Acute disseminated encephalomyelitis post-SARS-COV-2 vaccination with Chadox1 nCov-19 (AZD1222) – A rare case report

Meghna Sivji[1], M V Vidya[2], Thara Pratap[3], Muhammed Jasim Abdul Jalal[4]

From [1]Intern, Department of Internal Medicine, Pushpagiri Institute of Medical Sciences and Research Centre, Thiruvalla, [2]Senior Consultant, Departments of Neurology, VPS Lakeshore Hospital, Kochi, [3]Senior Consultant, Department of Radiology, VPS Lakeshore Hospital, [4]Consultant, Department of Internal Medicine and Rheumatology, VPS Lakeshore Hospital, Kochi, Kerala, India

Correspondence to: Muhammed Jasim Abdul Jalal, Department of Internal Medicine and Rheumatology, VPS Lakeshore Hospital, Kochi, Kerala, India. E-mail: jasimabduljalal@yahoo.com

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ABSTRACT

Background: Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disease of the CNS, characterized by fulminant multifocal neurologic injury and distinct neuropathologic findings. **Case Report:** We report a case of a 49-year-old female who presented with progressive weakness of the right side of the body of 1-week duration. Clinical, laboratory and radiological features favored demyelination. There was temporal association with taking SARS-COV-2 vaccination (ChAdOx1 nCoV-19 [AZD1222]). She was treated with a course of steroids and made a good recovery. **Conclusion:** To the best of our knowledge, this is a rare case of ADEM noticed after ChAdOx1 nCoV-19 vaccine (AZD1222).

Key words: *ADEM, ChAdOx1 nCoV-19 (AZD1222), COVID-19 infection, Covishield, SARS-COV-2 infection, SARS-COV-2 vaccination, SARS-COV-2 virus, Vaccine adverse events*

Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disease of the CNS, characterized by fulminant multifocal neurologic injury and distinct neuropathologic findings [1]. ADEM is classically thought to be preceded by vaccination or a systemic infection, usually upper respiratory tract infections [2]. Viral infections appear to trigger approximately up to three-quarters of ADEM cases. About 5% of ADEM events are associated with immunization for varicella, rabies, measles, mumps, rubella, influenza, hepatitis B, Japanese B encephalitis, diphtheria, pertussis, and tetanus [3].

Most ADEM cases are clinically monophasic, but a small number are recurrent (multiphasic disseminated encephalomyelitis) [4] or subsequently realized to be the initial presentation of a relapsing CNS demyelinating disease such as MS, myelin oligodendrocyte glycoprotein (MOG) antibody disease, or neuromyelitis optica spectrum disorder.

In one study, it was noted that 61% of ADEM cases developed symptoms 2–31 days after vaccination [5]. Another study involving 64 million vaccine doses did not show a significant association between ADEM and prior immunization [6].

CASE REPORT

A 49-year-old female previously asymptomatic presented with complaints of the right lower limb paresthesia of 1-week duration. It started in the right foot and slowly ascended up to the waist level. She also noted difficulty in walking in the form of buckling of knees and difficulty in climbing stairs. She noted weakness of the right hand in the form of difficulty in writing for the past 2 days and had slurring of speech since a day. There was no history of headache or vomiting or fever. She gave history of taking second dose of SARS-COV-2 ChAdOx1 nCoV-19 vaccine (AZD1222) (COVISHIELD) 3 weeks before the onset of symptoms.

Clinical examination revealed a hemodynamically stable patient with blood pressure of 130/80 mmHg and heart rate of 80/min. Higher mental functions were normal. Pupils were equal and reacting to light without afferent pupillary defect. Fundus examination was normal. She had mild right upper motor neuron facial weakness, other cranial nerves being normal. She had weakness involving right hand grip and intrinsic muscles, proximal power being normal. Hip flexion was 2/5 and power in all other groups being normal. She had sensory impairment for all sensory modalities below T12 level on the right side. Her deep tendon reflexes were brisk bilaterally and plantar response was extensor on right side.

Blood investigations including complete blood counts, renal and liver function tests, thyroid function tests, and electrolytes were all normal. B12 levels were on the lower limit of normal. Vasculitis works up including antinuclear antibodies, antiphospholipid antibody, and ANCA serology were negative. SARS-COV-2 RTPCR was negative.

MRI brain favored a diagnosis of tumefactive demyelination (Fig. 1). FLAIR sequences showed hyper intense lesion in the left

posterior temporal region with other similar hyper intense lesions in the right temporal and ganglionic nucleus. She underwent a controlled lumbar puncture – cerebrospinal fluid analysis which showed protein of 29 mg%, glucose of 85 mg% (corresponding blood sugar 118 mg%) without any cells. CSF cytology was negative for atypical cells. An infective panel for bacteria, viruses, and fungi was negative. Anti-NMOSD panel including aquaporin 4 and MOG antibodies was negative. Multiple sclerosis evaluation panel revealed no evidence of oligoclonal bands or intrathecal IgG synthesis. Visual Evoked Potentials showed marginal increase in P100 latencies bilaterally.

Hemogram was normal. CRP was negative. Procalcitonin was normal. CSF study did not show any infective etiology. Blood, urine, and CSF cultures did not show growth of any organisms.

Overall features were suggestive of tumefactive demyelination and there was a temporal association with SARS-COV-2 vaccination. She was given IV Methyl Prednisolone 1 g for 5 days with which she had marked improvement in her limb power. She had 5/5 power in both upper and lower limbs and was able to walk unsupported. She was sent home on a short course of oral steroids (Oral Prednisolone 1 mg/kg tapered over 2 weeks).

However, on stopping steroids, she was noted to have weakness on the right side. Repeat MRI was done which revealed moderate resolution of almost all lesions; however, there was minimal enlargement of the left parasagittal lesion with persisting enhancement (Fig. 2). The lesion in the left centrum semi-ovale appeared conspicuous with open ring enhancement.

She was given another course of IV methyl prednisolone and her weakness improved to 5/5. We had thought of starting alternate immunotherapy such as plasmapheresis or immunoglobulins; however, the plan was deferred in view of good improvement. Since then, the tapering of steroids was done slowly over 10 weeks monitoring any clinical deterioration. Finally, we could taper off steroids fully by the end of 3 months after a follow-up MRI which revealed (Fig. 3) significant resolution of all lesions with only faint enhancement of lesion in centrum semi-ovale.

DISCUSSION

ADEM can be classified as an adverse event following immunization, defined as any untoward medical occurrence that follows immunization and does not necessarily have a causal relationship with the usage of the vaccine [7].

ChAdOx1 nCoV-19 vaccine (AZD1222) consists of a replication-deficient chimpanzee adenoviral vector ChAdOx1, containing the SARS-CoV-2 structural surface glycoprotein antigen (spike protein; nCoV-19) gene [8]. In addition to local and systemic side effects of the ChAdOx1 nCoV-19 vaccine without major clinical relevance, the growing number of recent reports of autoimmune induced thrombocytopenia with subsequent thrombosis has become a cause for concern.

Vaccinations can cause a strong expression of pro-inflammatory cytokines and a T cell response. This was also demonstrated for ChAdOx1 nCoV-19 vaccine [9]. After vaccination, antigens are recognized as potential pathogens by both conserved pathogen and damage-associated molecular patterns as well as pattern-recognition receptors that are found on local or peripheral circulating immune cells (e.g., monocytes and macrophages) and on resident stromal cells [10]. Induction and transcription of many target genes occur, resulting in synthesis and release of pyrogenic cytokines (i.e., interleukin IL-1, IL-6, tumor necrosis factor-alpha, and prostaglandin-E2) into the bloodstream that mimics the response to natural infection. Subsequent to stimulation, the immune system initiates a complex 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 in the circulation can affect other body systems to cause systemic side-effects and ultimately can cause neuroinflammation in some subjects after microglia activation, depending on the immunogenetic background and the innate This could be a possible explanation for association between vaccination and ADEM.

ADEM is more common in children, consensus criteria for clinically diagnosing ADEM exist for children only [1]. In the absence of a biomarker, the diagnosis of ADEM is largely reliant on the clinical presentation supported by typical MRI findings and the exclusion of competing diagnoses through ancillary testing. Encephalopathy was not required for inclusion, in line with multiple studies suggesting its lower prevalence in adult populations [2,12].

ADEM is characterized by multifocal lesions involving asymmetrically the white matter which can be large and tumefactive [11,12], while CSF may be normal in as many as 60% of the cases.

Reviewing the literature, we could get only a few reports of SARS-COV-2 vaccination associated ADEM. Two cases of patients

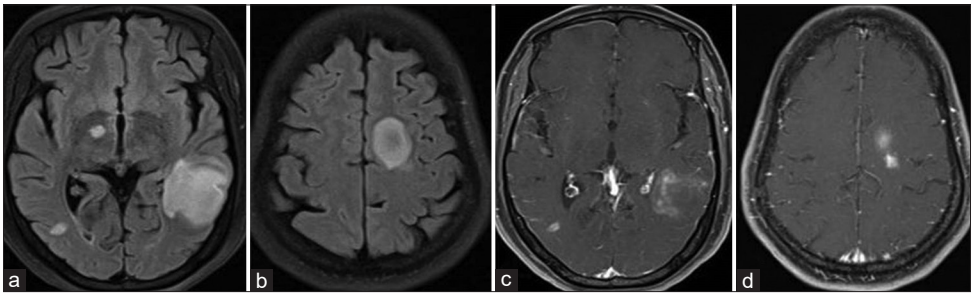

Figure 1: (a) FLAIR hyperintense lesion in the left posterior temporal region other similar hyperintense lesions in the right temporal and ganglionic nucleus. (b) Similar lesion in the left centrum semi-ovale. (c and d) Post-contrast study shows patchy enhancement of both lesions

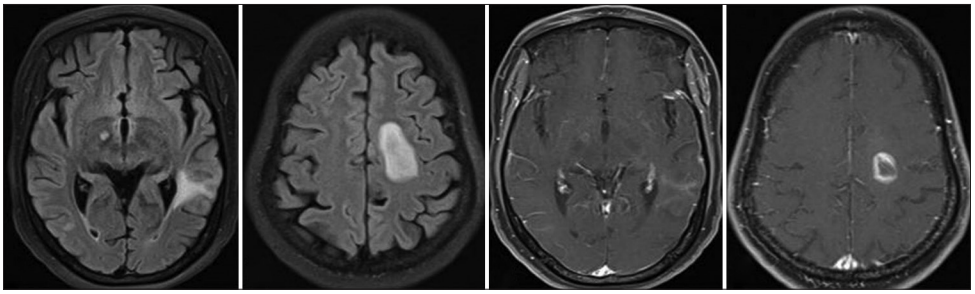

Figure 2: Follow-up MRI shows moderate decrease in size of lesions; however, the lesion in the left centrum semi-ovale appears conspicuous with open ring enhancement

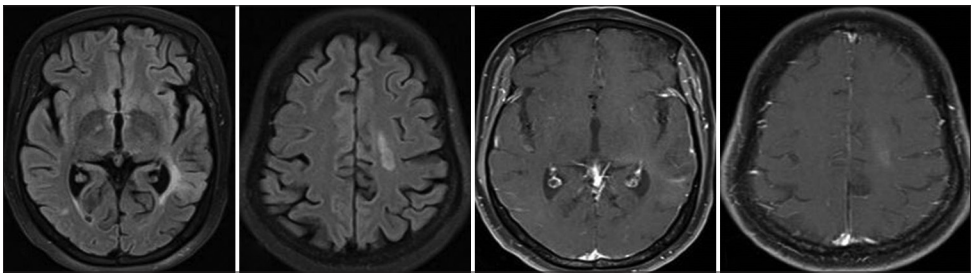

Figure 3: Significant resolution of all lesions with only faint enhancement of lesion in centrum semi-ovale

with ADEM following SARS-CoV-2 vaccination, two women both received inactivated SARS-CoV-2 vaccine of Sinovac (Vero Cells, Beijing Institute of Biological Products Co., Ltd., Beijing, China) [13,14]. The first woman revealed symptoms 2 weeks after vaccination; she presented with somnolence and memory decline and improved after steroids and IV immunoglobulin therapy. The second one was admitted to the hospital after the first tonic-clonic seizure 1 month after vaccination. She had typical scattered, demyelinating lesions in the brain, but due to lack of encephalopathy, it was called ADEM-like presentation.

In Italy, a 56-year-old woman with a previous history of post-infectious rhombencephalitis was diagnosed with ADEM 2 weeks after receiving the first dose of mRNA-based vaccine to SARS-CoV-2 [15]. She was treated with steroids and improved significantly over 50 days.

Another case has been reported of a 19-year-old female developing ADEM 2 weeks after she received the first dose of SARS-CoV-2 mRNA vaccine (Moderna COVID-19 Vaccine, ModernaTX, Inc. USA). She fully recovered with steroids [16].

Our patient was previously asymptomatic. The symptoms started 3 weeks after second dose of SARS-COV-2 vaccination. There were multifocal large lesions (tumefactive demyelination). Radiologically, it was more in favor of demyelination. Her cerebrospinal fluid cytology was negative for atypical cells. Infections were ruled out by extensive infective panel for bacteria, fungi, and viruses in CSF. Vasculitis work up was negative. Causes of recurrent demyelination such as NMOSD and multiple sclerosis were ruled out. Autoimmune encephalitis and paraneoplastic antibody panel were also negative. She had good initial improvement with steroids, who, however, had worsening in limb power on tapering steroids which needed a slow taper. Alternate immunotherapy was planned; however, it was deferred in view of good response to steroids.

To the best of our knowledge, this is a rare case of ADEM noticed after ChAdOx1 nCoV-19 vaccine (AZD1222). Until today, more than 3 billion doses of covid vaccine have been inoculated, which means that it is a very rare adverse event of the vaccine. Hence, it does not impair the importance of COVID-19 vaccinations during the pandemic, where one has the risk of numerous complications, and even death. Clinicians should be aware of such adverse events and should treat them promptly.

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