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Short report

Lifting the mask on neurological manifestations of post COVID-19 vaccination; Case series

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ABSTRACT

The most encouraging approach of struggling COVID-19 and limiting the course of this pandemic was certainly the universal vaccination of the population with safe and effective vaccines. As mass vaccination initiatives against COVID-19 ensued, adverse reactions began emerging. The current case series illustrated eleven (11) patients who presented with neurological sequelae after receiving different types of COVID vaccine. This was not the first case series that discusses post COVID-19 vaccine neurological problems worldwide but rare in Egypt. These case series included five (5) cases had cerebrovascular accident, two (2) cases presented with encephalitis, and only one was diagnosed as a central retinal vein occlusion; and another one had new onset seizure; meanwhile, headache was diagnosed in two (2) cases. It was suggested that after SARS-CoV-2 vaccination, a reactivation of the immune system causes neurological symptoms. However, further research was merited to provide more visions into this hypothesis drawn in this study.

Introduction

The most encouraging approach of struggling COVID-19 and limiting the course of this pandemic is certainly the universal vaccination of the population with safe and effective vaccines. Several vaccines are in the pipeline and some of them have already been approved or granted emergency use authorization and are administered in multiple countries globally [1, 2]. 100 reports of Guillian Barre Syndrome (GBS) following vaccinations with adenovirus vector COVID-19 vaccines were received from February 27th to June 30th, 2021 with approximately 12.2 million of doses administered [3]. The GBS reporting rate was highest among males aged 50–64 years. The median interval between vaccination and symptom onset

was 13 days (range: 0–75 days) [4]. Cases of acute transverse myelitis, as well as cases of acute disseminated encephalomyelitis have been described in the literature [5-7]. During post market surveillance, only a few cases of facial palsy following COVID-19 vaccination have been described [8,9]. As more patients gain access to the coronavirus disease 2019 (COVID-19) vaccines, neurologists are facing questions about potential neurological complications, benefits, and timing of vaccination. Although a causal relationship was not established, the recommendation for further monitoring has led to the publication of many case reports worldwide [10]. Multiple studies have reported neurological symptoms in patients with

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SARSCoV-2-infection, but information about neurological complications after SARSCoV-2 vaccination is sparse. Here, we outline the clinical manifestations, treatment response, and outcome of various cases that came to the hospitals of Aswan and Sixth October Universities between August 2021 and March 2022 with a variety of neurological presentations, summarized in **table (1)** after receiving varying COVID-19 vaccinations. To the best of the authors' knowledge, no case report of post-COVID-19 neurological manifestations has been published in Egypt, at the time of writing.

Methods

Ethics approval and consent to participate

The current study was approved by the Institutional Ethics Committee, Faculty of Medicine, our University. Approval for the study was obtained from the IRB committee of our Medical Faculty. All patients were provided with complete information about the study objectives, methods, and risk/benefit assessment. A written consent was obtained from each participant upon acceptance to take part in the study. The study was performed in accordance with the Declaration of Helsinki.

Consent for publication

A written informed consent for publication was obtained from each participant.

Availability of data and materials

The corresponding author takes full responsibility for the data, has full access to all of the data, and has the right to publish any and all data separate and apart from any sponsor.

Case 1 and 2 (Encephalitis)

Patient 1

A 56-year-old male patient, was known to have diabetes mellitus and hypertension, was admitted to our unit for high grade fever (39-41⁰c), truncal ataxia. His condition had acute onset that occurred 3 days after receiving first dose of Covid-19 vaccine (AstraZeneca). A non-contrast CT scan brain was performed and showed no definite findings. Two days later on, he developed quadriplegia and disturbed conscious level (stupor). 2nd brain imaging (MRI) showed brain edema without any other abnormalities (**Figure 1**). Electroencephalography (EEG) showed diffuse slowing brain dysrhythmia. His blood pressure was 190/100 mmHg. Laboratory tests included blood glucose level, liver function tests, and serum electrolyte levels, were normal. The

only abnormal laboratory findings was presence of renal impairment. Encephalitis was suspected. Before doing CSF examination, he was discharged on request on the 2nd day of admission.

Patient 2

A male patient aged 28y, cigarette smoker presented with low grade fever (38.5⁰C), behavioral changes in the form of hallucinatory behavior and auditory hallucination. He was disoriented for time, places and persons. 10 days before the onset of his complaint, he received second dose of Covid-19 vaccine (AstraZeneca). Electroencephalogram was done at admission and showed diffuse slowing while brain imaging (CT scan) showed no definite findings. CSF was done and showed no definite abnormalities. The patient condition was diagnosed as viral encephalitis. He received antiviral drugs (Acyclovir for 14 days), antibiotics (vancomycin and ceftriaxone), antipyretics (paracetamol) and I.V. fluids. Within 10 days after admission, the patient condition was improved completely.

Case 3,4,5,6 and 7 (Acute cerebrovascular stroke, AIS)

Patient 3

Male Smoker patient aged 36y old, known to be diabetic. There was no history of other risk factors. He was received Sino farm vaccine (1st dose) 5 days before onset of his complaint. He presented to our neurological emergency unit with acute onset of disturbed conscious level (Glasgow Coma Scale, GCS 5). He had low grade fever (37.8⁰C-38.5⁰C) associated with aspiration pneumonia. Blood analysis included serum level of electrolytes (calcium, phosphorus, magnesium, potassium and sodium), complete blood count, complete renal function tests, complete liver function tests and coagulation profile were done. The only abnormal finding was hypocalcemia. CT chest was done and revealed bilateral basal consolidation. MRI brain was done at admission, showing massive ischemic cerebral infarction (Water shed infarction) (**Figure 2**). Echocardiography detected no abnormal data. His respiration was tachypneic and dyspneic and so he was intubated. Patient was received pulse therapy for 5 days, I.V. fluids, antibiotics (Averozolid and Maxiflox), antipyretics (Paracetamol), antiplatelet (baby Aspirin) and anticoagulants to guard against deep venous thrombosis (DVT). Within 20 days after admission, he was died.

Patient 4

A 62 y-old male smoker patient, known to have diabetes mellitus and hypertension. He was presented at our neurological emergency unit by left focal motor (tonic-clonic fits affecting left upper and lower limbs) fits with secondary generalization & manifestation suggestive of COVID infection (generalized fatigue and malaise, cough, fever, dyspnea). Before the onset by 3 days, he was received AstraZeneca vaccine (2nd dose). At admission, laboratory investigations including complete blood count, complete liver function tests, renal function tests, blood glucose level and serum levels of electrolytes, were done and showed no abnormal data except for increased total leukocytic count (17.000/cmm). CT brain showed right cerebral ischemic Infarction (at basal ganglia). CT chest showed picture suggestive of CO-RAD5. The patient was transmitted to isolation ICU and nasopharyngeal swab was done whose result was positive for COVID-19 infection. Patient was received antiplatelet, antihyperlipidemic (Ator 40), antiepileptic (levetiracetam, 1000 mg twice daily) plus treatment of COVID infection. Within 10 days, the patient was discharged after complete improvement of his condition stoppage of fits.

Patient 5

A female patient aged 56ys old, presented by left hemiplegia and dysarthria of acute onset. She had diabetes mellitus and hypertension. Five days before her condition she was received anti-covid vaccination (AstraZeneca) 1st dose. The National Institutes of Health Stroke Scale (NIHSS) was 14. Brain imaging (CT) was done at admission and showed no abnormalities. The results of her laboratory studies were irrelevant. She was presented in time window (one and half hour) and so thrombolytic therapy was decided and actylase injection was administered. Within 24 hours her weakness was partially improved. After another 2 days she was discharged.

Patient 6

A male patient aged 58ys old, known to be diabetic and hypertensive. He was received 2nd dose of anti-covid vaccine (AstraZeneca) one day before his illness. He presented by acute onset of left sided hemiplegia and left facial nerve weakness of upper motor criteria. The results of his laboratory studies were irrelevant. Brain CT was done at admission and showed no abnormal data. She was received antiplatelet (Aspocid 75 mg two tablets once daily), brain nootropics (Stimulan tablets 800 mg twice

daily) and Vitamin B complex injection. On request, the patient was discharged at the day of admission before doing MRI brain.

Patient 7

A 56y, diabetic female was received 1st dose of anti-covid (AstraZeneca) 3days before admission. She presented with left sided hemiplegia, dysarthria. laboratory investigations showed no abnormal data. CT brain was normal (first CT) while, follow up CT (was done at second day of admission) showed right capsular ischemic infarction. Echocardiography showed no abnormality. She was received antiplatelet, antihyperlipidemic and brain stimulant. She was discharged within 5 days with residual left hemiparesis.

Patient 8 (Central retinal vein occlusion)

A 46y-old-highly functional female at baseline without significant comorbidities presented to the emergency department with acute onset of diminution of vision in left eye. She received her first dose of the Johnson COVID vaccine one week prior to presentation. By ophthalmological examination, there was no other abnormal data. Otherwise, her neurological examination was clinically irrelevant. Routine labs were unrevealing. MRI brain with contrast was performed and showed tiny right parietal subcortical focus of high T2 signal (**Figure 3 A**). MRV of brain showed no abnormalities. Her fundus Examination showed picture suggestive of central retinal vein occlusion. Angiography of both eyes showed impending central retinal vein occlusion in left eye (**Figure 3 B**). She was received anticoagulant therapy (Rivoraspire 15 mg once daily). Her condition was improved mildly within 5 days. After another 2 days, she was discharged on request without any noticeable improvement from before.

Patient 9 (New onset seizures)

A diabetic 51ys old previously well male patient without any other comorbidities, was received anti-Covid vaccine (AstraZeneca, first dose) one week before presentation. He was presented with four episodes of witnessed generalized tonic-clonic seizures. This was associated with low grade fever (37.7^oC-38.8^oC) and cough. CT chest was suspected and showed bilateral ground glass opacities. CT brain and MRI were performed and did not reveal any abnormality of the brain. He was admitted in isolation ICU and Nasopharyngeal swab was positive for Covid-19 infection. Electroencephalogram was not done because of

infection control. Laboratory investigations were irrelevant. He was received Levetiracetam (1000mg twice daily), antipyretics, steroids and antibiotics. He was discharged after 10 days with complete improvement.

Case 10 and 11 (Headache)

Patient 10

A female patient aged 45y old had hypertension, presented by severe headache 5 days after receiving second anti-covid vaccination (Pfizer). This headache was bursting in character, more at the vertex, lasted most of the day. It was not referred or radiated to any site. It was associated with dryness and tightness of her hands and feet. No other associated symptoms. Her laboratory investigations were irrelevant. Her brain CT scan and MRV showed no definite abnormalities. After receiving analgesics (Paramol 1 gm twice daily) plus steroid

injection (once daily) for two days, she was discharged with complete improvement.

Patient 11

A 35y old female patient had no diseases. She was presented by severe headache two days after receiving second anti-covid vaccination (AstraZeneca). This headache was bursting in character, more at the occiput. It was referred to the neck. It lasted whole day without changing in its intensity. It did not decrease with rest or sleep. It was associated with nausea but not with vomiting or blurring of vision. Her laboratory investigations (complete blood count, renal function tests, liver function tests) were irrelevant. Brain imaging (MRI) and MRV were normal. She was discharged at the 2nd day with complete improvement after receiving analgesics, steroid injection and tricyclic antidepressants (Tryptazol 25 mg) .

Table 1. shows all clinical, and demographic data of patients who presented with neurological sequelae after receiving different types of COVID vaccine

Type of vaccine	AstraZeneca (8 cases)								Pfizer (one case)	Sino farm (one case)	Jonson (one case)
Case No	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	2 nd	1 st	2 nd
Vaccine dose	1 st	2 nd	2 nd	1 st	2 nd	1 st	1 st	2 nd	2 nd	1 st	2 nd
Neurological complications	Encephalitis	Encephalitis	AIS	AIS	AIS	AIS	New onset Seizures	Headache	Headache	AIS	Central retinal vein occlusion
Days between vaccine and neurological complications	3 days	10 days	3 days	5 days	One day	3 days	7 days	2 days	5 days	5 days	7 days
Comorbidities and smoking	DM, HTN	Smoking	DM, HTN, Smoking	DM, HTN	DM, HTN	DM	DM	No	HTN	DM, Smoking	No

AIS: Acute Ischemic Stroke; DM: Diabetes mellites; HTN: Hypertension

Figure 1. Case 1, MRI shows brain edema

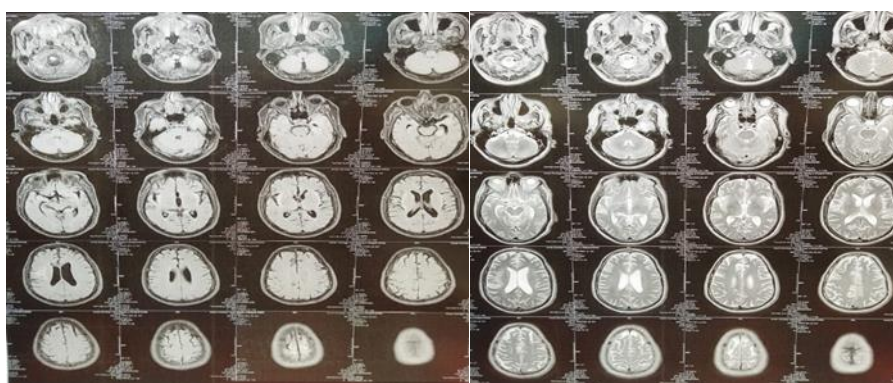


Figure 2. Case 2, MRI shows watershed cerebral infarction.

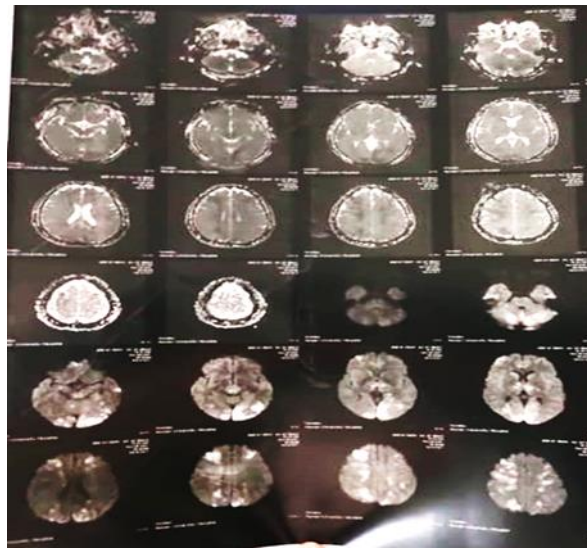
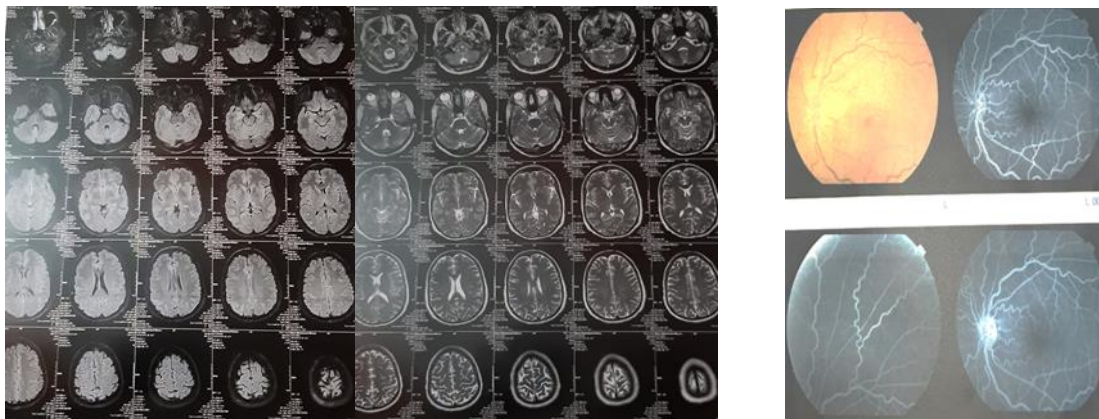


Figure 3. Case 4, (A &B) MRI shows tiny right parietal subcortical focus of high T2 signal. (C) Angiography of Lt eye shows impending central retinal vein occlusion.



Discussion

The most encouraging approach of struggling COVID-19 and limiting the course of this pandemic is indisputably the universal vaccination of the population with safe and effective vaccines [11]. To date, five vaccines against SARS-CoV-2 have received a conditional marketing authorization by the European Medicines Agency. These include two mRNA vaccines: BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna); two viral vector vaccines: ChAdOx1 nCoV-19 (Oxford-AstraZeneca) and Ad.26.COV2.S (Janssen/ Johnson & Johnson); and one adjuvanted, recombinant spike protein nanoparticle vaccine: NVX-CoV2373 (Novavax) [2]. All types of the currently approved circulating vaccines have shown to be safe and effective in reducing the risk for severe COVID-19

infection [11]. More recently, concerns have been raised about immune mediated neurological disorders post-covid-19 vaccination. Neurological symptoms reported after vaccination for COVID-19 are commonly mild, transient symptoms such as headaches, dizziness, myalgia and paresthesias. A wide spectrum of neurological complications is continuously being reported following COVID-19 vaccination. In fact, all kinds of vaccines are associated with the risk of several serious neurological complications, like acute disseminated encephalomyelitis, transverse myelitis, aseptic meningitis, Guillain-Barré syndrome and myositis.¹²

Several pathogenic mechanisms, like molecular mimicry, direct neurotoxicity, and aberrant immune reactions, have been attributed to explain these post-covid vaccines neurological

complications [13]. SARS-CoV-2 and adverse reactions to SARS-CoV-2 vaccines exhibit a tropism for neuronal structures and tissues [14]. Molecular mimicry with production of spike proteins, which these vaccines produce antibodies against, that bind to sialic acid-containing glycoproteins and gangliosides on cell surfaces [15] and stimulates the immune system to recognize and memorize it and attack it in the future [16].

In Mexico among subjects who received first doses of the Pfizer-BioNTech mRNA COVID-19 vaccine, 65% had mild neurologic manifestations as headache and transient sensory symptoms and only 17 serious adverse events including seizures, Guillain-Barré syndrome and transverse myelitis [17].

In South Korea, Kim and co-workers [18] noted that 91% of adenovirus-vectored vaccine and 53% of mRNA vaccine recipients had mild adverse reactions, like injection-site pain, myalgia, fatigue, headache, and fever.

We reported two cases presented with encephalitis. Both were injected by AstraZeneca COVID-vaccine, one by the first dose and the other by the second dose. Both were males. Their symptoms occurred within 3 and 10 days respectively, after receiving vaccine. Autoimmune encephalitides especially anti-GAD encephalitis was an important consideration. Anti-GAD antibody testing was not available in our venue. In line with our finding, **Zuhorn et al.** [19] detailed three cases of encephalitis following vaccination with ChAdOx1 nCov-19 vaccine. The onset of symptoms of encephalitis occurred within seven to 11 days of vaccination with the ChAdOx1 nCov-19. Twenty cases of unexplained encephalitis occurred following 110.6 million doses of the Pfizer-BioNTech mRNA vaccine (BNT162b2). The significant difference in case rates following the ChAdOx1 nCov-19 vaccine and Pfizer-BioNTech vaccine and lack of reports following other COVID-19 vaccines suggest a causal relationship [19].

We described five cases had post vaccination ischemic brain insult. Four cases were AstraZeneca recipients while one case was Sino pharm recipient. AIS was observed in two males and two females' patients above 55 years old and in one male patient under 40 years old. All patients had higher levels of C-reactive protein (CRP) and D-dimer levels. In the current study, AIS occurrence was more observed between those receiving the

Oxford AstraZeneca COVID-19 vaccines may indicate a the COVID-19 vaccine-triggered inflammatory condition like in the course of COVID-19 viral infection, which induces disseminated intravascular coagulation (DIC) concurrent with vascular endothelial dysfunction, leading to large-vessel stroke. Increasing number of reports about adenoviral vector (as AstraZeneca) vaccine-induced cerebral vascular adverse events, like cerebral venous thrombosis, arterial stroke, and intracerebral hemorrhage, is getting issued in chief medical journals. Reports of coagulopathy have appeared associated with COVID-19 vaccinations and particularly the ChAdOx1 nCov-19 vaccine. Vaccine-induced cerebral vascular adverse events are generally associated with severe immune-mediated thrombotic thrombocytopenia. Generally, Thrombocytopenia clinically manifests within 5 to 30 days after administration of adenovirus vector-based vaccines [12]. Post-vaccinations thrombotic thrombocytopenia, results in platelet destruction and trigger the intravascular blood clotting [20]. Our cases of AIS occurred 1-5 days after vaccination which in keeping with this suggested mechanism. The occurrence of stroke in COVID-19 vaccinated individuals in the current study seems to have the similar trend as those occurring in COVID-19 viral infections, with a predominance in older age [21]. Notably, in the current study, most of patients who experienced stroke had risk factors and common comorbidities such as dyslipidemia, hypertension, and diabetes, which is in agreement with previously reported stroke-predisposing factors in COVID-19 patients [22]. It is likely that a greater etiology of these strokes are the classic risk factors (older age, dyslipidemia, hypertension, type II diabetes mellitus, overweight/obesity, and cerebrovascular disease) that were going to cause them regardless of COVID-19 vaccination, given the high prevalence of IS risk factors in Pfizer COVID-19 bivalent vaccine and monovalent vaccine cohorts [23]. The COVID-19 vaccine can cause inflammation and the immune system to become activated, which can then cause a cytokine storm that lowers pancreatic blood flow or directly affects β -cell function by binding to ACE2 receptors. Alternatively, the inflammatory response can cause pancreatic fibrosis, which lowers insulin synthesis and secretion as well as insulin sensitivity in target tissues, ultimately raising blood glucose levels [24]. As metabolic anomalies, atherogenic dyslipidemia, hypertension, glucose intolerance, and a prothrombotic state are common

in patients with type 2 diabetes, individuals with metabolic syndrome have a pattern of coagulation factors that either promotes thrombosis or retards thrombolysis.

In line with our findings, **Bayas** and co-workers [25] described a case that presented with superior ophthalmic vein thrombosis, ischemic stroke, and immune thrombocytopenia, after administration of viral vector-based vaccine. Moreover, **Al-Mayhani et al.** [26] described three cases of vaccine-induced thrombotic thrombocytopenia, all presented with arterial strokes. Furthermore, **Blauenfeldt et al.** [27] described a 60-year-old woman, who presented (7 days after receiving the adenoviral (ChAdOx1) vector-based COVID-19 vaccine) with a massive right cerebral infarction, secondary to occlusion of the right internal carotid artery, that led to death of the patient. In contrast, Pottgård and Klungel [28] stated that neither the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) nor the BNT162b2 (Pfizer-BioNTech) vaccine was associated with an increased risk of neurological adverse events.

We described one case, that was injected by first dose of AstraZeneca COVID-vaccine, presented with new onset-seizures as a neurological complication. **Ritwik et al.** [29] reported seizures after vaccination in a 68-year-old man in India. As well as, Liu and his colleagues found 83-year-old woman and a 76-year-old man with no previous neurological diseases presented with seizures and encephalopathy after receiving Moderna COVID-19 vaccination. These COVID-19 vaccine-associated seizures could be attributed to the suggested hypothesis of an exaggerated inflammatory process induced by the vaccination that leading to glial cell activation and increase BBB permeability. This is Increased BBB permeability permits peripheral blood cells and albumin passage to the CNS, causing disruption of its osmotic balance and allowing the passage of peripheral cytokines into it, causing seizures [30]. The occurrence of seizures in the current study was typically in the patient vaccinated with AstraZeneca which is one of vaccines that causes a strong inflammatory reaction. Based on this hypothesis, the vaccine-triggered inflammatory condition may be considered the main pathway for the COVID-19 vaccines' neurological complications, in addition to cytokine-mediated neuroinflammation as documented by **Muccioli et al.** [31].

We reported 2 cases suffered headache after receiving second dose of COVID-19 vaccine (one was Pfizer and the other was AstraZeneca recipients) mostly 5-7 days after vaccination. Their headaches were severe in intensity, bursting in character, without other associated symptoms else. The onset of symptoms in these patients occurred shortly after vaccination, suggesting a direct correlation with COVID-19 vaccination. This headache may be attributable to activation of immunoinflammatory mediators. The second hypothesis states that neurological symptoms after vaccination might be due to reactivation of the immune system in patients previously infected with SARS-CoV-2 or a related pathogen. However, this hypothesis could not explain the occurrence of headache in our patients based on their medical history that negate their previous infection with COVID. In the third hypothesis, the authors proposed that headache is known neurological manifestations of SARS-CoV-2-infection due to virus-induced systemic hyper inflammation by an extensive cytokine release. Again, this does not explicitly explain the occurrence of headache in our patients because they were COVID-19 vaccinated without preceding SARS-CoV-2 infection. In line with our findings, **Garg et al.** [12] stated that headache is one of the most frequent mild neurological complaints reported by a large number of COVID-19 vaccine recipients, soon after they receive vaccine. In a multicenter observational cohort study, **Göbel et al.** [32] recorded clinical characteristic of headache occurring after the mRNA BNT162b2 mRNA COVID-19 vaccination that started 18.0 ± 27.0 hours after vaccination and persisted for 14.2 ± 21.3 h. In majority, the headaches were bifrontal or temporal, dull aching character and were moderate to severe in intensity. The common accompanying symptoms were fatigue, exhaustion, and muscle pain.

Conclusion

To summarize, these case series demonstrated new-onset neurological symptoms shortly after the SARS-CoV-2 vaccination where we reported post COVID-vaccine associated different types of neurological disorders in our community. Our finding suggests that after SARS-CoV-2 vaccination, a reactivation of the immune system causes neurological symptoms. However, further research is merited to provide more visions into the hypotheses drawn in this study. Moreover, future studies should emphasis on establishing a direct

relationship between COVID-19 vaccination and neurological symptoms, concurrently rejecting other etiologies.

Authors' contribution

Dr. Abeer A.Tony did the acquisition, analysis, and interpretation of data; Professor Dr. Effat AE.Tony had drafted the work or substantively revised it. Dr. Dalia B.Elgedy did the acquisition of cases. Dr. Mohamed R.Khodair had revised it. All authors agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work.

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Abbreviations

COVID-19: Coronavirus disease-19

SARS-COV-2: Severe acute respiratory syndrome coronavirus 2

GBS: Guillain Barre Syndrome

CT: Computerized tomography

MRI: Magnetic Resonance Imaging

EEG: Electroencephalogram

CSF: Cerebrospinal fluid

GCS: Glasgow coma scale

DVT: Deep venous thrombosis

CO-RADS: The COVID-19 Reporting and Data System

NIHSS: The National Institutes of Health Stroke Scale

MRV: Magnetic Resonance Venography

mRNA: Messenger RNA

CHAdOX1 nCOV-19: Chimpanzee adenovirus vector for vaccine developed by University of Oxford

NVX-COV2373: Novavax COVID-19 vaccine

Competing interest

The authors report no conflicts of interest for this work.

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