negative serum anti-NMO (CBA 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 TDS for 10 days. After 10 days of treatment, the patient reported a significant improvement in symptoms and was discharged. On the first follow-up session one month later, his visual acuities were 6/7.5 in both 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 and no old erythrocytes and leukocytes. The oral acetazolamide dose increased to 500 mg BID because intracranial pressure was still high. On the second follow-up session three months after treatment,

he needed no medical treatment due to visual acuities of 6/6 in both eyes and near-normal visual fields (Fig 2).



**Figure 2:** Three months after the initiation of treatment. A) There was a persistent resolution of papilledema with mild gliosis of both optic nerves dilated fundus examination, B) Humphrey visual field demonstrated mild

enlargement of both blind spots and nonspecific depression, and C) OCT indicated normal retinal nerve fiber layer thickness.

Based on the FAA 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:**

Intracranial hypertension (IH) has many causes that include; idiopathic intracranial hypertension (IIH), intracranial space-occupying lesions (tumor, hemorrhage, foreign body, etc.), cerebral venous sinus thrombosis (CVST), increased CSF production (obesity), reduced CSF absorption (COVID-19 infection), medical and psychological conditions (renal frailer, obstructive sleep apnea syndrome, Addison's disease, severe anemia, depression), medications (vitamin A, oral contraceptive pills, tetracycline, etc.). Obesity (BMI>30 kg/m<sup>2</sup>), CSF dysregulation, glucagon-like peptide 1, glucocorticoid metabolism, hormonal dysregulation, venous hypertension, SARS-CoV-2 Infection (intracranial venous thrombosis) are the risk factors for IH. Idiopathic intracranial hypertension (IIH) is a neurological disorder characterized by increased intracranial pressure without evidence of intracranial space-occupying lesions (tumor, hemorrhage, foreign body, etc.) 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 ages and who have a body mass index (BMI) greater than 30 kg/m<sup>2</sup> have more risk of IIH development than men. IIH is more common in the UK, Italy, Israel, and the US, but Asia has a lower incidence. IH has a spectrum of manifestations; the most common were presented in

Table 1. [8-11]

Symptoms of raised ICP:
1-Throbbing intense daily headaches
2-Pulsatile unilateral or bilateral tinnitus
3-Nausea
4-Dizziness
5-Transient visual obscurations as 'greying' or 'blacking out' of vision in one or both eyes and lasting seconds
6-Unilateral or bilateral sixth-nerve palsy as horizontal diplopia
7-Cognitive impairment
8-Papilloedema
Normal neurological examination (with exception of sixth-nerve palsy)
Normal brain imaging (CT-scan, MRI, CT or MR venography)
Raised LP opening pressure (>25 cm H <sub>2</sub> O) with normal CSF
Alert and awake patient

Table 1: Modified Dandy criteria for IIH diagnosis

Papilloedema is a neuro-ophthalmological emergency requiring eminent identification, investigations, and rapid multidisciplinary management. [12] Papilloedema in dilated fundus examination confirms IH diagnosis. The guidelines recommend that papilloedema

must be confirmed by an experienced specialist. Fundus photography is a sensitive method for the detection of papilloedema, especially by non-expert physicians. However, OCT, OCT angiography, and fundus fluorescence angiography (FFA) are helpful too. Due to diagnostic and management importance, 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, MRI, or CT/MR venography) is necessary to exclude secondary causes of elevated ICP and to identify structural alterations associated with raised ICP, especially before LP. If neuroimaging was normal, the patient undergoes a lumbar puncture in the left lateral recumbent position to assess CSF constituents (which should be normal in IIH) and checks the opening pressure. [8-11]

The IIH guideline suggests three 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 gave consensus recommendations for attention to co-morbid conditions, pregnancy, managing headache in the shunted patient and IIH without papilloedema, 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 intracranial hypertension may be medical, surgical, or hybrid. The oral acetazolamide, a carbonic anhydrase

inhibitor, is usually prescribed 250 or 500 mg two or three times a day, up to a maximum dose of 1500 mg. Paraesthesia, 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, paraesthesia, and cognitive and concentration impairment.

Surgical shunting is definitive management and has disadvantages of invasion, and infection risk and may require revisions in up to one-third of patients. 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 anti-siphon devices) can reduce the risk of low-pressure headaches in the long term. Optic nerve sheath fenestration (ONSF) 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 papilloedema, and reducing ICP in obese patients. Bariatric surgery is the most effective method for sustained weight loss, which results in 15-30% weight loss over 15-20 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 papilloedema, 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 utilized to objectively monitor changes in the retinal nerve fibre layer (RNFL) and the optic nerve head disc (ONH) volume to track papilloedema.

The severity of papilloedema (as graded using the modified Frisén scale) is a predictor of final visual outcome, rather than cotton wool spots or retinal hemorrhages, as previously thought (Figure 3). [8-10, 13]

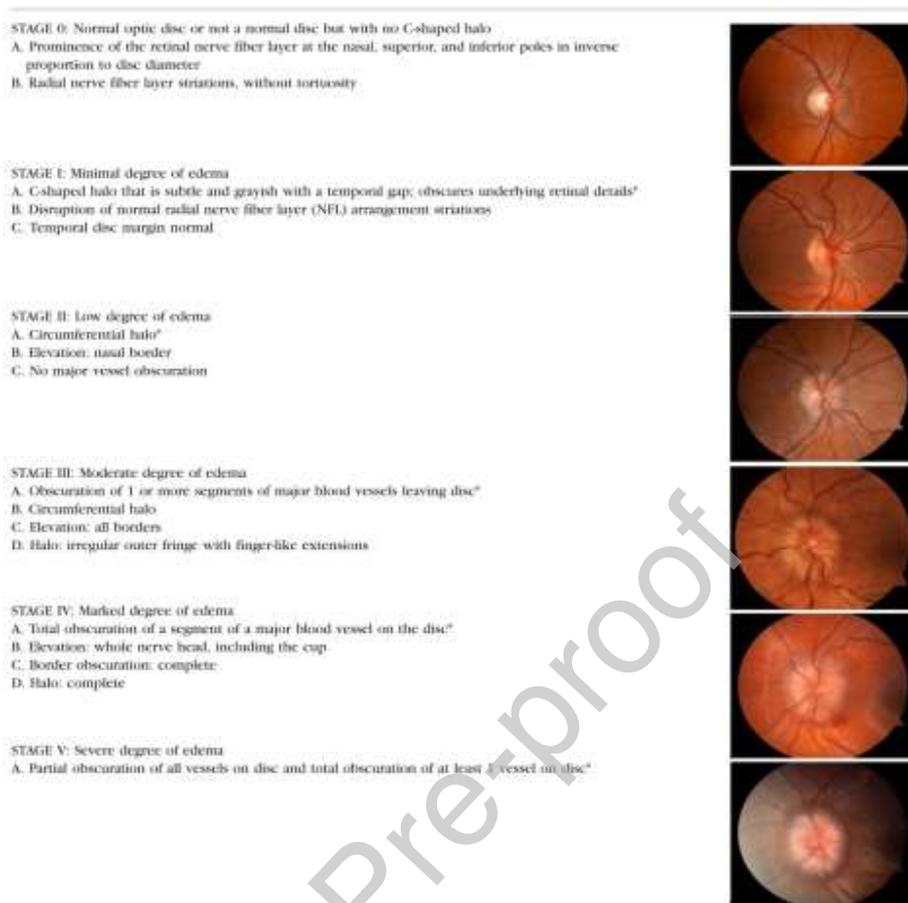


Figure 3: Modified Frisén Scale of Papilledema [10]

Weight gain and lack of exercise promote the development of headaches, sleep disturbances, depression, and recurrent episodes of IIH in the future. [10, 11]

The Mil Mi-17 is a Russian medium twin-turbine transport helicopter that uses a powerful engine with a five-blade, 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, FLIR system, and emergency flotation system. This helicopter has a crew of 3, including the pilot, co-pilot, and flight engineer. The Mil Mi-17 can carry 24 passengers or even small vehicles. This helicopter is one of the most prolific utility helicopters ever built and is well-suited for regional military or commercial transport needs.

Based on the FAA 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 Regarding AME Evaluations of Airmen and ATCS with a History of COVID-19 or vaccination [14].

Idiopathic intracranial hypertension (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 twelve days ago), and presentations of several extra-pulmonary complications following the COVID-19 pneumonia or COVID-19 vaccines in literature indicated that the Sputnik V vaccine may be the main cause for our case

neuro-ophthalmic abnormalities. 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 neurological complications. There were many reports of intracranial hypertension and papilledema associated with COVID-19 infection in the literature. Air medical transportation pilots are involved with operational and medical stressors, and so the pilots' health becomes a prominent factor in-flight safety. [1-4, 8, 13] We reported the first case of papilloedema and intracranial hypertension following the adenoviral DNA vector-based COVID vaccination after ruling out the other possible causative or predisposing factors. However, confirmation of intracranial hypertension as a complication of adenoviral DNA vector-based COVID vaccines needs more accurate investigations in the future. The authors recommended 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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Investigation, Resources, data curtain, Writing - Review & Editing, Visualization and Project administration.

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Conceptualization, Validation, Investigation, Resources, data curtain, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision and Funding acquisition.