

# Covid-19 Vaccination Induced Encephalitis: A Review

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**Abstract:-** Although the most recorded adverse events of COVID-19 vaccination includes local injection site effects like pain, redness or swelling, headache, fever and chills, fatigue, myalgia and arthralgia, the rare neurological side effects such as encephalitis has been reported. We conducted a thorough search through PubMed and applicable literatures were selected. All the reported cases of encephalitis in our study were announced after AstraZeneca (13), Pfizer-BioNTech (5), Moderna (3), Sinopharm (2) and Sputnik V (1) vaccination, involving 15 females, 8 males and 1 trans-male, ranging in age between 16 and 77 years. The study includes cases of 1 pediatric, 9 young adults and 14 older adults. Most of the patients showed a symptom onset that started within a week post vaccination where 15 patients developed symptoms following the first dose, 5 patients following the second dose and 1 patient following the booster dose. Fever and headache were the most frequent presenting symptom. In most of the cases, CSF analysis, EEG and other neuroimaging reports showed abnormality. Most of the patients were treated with IV methylprednisolone and some of the patients had undergone plasmapheresis. Majority of the patients showed positive response to the treatment and their clinical conditions improved. Out of 24 patients, 2 had died.

**Keywords:-** COVID-19, corona virus, vaccination, encephalitis.

## I. INTRODUCTION

The first COVID-19 infection rooted by the novel severe acute respiratory syndrome-corona virus 2 (SARS-CoV-2) was reported in Wuhan, China, in December 2019 and on March 2020, WHO has proclaimed it as a global pandemic.<sup>[1]</sup> As per the latest WHO report of May 2022, there were 521,920,560 confirmed COVID-19 cases, comprising 6,274,323 deaths.<sup>[2]</sup> To bring this pandemic to an end, production of vaccines has increased, leading to the emergence of new and efficient vaccines against COVID-19.<sup>[3]</sup>

Globally available COVID-19 vaccines act by four different mechanisms. The mRNA-based vaccines (Pfizer-BioNTech and Moderna) consist of genetically engineered RNA or DNA that give rise to a viral protein having the ability to induce an immune response. The inactivated/

attenuated viral vaccine (Sinopharm, Sinovac Corona Vac) introduces a killed or weakened COVID-19 virus that acts by triggering the immune system.<sup>[4][5]</sup> The viral vector-based vaccines (Janssen, Sputnik V and AstraZeneca) introduce a genetically engineered virus that yields corona virus proteins leading to an immune response. Protein subunits vaccines (Corbevax, Novavax) introduce the spike protein or its fragments resembling the COVID-19 giving rise to an immune response.<sup>[5]</sup> The recent WHO data show that, as of 16 May 2022, a total of 12,186,798,032 vaccine doses have been administered globally.<sup>[2]</sup>

The most common neurological adverse effects after vaccination includes fever and chills, headache, fatigue, myalgia and arthralgia, or local injection site effects like swelling, redness, or pain. The major neurological post-vaccination complication of concern is cerebral venous sinus thrombosis, Bell's palsy, Guillain-Barré syndrome, seizure, anaphylaxis, syncope, encephalitis, thrombocytopenia and vasculitis.<sup>[6]</sup> A strong expression of proinflammatory cytokines and a T cell response can be caused by vaccination. Peripheral proinflammatory cytokines are considered to be causal by reaching the brain which results in neuroinflammation after microglia activation, depending on the immunogenetic background and the innate immune memory.<sup>[7]</sup>

In this study, the encephalitis cases reported following COVID-19 vaccination were reviewed. We are discussing their clinical and laboratory features and the diagnostic and management implications.

## II. SEARCH STRATEGY

A thorough search has been conducted for all type of documents in PubMed on May21, 2022, using the keywords 'COVID-19 vaccination', 'SARS-CoV-2 vaccines', 'COVID-19 vaccine and CNS complications', 'COVID-19 vaccine and encephalitis' and 'SARS-CoV-2 vaccine and neurological manifestations'. From the appeared documents, only initially detected relevant titles regarding the topic were taken. The literatures were reviewed by the authors and most of the articles were excluded after viewing the title or abstract. The repetitive articles were also excluded. Only those reports that convincingly reported encephalitis followed by COVID-19 vaccination were included.

### III. RESULTS AND DISCUSSION

A total of thirty articles were found relevant, from which twenty were selected after the literature review yielding to twenty-four patient cases. By reviewing the selected articles, demographics, type of encephalitis, period after vaccination, clinical features, neuroimaging, CSF analysis and treatment details were collected.

#### A. AstraZeneca COVID-19 vaccine

The AstraZeneca COVID-19 vaccine (AZD1222, ChAdOx1) is a viral vector-based vaccine used for COVID-19. The efficacy of vaccine more than 14 days after the second dose was about 66.7%. Commonly reported adverse effects involve injection-site reaction and pain, headache, malaise, and nausea, typically settling within a few days.<sup>[8]</sup>

Table 1 outlines those articles that reported encephalitis following the AstraZeneca COVID-19 vaccine. In this category, we obtained 9 articles, which describe the clinical features of 13 patients. From the reported cases, 2 patients had died.

Author	Age/sex	Type of encephalitis	Period after vaccination	Clinical features	Neuroimaging & CSF analysis	Treatment
Takata et al. <sup>[9]</sup>	22/F	AE (possible)	Few days (2 <sup>nd</sup> dose)	Headache, fatigue, confusion, agitation, hallucinations, fever, disorientation	CSF: opening pressure of 30cm H <sub>2</sub> O, pleocytosis, IgG oligoclonal bands(+ve)	Ceftriaxone, acyclovir, lorazepam, olanzapine
Zuhorn et al. <sup>[10]</sup>	21/F	AE	5 days (1 <sup>st</sup> dose)	Headache, attention, concentration difficulties	CSF: pleocytosis EEG: diffuse slow theta rhythm	Dexamethasone
	63/F	AE	6 days	Gait deterioration, vigilance disorder, twitching, opsoclonus-myoclonus syndrome	EEG: diffuse slow theta rhythm CSF: pleocytosis	Methylprednisolone
	63/M	AE	8 days	Fever, aphasia	CSF: pleocytosis	-
Shin HR et al. <sup>[11]</sup>	35/F	AE	5 days (1 <sup>st</sup> dose)	Dysarthria, abnormal movements, anxiety, fever, rigidity, dystonia, motor aphasia, opening of jaw, hypophonia, drooling	MRI: swelling of the hippocampus, encephalomalacia in frontoparietal lobes EEG: diffuse beta wave activity, intermittent generalized delta activity	Methylprednisolone, immunoglobulins, rituximab
Kwon et al. <sup>[12]</sup>	57/F	AE	5 days (1 <sup>st</sup> dose)	Headache, fever, generalized convulsive seizure	MRI: restricted diffusion through the left insular and mesial temporal cortices, contrast enhancement CSF: pleocytosis, elevated protein, oligoclonal band (+) EEG: intermittent generalized delta activity	Methylprednisolone, Immunoglobulin, Rituximab
Permezel et al. <sup>[13]</sup>	63/M	ADEM	12 days (1 <sup>st</sup> dose)	Vertigo, fatigue, abdominal pain, disorientation, declining cognition, impaired attention, poorly responsive	MRI: bilateral foci (>20) of high T2 & FLAIR signal in the white matter	Corticosteroids, plasmapheresis  (Patient died)
Al-Quliti et al. <sup>[14]</sup>	56/F	ADEM	10 days	Generalized weakness, lower extremity myalgia, difficulty in the	MRI: T2&FLAIR showed hyperintensities in the subcortical & deep white matter involving	Hypertonic saline, methylprednisolone

				articulation of speech, anorexia, dysmetria	basal ganglia CSF: protein& glucose elevated	
Ancauet.a 1 <sup>[15]</sup>	61/ M	AHEM	4 days (1 <sup>st</sup> dose)	Fever, headache, apathy, generalized seizure	CT: diffuse hypodense areas in the right subcortical, frontotemporal&right thalamic region MRI: bilateral confluent cortical & subcortical FLAIR hyperintense lesions with hemorrhagic involvement of the basal ganglia CSF: moderate disturbance of the BBB	Methylprednisolone, plasmapheresis
	25/F	AHEM	2 days (1 <sup>st</sup> dose)	Cephalgia, back pain, fatigue, lack of sensation in legs, paraplegic syndrome, absent tendon reflexes, detrusor areflexia, difficulty urinating	MRI: longitudinal edema along the thoracic spinal cord with contrast enhancement, focal central hemorrhage, bi-hemispheric white matter lesions with focal contrast enhancement CSF: pleocytosis, increased albumin, intrathecalIgM synthesis	Methylprednisolone, Plasmapheresis
	55/F	AHEM	9 days (1 <sup>st</sup> dose)	Nausea, dizziness, meningism, spastic tetraparesis, coma	MRI: multiple FLAIR hyperintense&hemorrhagic lesions in the right temporal & parietal lobes, bilaterally in fronto-temporal distribution and in the right occipital lobe & left fronto-basal region CSF: pleocytosis, intrathecalIgM, IgG& IgA, trans-tentorial herniation, hydrocephalus occlusion	Right-sided decompressivehemispherectomy, Methylprednisolone  (Patient died)
V Rinaldi, G Bellucci et al. <sup>[16]</sup>	45/ M	ADEM	12 days (1 <sup>st</sup> dose)	Numbness of limbs, trunk & legs, limited visual acuity, slurred speech, difficulty swallowing, clumsy right hand movements, urge incontinence	MRI: large, poorly marginated T2-weighted hyperintensities in the pons, right cerebellar peduncle, right thalamus & multiple spinal cord segments. All lesions except the thalamic one & a single dorsal spinal area, showed blurred gadolinium enhancement on T1-weighted images CSF: pleocytosis	Methylprednisolone
Nagaratnam et al. <sup>[17]</sup>	36/F	ADEM	14 days (1 <sup>st</sup> dose)	Headache, fatigue, photophobia, bilateral visual disablement, subjective colour desaturation, aching	MRI: T1/FLAIR hyperintense lesions involving the subcortical white matter, posterior limb of bilateral internal capsules, pons& left	Methylprednisolone

				eye movements,	middle cerebellar peduncle, multiple internal punctuate foci of gadolinium contrast enhancement	
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Table 1: Reports of encephalitis post-AstraZeneca COVID-19 vaccination

**B. Pfizer-BioNTech COVID-19 vaccine**

The Pfizer-BioNTech COVID-19 vaccine consists a non-irritant mRNA.<sup>[18]</sup> This vaccine has 95% efficacy against COVID-19. According to WHO, two doses has to be administered with a 21 to 28 day interval for obtaining complete protection.<sup>[19]</sup> Side effects within 7 days post-vaccination are common and mild. Fever, chills, tiredness, and headache are commonly seen after the second dose of the vaccine.<sup>[18]</sup>

Table 2 outlines those articles that reported encephalitis following the Pfizer-BioNTech COVID-19 vaccine. In this category, we obtained 5 articles, which describe the clinical features of 5 patients. From the reported cases (5 patients), nobody had died.

Author	Age/sex	Type of encephalitis	Period after vaccination	Clinical features	Neuroimaging & CSF analysis	Treatment
Zlotnik et al. <sup>[20]</sup>	48/M	AE	18 days (2 <sup>nd</sup> dose)	Fatigue, memory deficit, anterograde amnesia	MRI: hyperintense signal on both medial temporal lobes	Methylprednisolone
Fernandes et al. <sup>[21]</sup>	16/M	Anti-GAD encephalitis	7 days (1 <sup>st</sup> dose)	Generalized tonic clonic seizures	EEG: bitemporal focal slowing with admixed sharp waves CSF: pleocytosis, protein elevation	Dexamethasone
Y. Kobayashi et al. <sup>[22]</sup>	46/F	Brainstem encephalitis	5 days (2 <sup>nd</sup> dose)	diplopia	MRI: lesion on the dorsal pons across the midline & no gadolinium enhancement	Methylprednisolone
A. Vogrig et al. <sup>[23]</sup>	56/F	ADEM	14 days (1 <sup>st</sup> dose)	Malaise, chills, unsteadiness of gait	MRI: hypeintensities on FLAIR sequences involving the left cerebellar peduncle, with moderate mass effect on the 4 <sup>th</sup> ventricle	Prednisone
Walter et al. <sup>[24]</sup>	30/M	RE	21 days (2 <sup>nd</sup> dose)	Malaise, headache, taste disorder, facial paralysis (left side), gait disturbance by ataxia, hypoglossal nerve paralysis	MRI: weak FLAIR hyperintensity of the brainstem, mesencephalon & cerebellar around 4 <sup>th</sup> ventricle without contrast enhancement CSF: pleocytosis	Methylprednisolone

Table 2: Reports of encephalitis post-Pfizer-BioNTech COVID-19 vaccination

**C. Moderna COVID-19 vaccine**

The Moderna COVID-19 vaccine is an mRNA-based vaccine which required to be taken as 2 doses, given 4-8 weeks apart. Those who are of 18 years and older who received a Moderna primary series should get a booster dose.<sup>[25]</sup> This vaccine has approximately 94.1% efficacy against COVID-19.<sup>[26]</sup> The most common side effects were pain at the injection site, chills, vomiting, arthralgia, fatigue,

nausea, headache, myalgia, axillary swelling and erythema at the injection site.<sup>[27]</sup>

Table 3 outlines those articles that reported encephalitis following Moderna COVID-19 vaccine. In this category, we obtained 3 articles, which describe the clinical features of 3 patients. From all reported cases (3 patients), nobody had died.

Author	Age/s ex	Type of encephalitis	Period after vaccination	Clinical features	Neuroimaging & CSF analysis	Treatment
Torrealb a-Acosta Get al. [28]	77/M	Meningoencephalitis	2 days (1 <sup>st</sup> dose)	Dizziness, fever, rashes, headache, double vision, confusion	CSF:pleocytosis, increased protein  vEEG: generalized slow theta range with state changes and reactivity	Methylprednisolone (4 days) following prednisone
Sluyts et al. [29]	48/ trans male	AE	6 days (booster dose)	Agitation, physical aggression, mutism, left arm: paretic &atactic, bradyphrenic, confused	CSF: pleocytosis, elevated protein MRI: small left internal capsule developmental venous anomaly	Ceftriaxone, amoxicilline, acyclovir
K. Kania et al. [30]	19/F	ADEM	14 days (1 <sup>st</sup> dose)	Headache, fever, nausea, vomiting, back & neck pain, urinary retention	MRI: multiple hyperintense lesions in T2 weighted & FLAIR images located in both brain hemispheres, pons, the medulla oblongata, and cerebellum CSF: pleocytosis, elevated protein and RBC	Methylprednisolone

Table 3: Reports of encephalitis post-Moderna COVID-19 vaccination

*D. Other Vaccines (Sinopharm and Sputnik V)*

Sinopharm COVID-19 vaccine is an inactivated vaccine having a dead copy of corona virus.<sup>[31]</sup> It is recommended by the WHO that an interval of 3–4 weeks should be given between the first and second dose. The vaccine is not advocated for persons younger than 18 years of age.<sup>[32]</sup>

The Sputnik V COVID-19 vaccine is a vector vaccine having two vectors (Ad26 priming and Ad5 boost).<sup>[33]</sup> This

vaccine has a high efficacy of >90% in preventing symptomatic cases in phase III trials.<sup>[34]</sup> The common adverse effects include flu-like symptoms, headache, fatigue and injection site reactions.<sup>[35]</sup>

Table 4 outlines those articles that reported encephalitis after the Sinopharm and Sputnik V. In this category, we obtained 3 articles, which describe the clinical features of 3 patients. From all reported cases (3 patients), nobody had died.

Author	Age/s ex	Type of encephalitis	Period after vaccination	Clinical features	Neuroimaging & CSF analysis	Treatment
M. Etemadi faret al. [36]	50/F	Anti-NMDAR encephalitis	20 days (2 <sup>nd</sup> dose)	Behavioural differences, muscle pain, vomiting, limb weakness, ataxia, dizziness, weakness, agitation, Babinski signs	MRI: plaques in periventricular, juxtacortical and cortical area	Methylprednisolone
Cao et al. [37]	24/F	ADEM	14 days (1 <sup>st</sup> dose)	Reduced memory, headache, fever, spasticity, weakness in extremities, loss of appetite	CSF:pleocytosis, oligoclonal band (+) MRI: abnormal signals in the B/L temporal cortex, lesions EEG: epileptiform waves	Immunoglobulin, diazepam, levetiracetam
L.G.Lazaroet al. [38]	26/F	ADEM	28 days (1 <sup>st</sup> dose)	Disorientation, inappropriate behaviour, headache, gait imbalance, declined memory, hypoprosia, anosognosia, incoherent speech, visuospatial failures, right upper limb weakness, gait ataxia	CSF: normal, OCB (+) MRI: nodular hyperintense lesions on T2/FLAIR without restricted diffusion	Methylprednisolone

Table 4: Reports of encephalitis after Sinopharm and Sputnik V COVID-19 vaccination

### E. Encephalitis

Encephalitis can result in morbidity and mortality worldwide. Neurologists should directly care the patients with encephalitis and should be able to differentiate between encephalitis and the many conditions that mimic it. Encephalitis occurs as a result of the brain parenchyma inflammation, and also may be caused by infections or autoimmune conditions.<sup>[39]</sup> Even if encephalitis occur in people of all ages, the incidence is higher in paediatric group. Most studies show a slight predominance of encephalitis in males.<sup>[40]</sup> Encephalitis leads to a change in the state of consciousness. The clinical features include headache, disorientation, fever, seizures, particular neurological findings, behavioural disturbances, abnormal brain waves or abnormal diagnostic imaging. The disease is distinguished by a decline of the senses that extent from drowsiness to coma. The neurological findings include staggering, declined reflexes, difficulty urination and vision loss.<sup>[41]</sup>

### F. Characteristics of Reported Cases of Encephalitis Following COVID-19 Vaccination

The entire cases of encephalitis in this study were announced after AstraZeneca (13), Pfizer-BioNTech (5), Moderna (3), Sinopharm (2) and Sputnik V (1). A female predominance was noted in overall cases involving 15 females (62%), 8 males (33%) and 1 trans-male, ranging in age between 16 and 77 years. There was 1 paediatric case, of age 16. Young adult cases included 9 patients, 1 male and 8 females, ranging from 19 to 36 years. Older adult category included 14 patients, 6 males, 7 females and 1 trans-man, ranging from 46 to 77 years of age.

Most patients showed a symptom onset within a week following vaccination (range: 2-7 days). The reports had shown that 15 patients evolved symptoms after the first dose, 5 patients after the second dose, 1 patient after the booster dose and in 3 cases the dose (1<sup>st</sup>/2<sup>nd</sup>) was not mentioned. Fever and headache were the typical presenting symptom in the patients. Additionally, symptoms such as fatigue, vomiting, myalgia, gait disturbances, movement disorders, behavioural changes etc. were reported.

By analysing cerebrospinal fluid, pleocytosis was found in 14 patients (58 %) and elevated protein levels were found in 7 patients (29 %). Electroencephalographic abnormalities were seen in 7 patients (29%) and diagnostic imaging abnormalities were noted in 18 patients (75%).

Most of the patients were treated with intravenous methylprednisolone and some of the patients had undergone plasmapheresis. Majority of the patients showed positive response to the treatment and their clinical conditions improved. Out of 24 patients, 2 had died.

### G. Pathogenesis

Vaccinations can lead to a strong expression of pro-inflammatory cytokines and a T cell response. This was also seen in COVID-19 vaccine. Following vaccination, antigens are identified as potential pathogens. Induction and transcription of many target genes occurs which leads to synthesis and release of pyrogenic cytokines (IL-1, IL-6,

TNF- $\alpha$ , and PG-E2) into the bloodstream that mimic the response to natural infection. The immune system then begins a series of innate immune events including phagocytosis, release of inflammatory mediators including chemokines and cytokines, activation of complement, and cellular recruitment. Mediators and products of inflammation can influence other body systems causing systemic side-effects, and neuroinflammation in some subjects after microglia activation, depending on the immunogenetic background and the innate immune memory.<sup>[10]</sup>

### H. Diagnosis

Diagnosis is done by a combination of clinical, laboratory, neuroimaging, and electrophysiologic findings.<sup>[39][42]</sup> To differentiate encephalitis from encephalopathy, key features include presence of fever, CSF pleocytosis, or MRI or EEG changes compatible with encephalitis. Even if such factors capture most patients with clinically significant encephalitis, some will be missed. For instance, localized forms of brain inflammation may cause focal neurologic deficits without affecting consciousness or behavior.<sup>[39]</sup>

- Major diagnostic criterion for encephalitis:
  - Patients presenting with altered mental status (declined or altered consciousness, lethargy or personality change) lasting  $\geq 24$  hour with no alternative cause identified.
- Minor diagnostic criteria for encephalitis:
  - Fever of  $\geq 38^{\circ}$  C ( $100.4^{\circ}$ F) within 72 hour
  - Generalized or partial seizures not fully connected to a pre-existing seizure condition
  - Newly discovered focal neurologic findings
  - CSF WBC count  $\geq 5$ /cubic mm
  - Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis
  - Abnormal electroencephalography that is consistent with encephalitis and not connected to another cause.<sup>[43]</sup>

### I. Treatment Strategies for Autoimmune Encephalitis

Suitable plan of action for immune modulation must be instigated in patients with autoimmune etiology. First-line agents for acute immune-mediated encephalitis generally include corticosteroids, i.e. IV methylprednisolone, 1g daily for 3-5 days; IV immunoglobulin, typically 2 g/kg body weight given over 5 days (400 mg/kg/day), and plasmapheresis, 1 session every other day for 5-7 cycles, either alone or in combination.<sup>[44]</sup>

If there is no proper response to first-line therapy after 2-4 weeks, it is recommended to add second-line agents, including rituximab 375 mg/m<sup>2</sup> weekly for 4 weeks or two doses of 1000 mg 2 weeks apart, or, cyclophosphamide, 600-1000 mg/m<sup>2</sup> for 3-6 months.. A few case series have shown response to alternative therapy including proteasome inhibitors that block plasma-cell generation (bortezomib), interleukin (IL)-6 inhibition (tocilizumab), or low dose IL-2 in patients who did not respond to conventional second-line agents.<sup>[45]</sup>

Particularly, if the encephalitis is of unknown etiology, empiric immunosuppressive therapy should be considered.<sup>[39]</sup>

#### IV. CONCLUSION

Following COVID-19 vaccination, a broad range of serious neurological complications, including encephalitis, has been identified. In spite of being a rare condition, it is serious and likely fatal. Healthcare professionals should be conscious of the side effects and should pay attention to recognize them early. Diagnosing the condition early can quickly initiate appropriate treatment thereby provide the patients with a better outcome.

#### ACKNOWLEDGEMENT

We would like to express our gratitude to Dr. G. Jeladharan, senior gastroenterologist, SK Hospital, Trivandrum for guiding us in the preparation of this review article.

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