Post Covid19 vaccination Acute disseminated Encephalomyelitis: A case report in Bangladesh

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Abstract

Acute disseminated encephalomyelitis (ADEM) is an inflammatory usually monophasic demyelinating disease of the central nervous system. ADEM is one of several categories of primary inflammatory demyelinating disorders of the central nervous system. Other diseases include multiple sclerosis, optic neuropathy, acute transverse myelitis, and neuromyelitis optica (Devic's disease). Post infectious

And post-vaccination encephalomyelitis make up most of cases. Post-vaccination ADEM has been associated with several vaccines such as rabies, diphtheria–tetanus–polio, smallpox, measles, mumps, rubella, Japanese B encephalitis, pertussis, influenza and hepatitis B vaccine. We found a case of ADEM which is associated Covid19 vaccination as the precipitating factor. A patient presenting with altered level of consciousness & seizure within 3 weeks of "messenger RNA Covid 19 vaccination and diagnosed as ADEM after all investigations & completely cured after conservative management.

1. Introduction

ADEM is an immune-mediated disorder of the central nervous system (CNS), typically starts with subacute onset of neurologic symptoms and signs within days to weeks after a viral infection or vaccination. ADEM is also known as "postinfectious,""parainfectious," "postexanthematous," or "postvaccinal" encephalomyelitis[1].The incidence of ADEM has been reported to be between 0.4 and 0.8 per 100,000 of population[2] with a median age of onset of 4.5 to 7.5 in pediatric studies[3] and 33.5 in a study of adult patients[4]. ADEM typically appears with onset of neurologic symptoms 2 to 30 days after the occurrence of a preceding infection or vaccination[3]. In around one third of children and half of adults presenting with the disease a clear preceding infection or vaccination is not found[3]. ADEM usually presents as a monophasic immune mediated demyelinating disease, and neurologic manifestations depend upon site of involvement of CNS. The most common presentations including obtundation and depressed consciousness; unilateral or bilateral long tract signs (85%); acute hemiparesis (76%); and ataxia (59%)[3], Meningismus (26%–31%), caused by inflammation in subarachnoid space[5] . Motor deficits occur in both adult and pediatric cases but sensory deficits are more frequent in adults and seizures predominate in pediatric cases[3].

ADEM displays a monophasic disease course, rare cases of disease relapse have been described in some studies. Long-term clinical and imaging follow-up has shown the resolution of lesions with no long-lasting neurologic impairments in most of these multiphasic cases[6].

2. Case Presentation

A 55-year-old male presented in early February 2021 with a 1-week history of headache, history Of increasing daytime somnolence, fluctuating alertness and orientation consistent with delirium then 2 episodes of convulsion followed by loss of consciousness. He had received the Messanger RNA Covid 19 vaccine from Dubai where he did his job 3 weeks prior to symptom onset and now returning to Bangladesh when he felt sick. His past medical history was unremarkable and he was not receiving regular medication. On examination, his vitals are normal including saturation & respiratory rate & pattern. His GCS was 8 (E2, V3, M3) (Fig A). All cranial nerves were intact. Regarding motor examination he had spastic quadriplegia (All jerks of upper & lower limbs are exaggerated, plantar bilateral extensor with positive bilateral Hoffman sign) but sensory examination could not be evaluated properly. The remainder medical examination was otherwise unremarkable. He underwent an initial brain MRI, which showing bilateral symmetrical T2 hyperintensity involving predominantly white matter (Fig B, D, and E)

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Investigations revealed normal full blood count (FBC), erythrocyte sedimentation rate (ESR) and biochemistry. A CT brain scan was normal. An initial lumbar puncture found a CSF protein concentration of 0.75 g/L (Normal < 0.40) and glucose of 3.1 mmol/L (Normal = 2.4–5.4) with 200 white blood cells per cmm (95% mononuclears). Herpes simplex 1 & 2, Varicella zoster, enterovirus and tuberculosis polymerase chain reaction (PCR) were negative.

The patient was diagnosed with ADEM and treated with high dose intravenous steroids consisting of 1g Methylprednisolone daily for 5 days followed by oral tapering steroids along with other supportive cares. His orientation and alertness returned to normal within 2 weeks. On follow-up review 1 month later, he had fully recovered Fig C). A repeat MRI of the brain was significantly improved. The patient's clinical presentation was most likely due to post-covid 19 vaccination ADEM.

A patient with clinical presentation was most likely due to post-influenza vaccination optic neuritis and encephalomyelitis was found[7].Another patient with a similar biphasic presentation followed an anti-rabies vaccination[8] has been reported in a 45-year-old male who presented with transverse myelitis 14 days after anti-rabies vaccination and developed bilateral optic neuritis 1 month later.

Fig A

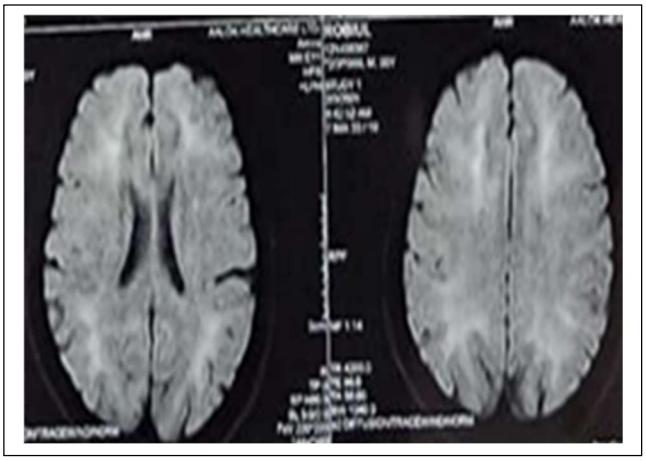

Fig B: MRI FLAIR

Fig C

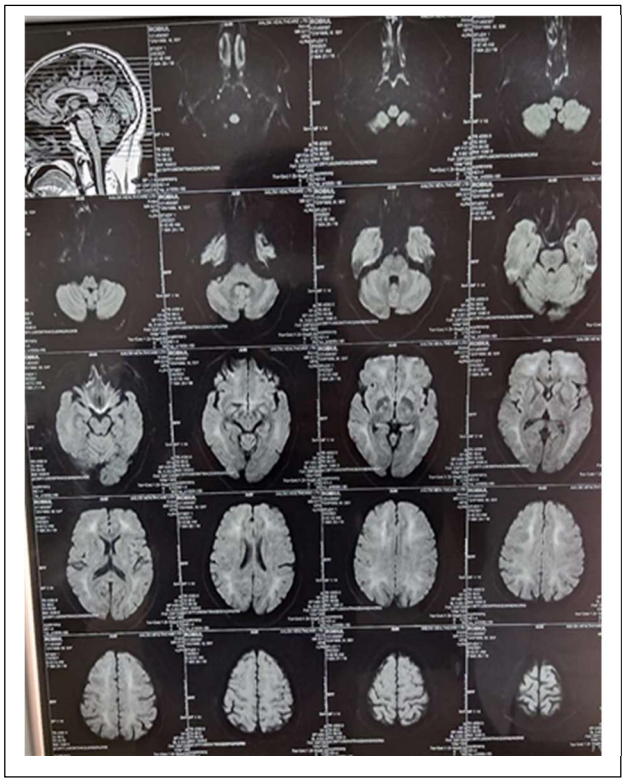

Fig D: MRI FLAIR

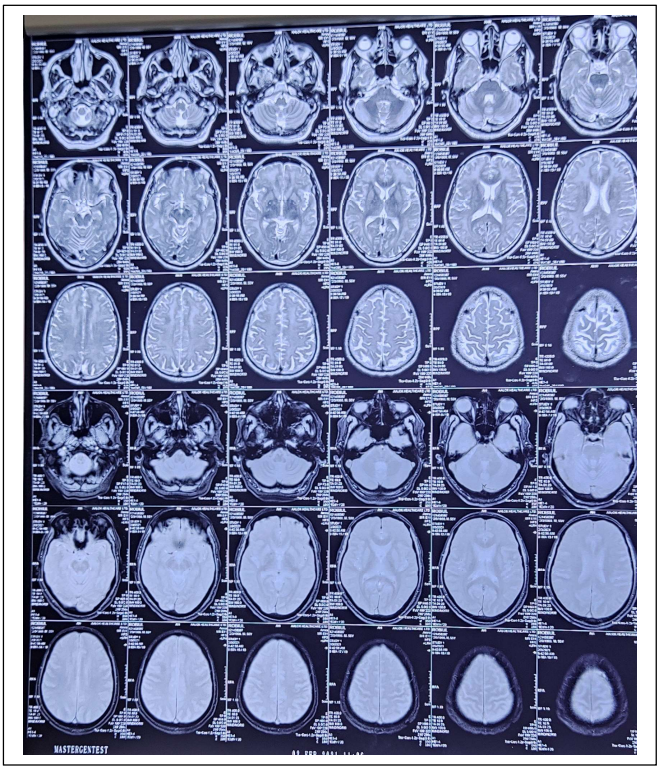

Fig E: MRI T2W & GRE

3. Discussion

3.1 Case definitions for ADEM

The following case definitions for ADEM have been extractedbfrom Sejvar et al. and the Brighton Collaboration Encephalitis Working Group[9]. The case definitions are structured in three different levels of diagnostic certainty.

a) Level 1 of diagnostic certainty

i. Demonstration of diffuse or multifocal areas of demyelination by histopathology.

OR

ii. Focal or multifocal findings referable to the central nervous system, including one or more of the following:

Encephalopathy (see case definition for encephalitis for specification of encephalopathy),

Focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness),

Cranial nerve abnormality/abnormalities,

Visual field defect/defects,

Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex),

Motor weakness (either diffuse or focal; more often focal),

Sensory abnormalities (either positive or negative; sensory level),

Altered deep tendon reflexes (hypo- or hyperreflexia, asymmetry of reflexes), or

Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus,

AND

iii. MRI findings displaying diffuse or multifocal white matter lesions on T2-weighted, diffusion-weighted

(DWI), or fluid-attenuated inversion recovery (FLAIR) sequences (± gadolinium enhancement on T1 sequences),

AND

iv. Monophasic pattern to illness (absence of relapse within a minimum of 3 months of symptomatic nadir).

b) Level 2 of diagnostic certainty

i. Focal or multifocal findings referable to the central nervous system (as outlined in the Level 1 of diagnostic certainty section),

AND

ii. Magnetic resonance imaging (MRI) findings (as outlined in the Level 1 of diagnostic certainty section),

AND

iii. Insufficient follow-up time achieved to document absence of relapse within a minimum period of 3 months following symptomatic nadir.

c) Level 3 of diagnostic certainty

i. Focal or multifocal findings referable to the central nervous system (as outlined in the Level 1 of diagnostic certainty section),

d) Exclusion criteria for all levels of diagnostic certainty

i. Presence of a clear alternative acute infectious or other diagnosis for illness,

ii. Recurrence or relapse of illness at any point following a 3 month period of clinical improvement from symptomatic nadir, or

iii. If known, MRI findings or histopathologic data inconsistent with the diagnosis of ADEM.

3.2 Etiopathogenesis

ADEM is more commonly preceded by a viral infection, with measles, varicella, rubella, mumps, and influenza being the more frequently reported infections (Box 1). The incidence of ADEM is 1 to 2 per 1000 measles infections, being more common in children above 5 years of age[10]. Compared with measles, neurologic complications of acute varicella zoster virus infection are much less common (1:10,000 of infections), with acute cerebellar ataxia and acute toxic encephalopathy being the most common forms. Neurologic complications of rubella are even less common that varicella, with an incidence of around 1:20,000 infections, but with a high mortality rate of approximately 20%[11].

Box 1. Causes of postinfectious and postvaccinal encephalomyelitis

Viral infections

- Measles
- Varicella-zoster
- Rubella
- Mumps
- Influenza A and B
- Hepatitis A
- Hepatitis C
- Epstein-Barr virus
- HIV
- Nonspecific upper respiratory tract infection
- Human herpsevirus-6 a
- Herpes simplex virus a
- Dengue virus a
- Coxsackie B a
- Coronavirus a

Nonviral infections

- Group A b-hemolytic streptococci
- Legionella pneumophila
- Salmonella typhi
- Leptospirosis
- Plasmodium falciparum
- Mycoplasma pneumoniae
- Rickettsia rickettsii
- Borrelia burgdorferi

Postvaccinal ADEM

- Rabies vaccine made in brain or spinal cord preparations
- Measles
- Japanese encephalitis virus
- Oral polivirus

- Tetanus toxoid
- Influenza
- Hepatitis B recombinant vaccine
- Tick-borne encephalitis

a Denotes single case-reports.

Postvaccinal acute disseminated encephalomyelitis

Vaccines produced in CNS tissue causing a higher risk of postvaccinal encephalomyelitis. After availability of nonneural human diploid cell vaccines for rabies, ADEM induced by rabies neural vaccine (Semple form) is now only of historical event[12]. Vaccines to Japanese encephalitis virus prepared from mouse brain–derived virus, however, is still the principal form of vaccine used for this mosquito-borne encephalitis that occurs throughout East Asia and Australia. Encephalomyelitis, have been described after Japanese encephalitis virus vaccinations[13]. The occurrence of postvaccinal encephalomyelitis following vaccination with live attenuated measles vaccine is not well documented. Encephalomyelitis associated with tetanus toxoid[14], oral polio[15], influenza[16], and hepatitis B recombinant vaccines have also been described[17].

The pathogenic process leading to development of postvaccinal encephalomyelitis is generally believed to be the same as the virus-associated ADEM (ie, molecular mimicry or altered immunoregulation). Antigenic epitopes, comprising of delicate structural or partial amino-acid sequence homologies, are shared between an inoculated pathogen or vaccine, and a host CNS protein[18]. As a result, the pathogen is not recognized as "foreign" for elimination, nor "self" for immune tolerance. At the inoculation site the pathogen is initially processed by T cell activation and cross activation of antigen-specific B cells. These autoreactive cells can enter the CNS during immune surveillance and by chance, may encounter the homologous myelin protein. The local reactivation by antigen presenting cells subsequently culminates in a destructive autoimmune process in the CNS[18]. Much research has focused on T cell mediated autoimmune response to myelin autoantigens, such as MBP, proteolipid protein and myelin oligodendrocyte glycoprotein, which can induce ADEM[19]. Some studies have suggested a role for B cells and antibodies to gangliosides such as GM1 and GD1a, while others have identified T helper 2 cells reactive to MBP, which were found in the peripheral blood of ADEM patients[19].

Currently, a number of COVID-19 Vaccines have been launching to the market, and the others are still in phase 3 clinical trials. Different techniques and mechanism are in use to develop them.

Given the speed of this development and issuing, concerns exist. It becomes increasingly vital to emphasize the safety of the coming vaccination options in neurological disorders. Some studies also suggest that post-vaccination demyelination is most likely acting as triggers of clinical disease expression in individuals who already have an underlying disease process[20].

3.3 clinical presentation

Classic descriptions of ADEM involve a preceding illness, or less often a vaccination, in most but not all cases. After a lag time of a few days to two months (mean 26 days) [21], the typical presentation involves the acute onset of multifocal neurologic symptoms, often with rapid deterioration prompting hospitalization[21].

Nonspecific signs that can accompany ADEM include headache, fever, nausea, and vomiting[22]. Altered mental status (ie, encephalopathy) is present in 20 to 56 percent of adult cases, ranging from irritability, confusion, and psychosis to somnolence and coma[22]. Most patients present with motor deficits; these may involve a single limb or result in paraparesis or tetraparesis[23]. Sensory deficits are frequent. Brainstem involvement is also common, including oculomotor deficits and dysarthria[24]. Additional signs and symptoms may include meningismus, ataxia, aphasia, optic neuritis (sometimes bilateral), nystagmus, extrapyramidal movement disorders, urinary retention, seizures, and increased intracranial pressure[23].

3.4 Investigations

Neuroimaging — MRI is the imaging modality of choice, although an urgent CT scan may be necessary in order to exclude other causes of neurologic disease. Lesions associated with ADEM are typically bilateral but may be asymmetric and tend to be poorly marginated[25]. Most patients have multiple lesions in the deep and subcortical white matter, characteristic of demyelination. On MRI, the lesions of ADEM are hyperintense on T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences and are usually inconspicuous on unenhanced T1-weighted sequences. Lesions may be seen in the periventricular and subcortical white matter, including corpus callosum and centrum semiovale, as well as in the gray matter, including the cortex, basal ganglia, and thalamus[25]. Infratentorial lesions in the brainstem, cerebellum, and spinal cord are common[23].Gadolinium enhancement of MRI lesions in ADEM is variable. Enhancing and nonenhancing lesions may appear together in the same scan[23, 25]. With diffusion-weighted MRI imaging (DWI), lesions associated with ADEM show restricted diffusion (ie, decreased apparent diffusion coefficient [ADC] values) in the acute stage, defined as within seven days from symptom onset, whereas increased diffusivity and normalization of the ADC is seen within a few weeks after the initial presentation[26].

Head CT is often normal, especially early in the course of ADEM[27]. However, some patients may have evidence of focal or multifocal white matter damage on head CT.

Lumbar puncture — Cerebrospinal fluid (CSF) findings in ADEM are variable; abnormalities are present in 50 to 80 percent of patients[23, 25]. Typical abnormalities in ADEM are nonspecific and include a lymphocytic pleocytosis, usually with a CSF white blood cell count <100 cells/mL, and a mildly elevated CSF protein of <70 mg/dL, although higher counts have been reported. Oligoclonal bands are present in 6 to 65 percent of patients with ADEM[23].

Other studies — Ancillary tests, including evoked potentials and electroencephalogram (EEG), have been studied in ADEM, but the findings are usually nonspecific. Visual evoked and

somatosensory evoked potentials may be abnormal depending on the localization of central nervous system (CNS) lesions; however, these studies do not often contribute to the diagnosis.

3.5 Treatment

Glucocorticoids — In uncontrolled observational studies, treatment of adults with ADEM using intravenous methylprednisolone (1000 mg daily for three to five days), followed by an oral glucocorticoid taper over four to six weeks, was associated with substantial clinical improvement in a majority of patients[28].

Intravenous immune globulin — Intravenous immune globulin (IVIG) can be used if the response to a five-day course of glucocorticoids is poor. In one report, three patients with classic ADEM who failed glucocorticoids were treated with IVIG (0.4 g/kg intravenously daily for five days) and demonstrated improvement in the first week of therapy, reaching maximum benefit within the first three weeks[29].

Plasma exchange — Plasma exchange has also been used for ADEM in adults who have failed glucocorticoids, but data are limited. One retrospective cohort study of plasma exchange for all demyelinating diseases, including 10 patients with ADEM, showed that male sex, preserved reflexes on exam, and early initiation of therapy were associated with improved outcomes[30]. Plasma exchange for ADEM is generally given as five to seven exchanges over 10 to 14 days. One reasonable regimen is six exchanges, one every other day, with each exchange consisting of 1 to 1.5 plasma volumes.

3.6 PROGNOSIS

Compared with ADEM in children, the available studies suggest that the clinical course is more severe and outcome is less favorable in adults with ADEM[23]. Nevertheless, most patients improve with treatment, and spontaneous recovery has occurred in patients with mild symptoms[29]. Complete recovery has been reported in 10 to 46 percent of adult patients[23]. Cognitive impairment, mostly affecting attention and concentration, has persisted in some. Death may occur, especially in those with fulminant disease, with mortality rates of 4 to 12 percent reported in larger modern series[23, 25, and 29].

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