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ORIGINAL ARTICLE

COVID-19 Vaccination Induced Neurological Complications; A Systematic Literature Review

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ABSTRACT

Introduction: Vaccination against COVID-19 is proved successful in reducing the transmission of disease globally along with reducing the severity of disease but vaccine associated adverse effects (VAERS) questions the safety profile of COVID-19 vaccines especially the serious neurological adverse effects that are responsible for post-vaccination mortalities globally.
Aim: To review the neurological adverse effects of COVID-19 vaccines and identify their possible pathophysiology
Method: The literature search was conducted by two researchers. The database of Google Scholar was used to search relevant literature. All the articles published between 1st Jan, 2018 to 1st Jan 2022 were screened for inclusion and exclusion criteria.
Results: The search strategy resulted in 278 articles of which, 1duplicates were removed and 277 articles were screened according to inclusion exclusion criteria, 103 articles were excluded and a total of 20 articles were included in review of which there were 17 case reports,1 observational studies, 1 case series and 1 case-control study.
Conclusion: The findings of review provide a deep insight of neurological complications that can occur in individuals after receiving COVID-19 vaccination and the clinicians should be conscious while dealing with a patient with new-onset neurological symptoms after vaccination against COVID-19 unless a causal association is developed between the vaccine and serious neurological adverse events by future researches.
Keywords: COVID-19, Post-vaccination, Neurological Complications, Vaccine Associated Adverse events, Acute Ischemic Stroke and GBS

INTRODUCTION

Since the advent of Coronavirus disease (COVID-19), a global pandemic originated in Wuhan back in the end of December, 2019, almost 614 million cases have been reported till 23rd September, 2022 with almost 6.53 million mortalities globally[1].COVID-19 belongs to a family of Coronaviruses that primarily affects the respiratory system of human body but sequentially involves other vital organ systems[2]. Several group of drugs including anti-bacterial, antivirals, antiparasitic as well as immunomodulators and immunosuppressants were used against COVID-19 disease by keeping in view the etiopathogenesis of coronavirus to keep the disease under control[3], but the excessive communicability of disease reinforced the need for vaccination against COVID-19[4]. Several vaccines against COVID-19 have been introduced till now including Pfizer-BioNTech, mRNA-1273, NVX-CoV2373, AZD1222 and Ad26.COV2.S with various levels of effectiveness against COVID-19[5]. According to one statistics, vaccination against COVID-19 has reduced the overall attack rate of COVID-19 from 9% to 4.6% within 10 months approximately[6]. Another study revealed an efficacy of Pfizer-BioNTech and Moderna vaccine of more than 90% in symptomatic severe coronavirus disease[7]. World-Health Organization declared the safety of ChAdOx1 COVID-19 vaccine in persons older than 18 years and Pfizer-BioNTech in persons older than 5 years on 12th January, 2022[8].

Despite proven efficacy of COVID-19 vaccinations in preventing the spread of disease or reducing the severity of illness, the risk-benefit analysis of vaccination is mandatory[9,10,11]. Several studies have reported post-vaccination complications of COVID-19[12,13,14,15,16]. According to Center for Disease Control and Prevention (CDC), the local and frequently reported complications of COVID-vaccination are Fatigue, Headache, Chills and mild fever, pain at the site of injection and myalgias[17]. While the serious, though not frequently encountered, complications include cardiac complications, (Myocarditis, Pericarditis),Thrombotic complications (Thrombosis with thrombocytopenia Syndrome) , anaphylaxis and neurological complications (Acute Ischemic Stroke, Meningitis, Encephalitis ,GBS,, Transverse Myelitis and several others)[18,19,20]. According to VaST and ACIP COVID-19 Vaccine Work Group assessments, almost 100 patients reported to hospitals with the diagnosis of GBS after Janssen COVID-19 vaccination from 27th February to 30th June, 2021 within a mean period of 13 days from vaccination and majority of these patients were males with almost 7.8 cases per million Janssen COVID-19 vaccine doses administered[21]. Similarly, 38 patients reported with a diagnosis of TTS at hospitals within 15 days interval from vaccination with almost 3 cases per million Janssen COVID-19 vaccine doses administered[21]. Similarly the reporting rate of myocarditis was 3.5 cases per million with mRNA COVID-19 vaccine[21]. Although, the benefit-risk assessment report by FDA and ACIP recommends the use of COVID-19 vaccines in patients older than 18 years, the novelty of COVID-19 Vaccination and scarcity of literature questions the occurrence of reported serious complications of COVID-19

vaccination, especially Neurological complications, that renders patient paralyzed. Hence, it is mandatory for the researchers to find a temporal association or biological plausibility of these complications with COVID-19 vaccine[22]. We therefore aim to systematically review the neurological complications of COVID-19 reported in literature within last five years.

MATERIALS AND METHOD

This review is being written in accordance to the guidelines presented in Cochrane Handbook for systematic reviews of interventions[23] and is being presented on the format developed by Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines[24].

Search Strategy: Two independent reviewers searched Google Scholar database by using COVID-19, Post-vaccination, Neurological Complications, Vaccine Associated Adverse events, Acute Ischemic Stroke and GBS as keywords. Further, the reference lists of articles were also reviewed for inclusion. The type of articles included were case reports, case series, case control studies, observational studies as well as cohort studies that discussed the neurological complications of COVID-19 vaccines. The search strategy was limited to articles published in last five years in English Language only. The search strategy was summarized using Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. In the first phase, the title and abstract of relevant articles were reviewed while the full-text of articles were reviewed only of short-listed articles. The PRISMA flowchart for search strategy is given below in Figure 1.

Data Extraction: The Data was extracted from included articles as Name of author, year of publication, study type, Number of cases, vaccine used, Dose of vaccine, Interval from vaccination and development of symptoms, Clinical presentation, Patient characteristics (Age, Gender, Past medical history), lab finding, Radiological Findings, Neurological diagnosis and Treatment done for the neurological ailment.

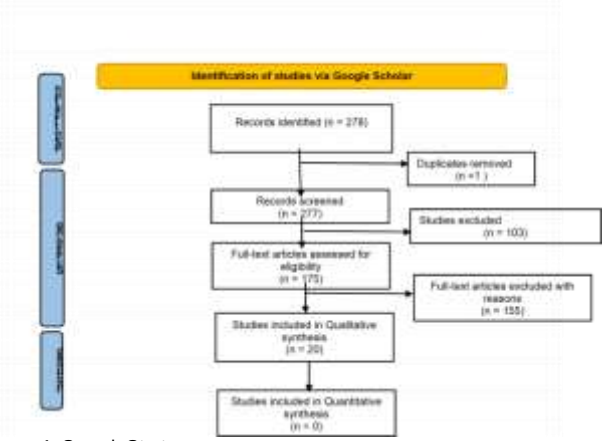

Figure 1: Search Strategy

Elligibilty Criteria: The Studies discussing neurological complications observed post-Covid-19 vaccination in patients aged 18 years old were included while studies were excluded on the basis of following exclusion criteria: 1)Review Articles and Metanalysis, 2)Studies published in language other than English, 3)Studies with no access / limited access.

RESULTS

The search strategy resulted in 338 articles of which, 1 duplicate was removed and 337 articles were screened according to inclusion exclusion criteria, articles were excluded and a total of 20 articles were included in review of which there were 17 case reports, 1 observational cohort study , 1 case-control study and 1 case series and 15 population based cohort study. The included articles are summarized below in Table 2.

Table 1: Methodology of Included studies

Title of Study	Type of Study	No of cases	Ref.
Clinical Manifestation, Management, and Outcomes in Patients with COVID-19 Vaccine-Induced Acute Encephalitis: Two Case Reports and a Literature Review	Case report	2	[25]
Acute Transverse Myelitis Following COVID-19 Vaccination	Case Report	1	[26]
Sudden onset of myelitis after COVID-19 vaccination: an under-recognized severe rare adverse event	Case Report	1	[27]
Acute dizziness and mental alteration associated with Moderna COVID-19 vaccine	Case Report	1	[28]
A case report of ChAdOx1 nCoV-19 vaccine–associated encephalitis	Case Report	1	[29]
Longitudinal extensive transverse myelitis following ChAdOx1 nCOV-19 vaccine: a case report	Case Report	1	[30]
Acute disseminated encephalomyelitis (ADEM) following recent Oxford/AstraZeneca COVID-19 vaccination	Case Report	1	[31]
Central nervous system adverse events after ChAdOx1 vaccination	Case series	4	[32]
Bilateral optic neuritis after COVID vaccination. Neurological Sciences	Case Report	1	[33]
A case of encephalitis following COVID-19 vaccine	Case Report	1	[34]
Aseptic meningoencephalitis after COVID-19 vaccination: a case report	Case Report	1	[35]
Aseptic meningitis following AZD1222 COVID-19 vaccination	Case Report	1	[36]
Post-COVID-19 vaccine Guillain-Barré syndrome; first reported case from Qatar	Case Report	1	[37]
Guillain-Barré syndrome is infrequent among recipients of the BNT162b2 mRNA COVID-19 vaccine.	Retrospective observational Cohort	7	[38]
Post-COVID-19 vaccine acute hyperactive encephalopathy with dramatic response to methylprednisolone: a case report	Case Report	1	[39]
Case report of acute encephalitis following the AstraZeneca COVID-19 vaccine	Case Report	1	[40]
A case of Guillain–Barre syndrome following Pfizer COVID-19 vaccine.	Case Report	1	[41]
Association of COVID-19 vaccination and facial nerve palsy: a case-control study	Case-Control	37	[42]
Pituitary apoplexy after COVID-19 vaccination	Case Report	1	[43]
Facial nerve palsy after COVID-19 vaccination–A rare association or a coincidence	Case Report	1	[44]
Status migrainosus: A potential adverse reaction to Comirnaty (BNT162b2, BioNtech/Pfizer) COVID-19 vaccine—A case report.	Case report	1	[45]

Table 2: Summary of findings from included studies

Author	Year	Vaccine	Dose of Vaccine	Time interval (days)	Neurological Diagnosis	Possible pathophysiology
Shyu S et al.[25]	2022	mRNA-1273	1st	7	Encephalitis	Cytokine-related neurotoxicity
Gao JJ et al.[26]	2021	mRNA-1273	1st	<1	ATM	Immune reaction (SARS-CoV-2 spike protein & myelin basic protein),Interaction between spike proteins and angiotensin-converting enzyme 2 (ACE2) receptors
Fitzsimmons W et al.[27]	2021	mRNA-1273	2nd	<1	ATM	Immunologic reaction to the spike protein misdirected to the spinal cord
Pinzon RT et al.[28]	2022	mRNA-1273	1st	1	Encephalopathy	Lack of anti-inflammatory effect of brain-derived neurotropic factor (BDNF) ,Increased interleukin-1 (IL-1) in the hippocampus
Takata J et al.[29]	2021	ChAdOx1	2nd	---	Encephalitis	---
Tan WY et al.[30]	2021	ChAdOx1	1ST	16	ATM	Delayed inflammatory reaction mediated by dendritic and T-cells due to molecular mimicry of viral vector gene
Permezel F et al.[31]	2022	ChAdOx1	1st	12	ADEM	T-cell mediated autoimmune response to Myelin based proteins
Maramattom BV et al.[32]	2022	ChAdOx1	1st	10	Limbic Encephalitis	---
		ChAdOx1	2nd	10	OMAS	---
		ChAdOx1	2nd	20	ADEM	---
		ChAdOx1	1st	4	ADEM	---
		ChAdOx1	1st	5	ADEM	---
Arnao V et al.[33]	2022	ChAdOx1	1st	14	RON	---
Consoli S et al[45]	2021	BNT162b2,	2nd	1	SM	Cytokine-mediated stimulation of trigeminal nociceptors
Kobayashi Y et al.[34]	2022	BNT162b2,	1st	1	Encephalitis	
Ahmad SA et al.[35]	2021	BNT162b2,	2nd	5	AME	Autoimmunity
Zavari A et al.[36]	2022	AZD1222	1st	1	Aseptic Meningitis	Cytokine-related neurotoxicity
Razok A et al.[37]	2021	BNT162b2,	2nd	20	GBS	
Al-Mashdali AF et al.[39]	2021	mRNA-1273	1st	2	AHE	Cytokine-mediated inflammatory process
Li SY et al.[40]	2022	Astrazeneca	1st	1	Acute Encephalitis	
Rao SJ et al.[41]	2021	Pfizer	2nd	7	GBS	Auto-antibodies against myelin
Pinar et al.[43]	2022	ChAdOx1-S	1st	5	Pituitary apoplexy	Vaccine- Induced Thrombocytopenia
Ish et al.[44]	2021	COVAX	2nd	21	Facial Nerve Palsy	Autoimmune mechanisms with interferons activation

ATM: Acute Transverse Myelitis, ADEM : Acute Disseminated Encephalomyelitis, OMAS: Opsoclonus-myoclonus-ataxia syndrome , RON: Retrobulbar optic neuritis, SM: Status Migranosus, AME: Acute Myelin encephalopathy, AHE: Acute Hyperactive Encephalopathy, GBS: Guillain-Barré syndrome

Table 3: Patient Characteristics of included case reports and Case series

Ref	Age/G/Clinical Features/Past History (if any)	Lab Findings	Radiological Findings	Treatment/ Diagnosis
[25]	58/M /Fever,Cognitive defects, Left deviation of the head and eyeballs, and Weakness of the right upper limb	CBC: N, COVID-PCR: -ve, CSF:Lymphocyte pleocytosis,elevated protein ,elevated CSF/serum albumin ratio, Infection screen -ve,Autoimmune profile -ve	UR	Encephalitis/IV Steroids
	21/M/Coma	CBC: N,COVID-PCR: -ve, CSF:no pleocytosis,elevated proteins, elevated microalbumin,Infection screen -ve, Autoimmune profile -ve	SPECTB:Hypoperfusion of R.Temporal Lobe,MRIB:UR,EEG:Slowing Theta & Delta waves	
[26]	78/F/Fever, Right arm and leg paraesthesia, Progressive gait disorder, Sacral parasthesia/Hypertension,Right sided Hearing loss	CBC: N, COVID-PCR: -ve, CSF:mild pleocytosis, neutrophil predominance,increased protein levels, No oligoclonal Bands, Infection screen -ve, Autoimmune profile -ve, AQP-4 : -ve	CTB: UR,MRIB: UR,CT Spinal Cord: Hyperintense intramedullary cervical cord at C2-C5 (T2), C3 (T1), EEG: Normal, NCS: Bilateral peroneal neuropathy,BAEP: Sensorineural hearing loss	ATM/IV and oral Steroids, Vitamin B12
[27]	63/M/Pain and numbness in both calves and feet, lower back pain, Gait disturbance , Difficulty in micturition	CBC: N, COVID-PCR: -ve, CBC: N	Increased T2 cord signal in the distal spinal cord and conus.	ATM/ IVIG, IV and Oral Steroids,
[28]	39/F/Behavioral changes, communication difficulties, social disengagement, and confusion, dizziness, nausea,vomiting, and epigastric pain/ Hypertension	CBC: Raised Neutrophil to lymphocyte ratio, COVID-PCR: -ve, CSF:UR, CRP: Increased	CT: Normal, MRI: ND, EEG: ND	Encephalopathy/ Antibiotics,PPI Antiemetics, Steroids, Antihistaminic
[29]	22/F/intermittent frontal headache,fatigue, confusion and hallucinations (visual and tactile)/Retinitis Pigmentosa	CBC: N, COVID-PCR: -ve, CSF: pleocytosis, Infection screen -ve, Autoimmune profile -ve	CT: UR, MRI: UR, EEG: UR	Encephalitis/ Benzodiazepene, Antipsychotics, Antibiotics

Table 4: Patient Characteristics of included studies

Ref	Age/G/Clinical Features/Past History (if any)	Lab Findings	Radiological Findings	Treatment/ Diagnosis
[30]	25/F/bilateral lower limb weakness and inability to walk, sensory level up to T8 with absent visual symptoms, urinary retention	CBC: N, COVID-PCR: -ve CSF:mild pleocytosis, neutrophil predominance,increased protein levels, No oligoclonal Bands, Infection screen -ve Autoimmune profile -ve, AQP-4 : -ve	CTB: UR, MRIB: UR, Contrast-MRI Spinal cord: Multi-segment T2-hyperintensities & variable cord enhancement post-contrast at T7-T8 lesion	ATM/Steroids, Antibiotics, DVT prophylaxis
[31]	63/M/vertigo, abdominal pain and fatigue/ IDDM2/IHD/AF	CBC: N, COVID-PCR: ND Brain biopsy: white matter edema ,focal perivascular hemorrhages,perivascular demyelination with axonal preservation, perivascular distribution of macrophages & lymphocytes	MRI Brain and Spinal cord: bilateral foci (> 20) of high T2 and FLAIR signal in the cerebral white matter, with both periventricular and juxtacortical involvement	ADEM/Steroids Plasmaphresis
[32]	64/M/Fever,drowsiness	CBC: N,COVID-PCR: -ve,CSF: lymphocytic pleocytosis, Increased ESR, CRP, d-dimer, ferritin, Anti-SARS-CoV-2 spike protein IgG antibody +ve		Encephalitis/Steroids Rituximab
	65/M/Behavioral changes, Jerky Movements	CBC: N, COVID-PCR: -ve, CSF:mild pleocytosis		Steroids IVIG
	64/M/Ascending paresthesias ,epigastric bandlike Sensation	CBC: N, COVID-PCR: -ve, Anti-SARS-CoV-2 spike protein IgG antibody, Infection screen -ve, Autoimmune profile -ve	MRI Brain: multifocal cord hyperintensities, bilateral hemispheric corticospinal tract hyperintensities	ADEM/Steroids,IVIG ,Rituximab
	46/M/Urinary problem, progressive lower limb weakness and numbness	CBC: Thrombocytopenia, COVID-PCR: -ve,LDH: Increased, Infection screen -ve, Autoimmune profile -ve	MRI Brain & Spinal cors ; supratentorial, infratentorial, and long segment spinal cord hyperintensities	ADEM/Plasmaphresis
	42/F/Headache,Photophobia	CBC: N, COVID-PCR: -ve, Raised CSF opening pressure, Infection screen -ve, Autoimmune profile -ve	MRI Brain: leptomeningeal enhancement, Brain biopsy: tumefactive demyelination	ADEM/Steroids
[33]	Middle age/F/Headache, painful blurred vision,decreased bilateral vision acuity	CBC: N, COVID-PCR: -ve, CSF: UR,Infection screen -ve, Autoimmune profile -ve, AQP-2: -ve	VEPs: bilateral latency delay , MRI Brain & Spine: increased signal of the left optic nerve	RON/Steroids

Table 5: Patient Characteristics of included studies

Ref	Age/G/Clinical Features/Past History (if any)	Lab Findings	Radiological Findings	Treatment/ Diagnosis
[45]	37/f/right pulsating headache, photophobia/phonophobia ,nausea,/ Migraine with aura	CBC: N, COVID-PCR: -ve,CSF: UR,Infection screen -ve Autoimmune profile -ve	MRI Brain: cystic degeneration, of epiphysis ,MRA: UR	SM/Steroids
[34]	46/F/Progressive diplopia	CBC: N,COVID-PCR: ND, CSF: Raised total proteins, OCBs: Absent ,AQP4: -ve, MOG: -ve, Infection screen -ve, Autoimmune profile -ve	MRI Brain: lesion on the dorsal pons across the midline , no enhancement ,MRA Brain: UR, MRI Spine: UR	Encephalitis/Steroids
[35]	62/F/Fever, Headache, Rigors, Inability to talk	CBC: Leukocytosis,Agranulocytosis, COVID-PCR: ND CSF: lymphocytic pleocytosis, Raised Protein,Low glucose, Raised Lactate	CT-Brain: UR, MRI Brain: UR	AME/Steroids, Acyclovir
[36]	26/F/Fever, Headache, Photophobia	CBC: N, COVID-PCR: -ve, CSF: lymphocytic pleocytosis, Raised Protein,Low glucose, Infection screen -ve, Autoimmune profile -ve	MRI-Brain: UR, MRA-Brain: UR, MRV-Brain: UR	AM/Steroids
[37]	73/M/Bilateral lower limb weakness, reflexes absent/Smoker, Hypertension,RA	CBC: Leukocytosis, COVID-PCR: -ve, CSF: Raised Total Protein and Albumin, Infection screen -ve, Autoimmune profile -ve	CT-Brain: UR, MRI Brain-UR,MRI Spine: Bilateral nerve root enhancement in the lumbar region and the upper part of the cauda equina,NCS & EMG: Nerve conduction study (NCS) bilateral absent H reflexes in the gastrocnemius muscles	GBS/IVIG
[39]	32/F/Disoriented, Amnesia	CBC: N, COVID-PCR: -ve, CSF: Raised Total Protein , Average cell count and glucose, Infection screen -ve, Autoimmune profile -ve	MRI-Brain: UR, EEG: slowed background activity	AHE/Antibiotic,Antivirals Benzodiazepenes, Antipsychotics
[40]	55/M/Fever, Disorientation, Progressive	CBC: N, COVID-PCR: -ve, CSF : Raised Total	MRA Brain: pachymeningeal	Acute

	weakness/Hypertension,Hyperlipidemias,Slee p Apnea	Protein , Riased lymphocyte cell count, ANA: +ve S.Ferritin: Raised, D-Dimers: Riased CRP: -ve, Infection screen -ve	enhancement	encephalitis/Antibiotic ,Antiviral,Steroids

Table 6: Patient Characteristics of included studies

Ref	Age/G/Clinical Features/Past History (if any)	Lab Findings	Radiological Findings	Treatment/ Diagnosis
[41]	42/F/symmetric, distal paresthesias, intractable pruritus, Weakness, gait instability	CBC: N, COVID-PCR: -ve, CSF: Raised Proteins, No white cells	MRI Spine: multilevel degenerative disc , NCS: Decreased conduction velocity, Absent F wave, sural sparing	GBS/IVIG
[43]	37/F/Frontal headache	CBC: ND, COVID-PCR: ND, Hormonal profile: N,Campimetry: N	MRI Brain: adenohypophysis hemorrhagic bleeding in association with a possible 10 mm intraglandular adenoma	Pituitary Apoplexy/
[44]	50/M/Inability to close right eye, redness,watering,loss of wrinkling on forehead, naso-labial fold, drooping of angle of mouth of the right side	CBC:ND, COVID-PCR:ND, Other: ND	ND	Facial Nerve palsy/ Antibiotic, Steroids

N: Normal, ND: Not Done, UR: UnremarkableATM: Acute Transverse Myelitis, ADEM : Acute Disseminated Encephalomyelitis, OMAS: Opsoclonus-myoclonus-ataxia syndrome , RON: Retrobulbar optic neuritis, SM: Status Migranosus, AME: Acute Myelin encephalopathy, AHE: Acute Hyperactive Encephalopathy, GBS: Guillain-Barré syndrome

DISCUSSION

COVID-19 disease was declared as pandemic by World Health Organization (WHO) on . Since then, the development of vaccine against COVID-19 was taken as challenge by many countries globally resulting in introduction of multiple vaccines like Moderna, Pfizer, Jansen and many more[46]. Although, the transmission rate of disease has been reduced by introduction of vaccinations, the lack of knowledge regarding safety profile of vaccination is a major concern[47]. According to Mexican Epidemiological Surveillance System, a total of 6536 reports of AEFI were received of which , 65.1% were neurological side effects[38]. The incidence of non-serious neurologic AEFI cases was 600 per every 100,000 administered vaccine doses whereas every 2.4 AEFI per 100,000 administered doses were serious neurological events including seizures, encephalitis, meningoencephalitis, transverse myelitis, Pituitary apoplexy, Ischemic stroke , GBS, Lumber radiculopathies and several others[38].

Encephalitis and Meningoencephalitis: Acute encephalitis is one of the serious but treatable neurological complications observed after COVID-19 vaccination in some studies[25,29,32,34]. COVID-19 mRNA vaccines basically comprise of SARS-CoV-2 mRNA which later undergo translation into SARS-CoV-2 spike proteins by ribosomes of host cell leading to activation of adaptive immunity. Additionally, vaccines are aberrantly identified as antigen by some host cells leading to activation of proinflammatory cascade. Both these responses lead to increased levels of cytokines in circulation. Further, SARS-CoV-2 spike proteins causes disruption of Blood Brain Barrier (BBB) leading to increased entry of cytokines in Central nervous system causing Neurotoxicity[25,29]. The alteration of CSF to Albumin ratio study by Shyu et al depicts the impairment of BBB and Negative autoimmune and undetected infection in patients, absence of risk factors and a drastic improvement with Intravenous steroids supports the diagnosis of COVID-1 vaccine induced encephalitis[25]. The occurrence of post-vaccination encephalitis is also supported by studies describing encephalitis caused after smallpox, measles and yellow fever vaccination[32,34].Studies have also explained the occurrence of aseptic meningitis by vaccination against small pox, measles , mumps, rubella and influenza[36,40]. The exact pathophysiology behind development of Aseptic meningitis or meningoencephalitis is not known but the proteins developed through vaccination may undergo molecular mimicry stimulating autoimmune process in which autoantibodies cross the blood brain barrier and affect the meninges as well as brain parenchyma[36].

Acute Transverse Myelitis: Acute transverse myelitis occurs in almost 9 cases out of every 51,755,447 patients vaccinated according to the statistics by ANA[26]. Level 2 diagnostic certainty is made when there is occurrence of symptomatic myelopathy along with any two of fever,>5 WBC/mm^3 pleocytosis and radiological findings of acute spinal cord demyelination while level 1 diagnostic certainty requires histopathological evidence of acute spinal cord demyelination[26,27]. Gao J et al confirmed the diagnosis of post-vaccination acute transverse myelitis by level 2 diagnostic certainty[26]. The development of demyelination after 48 hours of mRNA1273 vaccination in this patients is explained by the mechanism through which study suggested SARS-CoV-2 spike protein interact with myelin basic protein causing demyelination[26]. Further, the stimulation of Inflammatory response by the interaction between spike proteins and angiotensin-converting enzyme 2 (ACE2) receptors lying on spinal neurons can lead to demyelination[27,30].

Encephalopathy: The incidence of Post-COVID-19 vaccination induced Encephalopathy is 10.36 cases for every one million doses of vaccination[48]. According to one statistics, the incidence of encephalopathy induced by Pfizer was 7.80, by Moderna was 10.04, and by Janssen 49.89 for every 1 million vaccinations[48].The SARS-CoV-2 spike proteins due to their ability to bind the ACE2 receptors of BBB inhibits the anti-inflammatory action of brain-derived neurotropic factor (BDNF) on neurons leading to altered activation of neuronal signals which presents clinically as seizures and altered cognition. Further binding of SARS-CoV2 spike proteins to ACE2 enzyme receptors initiates a proinflammatory cascade with excessive circulatory Interleukin-6 and Tumor Necrosis Factor- α which crosses BBB and activates microglial cells. These microglial cells later release Interleukin-1 which gets concentrated in hippocampus and causes memory impairment and attention deficit disorders [28, 49].

GBS: GBS is a rapidly progressing polyradiculoneuropathy that presents acutely by symmetrical and ascending weakness along with hyporeflexia or areflexia[37]. It occurs due to demyelination and inflammatory response initiated by molecular mimicry by infection or vaccination[41]. Multiple cases of GBS have been reported after vaccination of influenza, Hepatitis A, rabies and Tetanus. Recently, after COVID-19 vaccination, an incidence of 0.18 per 100,000 administered doses of BNT162b2 mRNA Covid-19 vaccine is observed by García-Grimshaw M et al in his retrospective observational cohort[38].

Status Migranosus: Status migranosus , as defined by International Classification of Headache Disorders (ICHD-3) , is a clinical condition characterized by severe migraine attacks that last for more than 72 hours.[49] According to the available literature, Headache is one of the most frequently reported neurological side effect observed after COVID-19 vaccine.SARS-CoV-2 spike proteins developed by BNT162b2 stimulates an inflammatory response by activation of T-cells leading to release of cytokines which activates the trigeminal pain receptors along with sensitization of central trigeminal fibers that innervate the cerebral vessels leading to prolonged and severe attack of migraine[45].

Facial Nerve Palsy: Facial palsy after vaccination against COVID-19 has been observed during many trials of Pfizer/BioNTech , Moderna and ChAdOx1. The range of time interval during vaccination and development of facial nerve palsy lies from 0 to 79 days with a median time of 2 days while Ish et al reported duration of 21 days from second dose of COVAX till the development of Facial nerve palsy[44].Contrary to this, Shemer et al. in his case-control study, in which 21 of 37 patients with facial nerve palsy had had vaccination done (with either first or second dose of the BNT162b2 vaccine) in comparison to 44 of 74 in the control

group, revealed that the number of admission of patients with Bells' Palsy was same as admitted before the era of COVID-19 vaccination implying that there is no association between development of acute facial palsy with COVID-19 vaccination[42].

CONCLUSION

The occurrence of neurological adverse effects after COVID-19 vaccination has been reported by many clinical researchers in literature. Headache, myalgias, fever, numbness, tingling , tinnitus are some of the most commonly but non-serious neurological adverse effects of COVID-19 vaccination while the rare but serious neurological side effects of COVID-19 vaccine including Encephalitis, Meningitis, Meningoencephalitis, Acute Hyperactive encephalopathy, Acute disseminated encephalomyelitis , GBS, Status Migranosus, optic neuritis and Facial nerve palsy are also observed by many researchers highlighting the need to develop a causal association among these serious neurological events and COVID-19 vaccines by conducting studies on a large scale with large sample size.

Conflict of Interest: None to Declare
Disclaimer: None to Declare

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