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ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM) FOLLOWING PURIFIED CHICK-EMBRYO CELL ANTI-RABIES VACCINATION

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ABSTRACT

Acute disseminated encephalomyelitis (ADEM) is an acute widespread demyelinating condition, which principally affects brain and spinal cord. It usually follows an infection or vaccination. The ADEM is a monophasic disease characterized by multifocal white matter lesions on neuroimaging. A case of post-vaccinial encephalitis after purified chick-embryo cell anti-rabies vaccination is presented for its rarity. We are reporting a case report of patient of 25 years old male presented with paraplegia with bladder retention and diplopia with exaggerated DTR and extensor plantar of acute onset with recent history of ARV vaccination. Cerebrospinal fluid examinations shows raised proteins and MRI imaging showed demyelinating lesions characteristic lesions seen on MRI appear as patchy areas of increased signal intensity on conventional T2-weighted images and on fluid attenuated inversion recovery sequence (FLAIR) predominantly seen in bilateral asymmetric parieral region, basal ganglion, thalamus, brain stem, cervical and thoracic cord with patchy distribution and skip lesions of ADEM in light of clinical scenario. The patient was treated with methylprednisonlone and responded well, diplopia, bladder involvement and paraplegia recovered over ten days.

KEYWORDS: Post-vaccinial encephalitis Acute disseminated encephalomyelitis, antirabies vaccine, MRI, Methylprednisolone.

INTRODUCTION

Acute disseminated encephalomyelitis (ADEM) is an acute demyelinating disorder of the central nervous system, and is characterised by multifocal white matter involvement. Diffuse neurological signs along with multifocal lesions in brain and spinal cord characterize the disease. Typically, its clinical symptoms follow an infection or vaccination.[1] The true incidence of AEDM is unknown and in India, the disease is surely more frequent than reported. The exanthematous fevers, antirabies vaccination which predispose to ADEM. Semple antirabies vaccination is the common vaccination associated with ADEM. In a recent study, specific viral infections and Semple antirabies vaccination together accounted for 56.2% of antecedent events.[2] Adverse reactions to vaccines are greatly under-reported because the methods of tracking vaccine side effects are designed only to detect reactions occurring with in a few weeks of immunisations. ADEM typically begins within 6 days to 6 weeks following an antigenic challenge. Approximately 70% of patients report a precipitating event, e.g. viral or bacterial infections or vaccination.[3] The pathophysiology involves transient autoimmune response directed at myelin or other self-antigens, possibly by molecular mimicry or by nonspecific activation of autoreactive T-cell clones. The annual incidence of ADEM is reported to be 0.4-0.8 per 100,000 and the disease more commonly affects children and young adults. ADEM is a monophasic illness with favorable long term prognosis. The differentiation of ADEM from a first attack of multiple sclerosis is important. Uncommonly ADEM can relapse frequently. If these relapses are thought to represent part of the same acute monophasic illness, the term multiphasic ADEM is used. The reported incidence of neuroparalytic complications with the Semple type of antirabies vaccine varied between one per 600 to one per 1575 vaccinations. An incidence rate of one per 25 000 vaccinations occurred with duck embryo antirabies vaccine (non-neural tissue based vaccines) preparation containing minimal amount of neural tissue. Introduction of the non-neural human diploid cell vaccine has virtually eliminated neuroparalytic complications of rabies vaccinations. Most patients with ADEM improve with methylprednisolone. If that fails immunoglobulins, plasmapheresis, or cytotoxic drugs can be given.[4] We are reporting case of ADEM following purified chick-embryo cell anti-rabies vaccination.

Case report: A 25 year old male patient presented with acute onset weakness in both lower limbs with inability to pass urine and diplopia of one day duration. There was no significant medical illness or similar illness in the past. There was no history of fever, headache, vomiting, convulsions, back pain or trauma. Patient gives history of dog bite class III for which, he received two doses of purified chick-embryo cell anti-rabies vaccination one week back. There was no paresthesiae at the site of dog bite. Dog was alive without any features of rabies. On clinical general examination vitals were stable. There were no significant autonomic disturbances (tachycardia, bradycardia, perspiration, hypotension or hypertension). On systemic neurological examination revealed bilateral VIth cranial nerve palsy and left side IIIrd nerve palsy with diplopia in all gaze, with grade III nystagmus. The power was normal in both upper limbs and both lower limb power was grade-I. The exaggerated deep tendon reflexes and extensor plantar response. The superficial reflexes and sensory system were normal. There were no obvious cerebellar and posterior column signs. The higher functions, speech and pupils were normal. There were no meningeal signs. In view of antecedent history of ARV vaccination associated neurological deficits diagnosis of post vaccineal acute disseminated encephalomyelitis (ADEM) was considered on top priority. The fundoscopy was done which, was normal. Cerebrospinal fluid examinations showed raised proteins (128 mg/dL) and normal CSF sugar (59 mg/dL) with no cells. Electrocardiogram, chest radiogram, complete blood counts, platelet counts, ESR, serum electrolytes (Na^{+}, K^{+}, Ca^{++}, Mg^{++}), blood sugar level, kidney function tests, liver function tests, thyroid function tests, ultrasound abdomen were normal The HIV, HbSAg, VDRL, peripheral smear of malarial parasite, blood culture, widal were negative. MRI imaging showed demyelinating lesions as patchy areas of increased signal intensity on conventional T2-weighted images and on fluid attenuated inversion recovery sequence (FLAIR) predominantly seen in bilateral asymmetric parieral region, basal ganglion, thalamus, brain stem, cervical and thoracic cord with patchy distribution and skip lesions. In the light of clinical scenario the diagnosis of ADEM was confirmed. The patient was treated with methylprednisolone (Immunomodulation) in the form of intravenous methyl prednisolone as a first-line drug (1 g/day) for 3 days. Patient responded well to the parenteral methylprednisonone and diplopia, bladder retention and paraplegia recovered over period of next ten days. Patient became ambulatory with grade 5 power in both lower limbs. The patient was discharged after two weeks on oral steroid in tapering schedule over next six weeks. Till date he has no evidence of relapse or recurrence of signs and symptoms of ADEM even after stopping steroids for two weeks.

DISCUSSION

Acute disseminated encephalomyelitic (ADEM) is an uncommon inflammatory demyelinating disease of the central nervous system (CNS) and can be defined strictly as scattered focal or multifocal (disseminated) inflammation of brain and/or spinal cord. 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.[5] Post-infectious and post-immunisation encephalomyelitis (ADEM) make up about three-quarters of cases, where the timing of a febrile event is associated with the onset of neurological disease.[5] Semple rabies vaccine contains neural antigens that could excite a cross-reactive T-cell response with lymphocytic proliferation on exposure to myelin basic protein correlating with encephalomyelitis or polyneuritis. This suggests that myelin basic protein is the encephalitogenic protein in encephalomyelitis following anti rabies vaccination. Myelitis and myeloradiculitis are more commonly reported following Semple antirabies vaccination. Rabies is endemic in India and approximately 30,000 people die of the disease every year. More than 5,00,000 people take anti-rabies vaccination every year and of this 3 million receive Semple type of vaccine. Though it is inexpensive, it has a very high incidence of neurological reactions including postvaccinial encephalomyelitis – 1 in 220 courses, with a 3% mortality. The Semple type of vaccine is obtained from inactivated virus prepared in adult animal nerve tissue. It can manifest as mononeuritis multiplex, meningioencephalitis, and encephalomyelitis. In countries endemic to rabies, neuroparalytic complications following antirabies vaccination need to be differentiated from dumb or paralytic rabies. About 20% of cases of rabies result in spinal distribution producing a clinical syndrome of ascending paralysis. Paresthesiae at the site of bite, onset of weakness in the limb of bite, and significant autonomic disturbances suggest paralytic rabies.[3] The pathological hallmark lesion in ADEM is perivenular inflammation and demyelination. The distribution of lesions is heterogeneous and multiple foci of demyelination in the cerebrum, cerebellum, and brain stem have been described. The lesions described are rather extensive and symmetric or asymmetric and more often located in the peripheral subcortical cerebral white matter. Lesions in the thalami are more often described in ADEM than MS and may be a useful finding that suggests ADEM.[2] The cerebrospinal fluid (CSF) is abnormal in about two-thirds of patients and shows a moderate pleocytosis with raised proteins. Oligoclonal band in CSF is usually absent in ADEM whereas it is a common finding in the CSF in patients with multiple sclerosis (MS). Magnetic resonance imaging (MRI) is the imaging modality of choice to demonstrate white matter lesion in

ADEM and MS. The bilateral thalamic lesion may be diagnostic of ADEM.[4] The differentiation of ADEM from a first attack of multiple sclerosis has prognostic and therapeutic implications; this distinction is often difficult.[1] MRI is regarded as the diagnostic imaging modality of choice and typically demonstrates involvement of deep cerebral hemispheric and subcortical white matter as well as lesions in the basal ganglia, gray-white junction, diencephalon, brainstem, cerebellum and spinal cord.[6] Acute disseminated encephalomyelitis (ADEM) is typically a monophasic, demyelinating disease of the CNS. The diagnosis of ADEM is strongly suggested by a close temporal relationship between a viral infection or immunization and the onset of neurologic symptoms, and it is supported by extensive, multifocal, subcortical white-matter disease on brain magnetic resonance imaging and mild lymphocytic pleocytosis and elevated proteins are in the CSF in ADEM, oligoclonal bands are not always present.[7] The lesions of ADEM (postinfectious and postvaccinal encephalomyelitis) involved not only the brain and the spinal cord but also the peripheral nerve.[8] In the absence of specific biologic markers, the diagnosis of ADEM is still based on the clinical and radiologic features. Although ADEM usually has a monophasic course, recurrent or multiphasic forms have been reported, raising diagnostic difficulties in distinguishing these cases from multiple sclerosis (MS).[9] NS Neki et al stated that, encephalitis due to rabipur vaccination is extremely rare. They reported a 32 years old man presented with history of dog bite 1 month back for which he was vaccinated with Rabipur with partial right third nerve with bilateral sixth nerve palsy with horizontal nystagmus. Motor examination revealed weakness and the deep tendon reflexes were brisk favoring ADEM.[10] Similarly in our study A 25 year old male patient presented with weakness in both lower limbs with bladder retension and diplopia with bilateral VIth cranial nerve palsy and left side IIIrd nerve palsy with diplopia in all gaze, with grade III nystagmus with paraplegia. The deep tendon reflexes were exaggerated and extensor plantar response. CSF showed raised proteins (128 mg/dL). T2-weighted MRI images showed attenuated inversion recovery on sequence (FLAIR) predominantly seen in bilateral asymmetric parieral region, basal ganglion, thalamus, brain stem, cervical and thoracic cord with patchy distribution and skip lesions. CSF examination revealed proteins 112 mg/dl.[10] Rajesh Kumar et al reported a post Rabipur (Purified Chick Embryo Rabies Vaccine) ADEM in 21 year old female presented with altered behaviour and asymmetrical progressive weakness in all four limbs with nasal twang of voice with cranial nerves 3rd, 4th, 5th, 6th and 9th were involved with bilateral internuclear ophthalmoplegia with extensor plantar reflex after five doses of rabipur vaccine. MRI brain at admission showed multiple confluent scattered and confluent long TR hyper

intense lesions in centrum ovale, corona radiata and deep white matter and spine showed hyperintensity in C5- D2 suggestive of cord oedema and patient was managed pulse methylprednisolone.[11] Similarly in our study 25 year old male patient had diplopia with bilateral VIth cranial nerve palsy and left side IIIrd nerve palsy with diplopia in all gaze, with grade III nystagmus with paraplegia with exaggerated deep tendon reflexes and bilateral extensor plantar response. MRI brain and spinal cord shows bilateral asymmetric parieral region, basal ganglion, thalamus, brain stem, cervical and thoracic cord with patchy distribution and skip lesions. Our patient also responded well to methylprednisolone. Similar to our results Kulkarni V et al reported a case of a 45-year-old man with ADEM following Anti-Rabies vaccine (ARV) presented with quadriparesis sensory motar and cranial nerve with extensor plantars. CSF examination showed lymphocytic pleocytosis with normal sugar and proteins (15-mg%). MRI of cervical and dorsal spine showed a long segment intramedullary hypointense signal on T1 weighted images extending from C3 to D9 levels which became hyperintense on T2 weighted images suggestive of ADEM and was treated with injection methyl prednisolone.[12] Rajesh Kashyap, et al reported a 50 years old female presented with history of abnormal sensation of right half of whole body which changed to increased touch and pain with weakness of right half of body with past history of received anti-rabies Semple vaccine. She took a course of 10 injections subcutaneously for class- III wound caused by monkey. There was right sided 6th and 7th nerve supra-nuclear palsy. In right upper limb power was normal but reflexes were exaggerated. In the right lower limb tone was increased and reflexes were exaggerated with weakness. Brain MRI T2 weighted image showing multiple areas of high signals in the cerebral white matter, sub-cortial, and periventricular region suggestive of post vaccineal ADEM.[3] Pagano MA et al reported a case of a 41 year-old man with diagnosis of the association between ADEM and GBS (ASADEM-GBS) and treatment with corticosteroids and intravenous immunoglobulin was started. ASADEM-GBS is an uncommon entity generally considered of poor outcome; however a rapid diagnosis and treatment can substantially improve the prognosis.[13] Mohammed RR et al stated that, the concurrent GBS and ADEM are uncommon. They reported a 10-year-old girl who presented with acute quadriparesis, areflexia, and urinary retention. Lumber puncture revealed mild pleocytosis and elevated protein. She required mechanical ventilation and failed to improve after intravenous immunoglobulins. She subsequently developed double vision and disturbed level of consciousness. Brain MRI revealed multiple white matter lesions suggestive of ADEM.[14] Tan H et al reported a case in a 9-year-old patient who illustrates the importance of considering acute disseminated

encephalomyelitis in patients who develop multifocal neurologic signs after hepatitis A virus infection.[15] The mainstay of treatment of ADEM is immunomodulation in the form of intravenous methyl prednisolone which is the first-line drug (1 g/day) for 3 days with full recovery has been reported in 50%-80% of patients. Oral corticosteroid treatment is continued with gradual tapering over 6 weeks to reduce the risk of relapses. If this fails the next step will be plasma exchange (PE). Intravenous immunoglobulin (IVIg) (0.4 gm/kg/day for 5 days) is another option, but there is a constraint of high cost and the evidence for this modality of treatment in ADEM is Class IV. The plasma exchange or IVIg, could be the second-line treatment, when corticosteroids fail. Multiple or single extensive lesions on MRI lesions may be associated with disability. A hyperacute onset, severe neurologic deficits and unresponsiveness to steroids are poor prognostic indicators.[4]

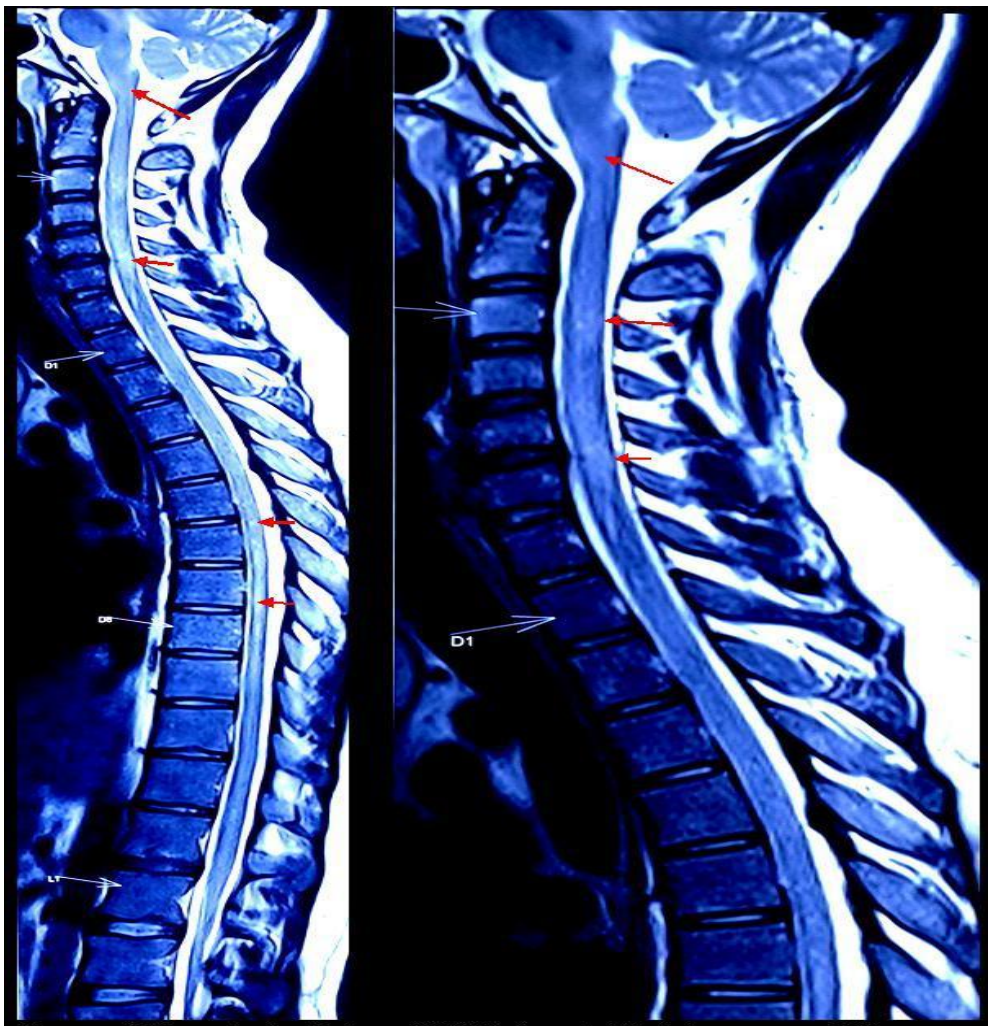

Figure no. 1: Demyelinating lesions of ADEM, characteristic lesions seen on MRI appear as patchy areas of increased signal intensity on conventional T2-weighted images and on fluid attenuated inversion recovery sequence (FLAIR) predominantly seen in brain stem, cervical and thoracic cord with patchy distribution and skip lesions.

Figure no 1: Shows demylinating lesion of ADEM, T2 images, involving brain-stem, cervical and thoracic spinal cord with skip lesions.

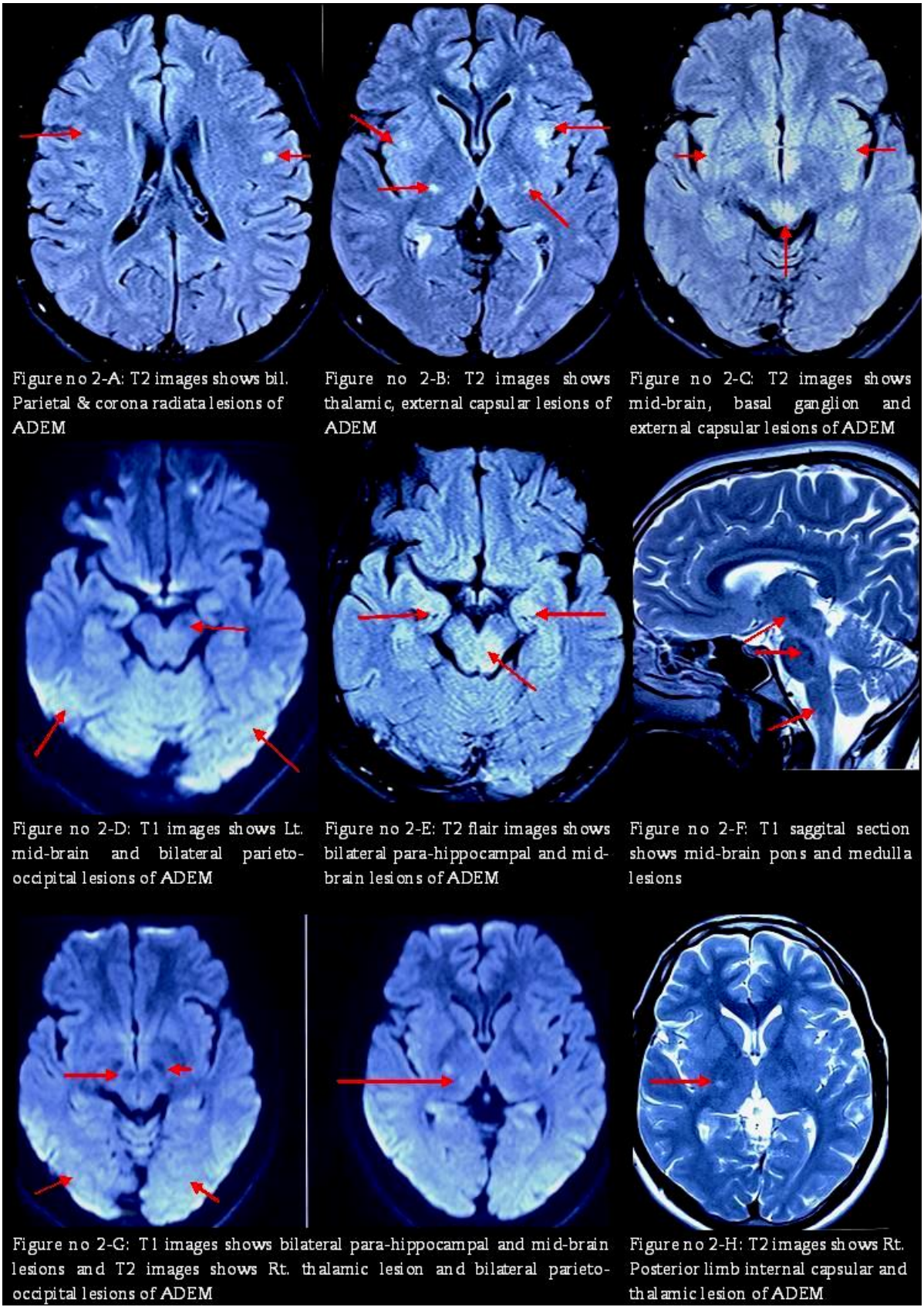

Figure no 2: Shows demylinating lesion of ADEM in T1, T2, and Flair images, [bilaterally asymmetric predominantly white matter, thalamus and basal ganglion]

CONCLUSIONS

Acute disseminated encephalomyelitis (ADEM) is an unusual demyelinating disease of the CNS. This disorder is often associated with a precedent infection or vaccination like anti-rabies vaccine but may also occur spontaneously. Although postinfectious encephalomyelitis typically involves the white matter, lesions in grey matter have also been seen, basal ganglia, thalamus, and even cortical grey matter may be involved. ADEM is a monophasic illness with favorable outcome. The paralytic rabies and first attack of multiple sclerosis should be wisely differentiated from ADEM. Most of the patients improve quickly with methylprednisolone like in our case. If that fails, immunoglobulin and plasmapheresis can be employed. It is important to differentiate ADEM from multiple sclerosis. Unlike MS, ADEM has a monophasic course and favourable long-term prognosis. The neuroparalytic complications following antirabies vaccination need to be differentiated from dumb or paralytic rabies. Administration of rabies post-exposure prophylaxis is a medical urgency, not a medical emergency but decision must not be delayed and possible complications with it should be explained to the patient.

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