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Plasma Exchange an Effective Measure in Rabies Vaccine Induced Acute Disseminated Encephalomyelitis

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Abstract

We describe a case of a 57 year of patient who had a history of dog bite and then was subsequently vaccinated with anti- rabies vaccine of 2 doses. She developed lower limb weakness and areflexia and was intubated after going into respiratory distress. She was given IV immunoglobulin, methyl prednisolone and then underwent seven cycles after which she showed improvement.

Case Report

A 57-year-old patient known patient with bronchial asthma was bitten by a dog and received ARV 2 doses and 3rd dose was not taken due to acute illness. She was admitted in district general hospital Chilaw with fever of four days duration .She developed lower limb weakness after almost one month of the dog bite .It was progressive weakness associated with areflexia .The patient had also associated fever ,myalgia and headache. There was no history of projectile vomiting, no photophobia or phonophobia. She had no history of toxic substance, allergy to drugs, surgery. The patient suddenly developed worsening respiratory distress with a T11 sensory level. The patient had a GCS of 8 on admission and was electively intubated in the neurology IC. It was found that the patient had right partial ptosis and bilateral pinpoint pupil and T12 sensory level. A working diagnosis of paralytic rabies, acute disseminated encephalomyelitis due to vaccine and guillian barre syndrome was also entertained. For the latter IV immunoglobulin was given as decided by the neurology team. There was not much response to the IV immunoglobulin. MRI brain that was done was reported as normal with the MRI spine showing features of acute transverse myelitis involving C3-C6 level of the spinal cord.

Second MRI brain was done two weeks later which showed multiple ill-defined/diffuse T2 high signal intensities noted in the subcortical and deep white matters mainly bilateral frontoparietal, corpus callosum, basal ganglia ,cerebellum, brainstem. The MRI features were compatible with classic rabies or possible ADEM. Other baseline investigations done on the patient were Hb=10.9,WBC=9.1 ,PLT=194,Na=135,K=3.7,Mg=1.8,Ca=8.7 ,Serum creatinine=0.21,total bilirubin=0.8,AST=63,ALT=69,CRP=12.

IV methylprednisolone pulses were given with oral prednisolone taper but they failed to show any response. EEG showed diffuse slowing. CSF studies were sent for rabies antibody, which was negative, and rabies PCR CSF was negative. Nerve conduction studies were done which showed Poly radiculitis associated with myelitis.

The patient was commenced on plasmapheresis; seven cycles were given. The patient had a GCS of 3 prior to initiation of PLEX and after seven cycles her GCS improved to E=4, M=3 and V=T. Due to the length of stay she had had a tracheostomy done.

Discussion

Acute disseminated encephalomyelitis (ADEM) is a demyelinating disorder that occurs after viral infection or vaccination. It is monophasic causing encephalopathy and multifocal neurologic symptoms. According to a case report by Kumar M et al, there is an involvement of the cerebral hemispheres, cerebellum, brainstem, spinal cord, and optic nerves caused by immune system

dysregulation in a genetically susceptible host and triggered by an infectious or other environmental agent [1].

The annual incidence of ADEM is between 0.8 per 100,000 with a median age of onset of 6.5 years. ADEM usually occurs in children. Optic neuropathy and ADEM are rare complications of vaccinations. Huynh W et al discussed about several vaccines including those for rabies, diphtheria–tetanus–polio, smallpox, measles, mumps, rubella, Japanese B encephalitis, pertussis, influenza, hepatitis B, and the Hog vaccine have been associated with ADEM. It is usually after primary vaccination rather than revaccination that ADEM usually occurs. At first post vaccination, ADEM was thought to be caused by the vaccines viral component, but it was later recognised that it could be due to the contamination of the CNS tissue in which the vaccine propagated [2].

Oedema is usually seen in gross neuropathological sequalae of patients with ADEM suggesting that these patients can improve with glucocorticoid treatment. Perivenous infiltration of lymphocytes; neutrophils, plasma cells, microglial cells, foamy macrophages, and eosinophilic granulocytes is the most common histopathological finding as mentioned in two articles by van der Knaap MS, Valk Jand in another article by Kepes JJ [3,4]. These perivenous lesions may collect to form confluent regions of demyelination. This differs from multiple sclerosis, which is typically associated with multifocal, discrete lesions as discussed by Young NP et al [5].

In the same follow up study by Young NP et al, classic descriptions of ADEM are elaborated as patients presenting with motor deficits involving a single limb or paraparesis or quadriparesis involvement of the brainstem with oculomotor deficits and dysarthria is also noted. Headache, malaise, meningismus, ataxia, aphasia, optic neuritis, nystagmus, extrapyramidal movement disorders, urinary retention, seizures, and increased intracranial pressure are also signs and symptoms of presentation in ADEM. In the same study, lesions which are typically presented are described on MRI brain as typically bilateral, asymmetric and usually poorly marginated. Demye linating multiple lesions are seen in the deep and subcortical white matter. The lesions are usually hyperintense on T2 and FLAIR (fluid attenuation recovery) sequences. In unenhanced T1 they usually present as inconspicuous lesions, but large lesions can be hypo intense. Periventricular, subcortical white matter, including corpus callosum and centrum semiovale, as well as in the gray matter, including the cortex, basal ganglia, and thalamus lesions can be seen. Infratentorial lesions in brainstem, cerebellum and spinal cord are quite common. Large confluent intramedullary lesions that extend over multiple segments are the lesions usually noted in the spinal cord however short and long segment cord lesions have also been reported [6]. At times there may be a delay in the appearance of lesions from symptom onset as long as eight weeks have been reported according to Lakhan SE [7].Usually MRI lesions disappear in 18 months although some patients may have residual lesions.

Höllinger P et al states that a Lumbar puncture is usually done in ADEM to find evidence of inflammation and to differentiate ADEM from other disorders such as multiple sclerosis while simultaneously ruling out infection. CSF findings in ADEM are nonspecific they include lymphocytic pleocytosis with a WBC <100 cells/ml and mildly elevated protein <70 mg/dl [8].

De Seze J et al have mentioned a set of diagnostic criteria which some investigators have proposed that helps to distinguish ADEM from multiple sclerosis.

- Presence of symptoms that are atypical for multiple sclerosis such as encephalopathy, defined as an alteration in consciousness (eg, stupor, lethargy or behavioural change) that cannot be explained by fever, systemic illness, or postictal symptoms.
- brain MRI gray matter involvement
- CSF absence of oligoclonal bands

The last part of the criteria is controversial as some patients with ADEM have oligoclonal bands [9].

In our patient the points in favour of ADEM are history of antirabies vaccination. Rapid deterioration of her clinical condition, patient had features of encephalopathy and developed multifocal neurologic symptoms involving higher mental functions, cranial nerves and motor system. In- addition there was no other etiology to explain her clinical condition and the MRI had features suggestive of ADEM. Points not in favour are poor response to IV methyl prednisolone and a normal cerebrospinal fluid.

Initial therapy with high dose glucocorticoids is recommended for patients with ADEM. The regime is usually 1000mg of methylprednisolone daily for three to five days with oral glucorticoid taper. Glucocorticoids are usually started concurrently on admission with acyclovir and antibiotics. The above regime is usually associated with good response . In a prospective cohort study by Marchioni E et al the findings were that for adults who don't respond to steroids IV immunoglobulin or plasma exchange is recommended. IV immunoglobulin can be given if the response to glucocorticoid is poor usually response is detected in the first week of therapy with the maximum benefit seen at three weeks. IV Ig was associated with a favourable outcome in about 50 % of patients in whom steroids were ineffective [10].

Plasma exchange is used as a form therapy also when glucocorticoids are ineffective it is given as five to seven exchanges over 10 to 14 days. A cohort study done on ADEM patients showed preserved reflexes on examination as well improved outcomes in patients [11]. Cyclophosphamide 1gram intravenously is also administered

for patients in whom glucocorticoids are ineffective. Repeated doses will need to be given to see a favourable response according to Schwarz S et al. [12].

Paralytic rabies can also be taken as a differential diagnosis. This mimics guillian barre syndrome in that it shows an ascending type of weakness. These patients however have little cerebral involvement until later on in the disease. The patients develops flaccid paralysis after prodromal symptoms. The paralysis is most prominent in the bitten limb and then spreads symmetrically or asymmetrically. Fasciculations are seen, deep tendon and plantar reflexes are lost. As the paralysis ascends, there is a dense paraplegia with a loss of sphincter tone and paralysis of the muscles of deglutition and respiration. Usually, patients die within two weeks of the onset of coma. Patients often die of complications such as asphyxiation and respiratory arrest as seen in a study done on post-mortem examinations [13].

Samples tested of CSF, saliva and urine for rabies by molecular methods are not always positive in ante mortem and post-mortem diagnostic tests done by Wacharapluesadee S, Hemachudha T [14]. Polymerase chain reactions of of nape of the neck skin biopsies was associated with high sensitivity and specificity (98 and 98.3 percent, respectively) and PCR testing of saliva had a sensitivity of 63.2 and 70.2 percent, respectively. The sensitivity of serum and urine samples was poor. As stated by Noah DL et al Serum antibodies to the virus will not present until days after the onset of clinical symptoms and usually even later in CSF. Antibody to virus regardless of immunisation usually suggests infection [15].

In our patient the lumbar puncture was done on the 9th day of the onset of symptoms, and we obtained a negative result which favours the diagnosis of vaccine induced ADEM rather than paralytic rabies since the patient did not suffer from any prodromal symptoms as well.

Fooks AR, Jackson AC claim there is no specific treatment approach for a patient with rabies. Immunotherapy with either rabies vaccine or rabies immunoglobulin is controversial however if the patient has not received post exposure prophylaxis it is reasonable to administer the vaccine. The development of an immune response is associated with the viral clearance of rabies and neutralising antibodies appear in CSF and in serum [16].

Three antiviral agents have been used to aggressively treat rabies interferon alpha, ribavarin and amantadine and these have been associated with the development of neuropsychiatric, hematologic, gastrointestinal, and/or autoimmune complications. Amantadine is part of the Milwaukee protocol as described by Warrell MJ et al. All these three agents have not shown any significant benefit in the treatment of rabies [17].

Early studies have shown that ketamine might be a promising neuroprotective therapy for rabies by studies done in vitro and in mouse model of rabies have failed to show efficacy. Corticosteroids are to be avoided in the treatment of rabies as immune mediated injury is thought not to play a significant part in the pathogenesis of rabies and may close the blood brain barrier and reduce the entry of drugs into the brain. In mouse models they have shown to shorten the incubation time and increase the mortality [16].

In a critical appraisal of Milwaukee protocol by Zeiler FA, Jackson AC; the use of high dose anaesthetic agents to achieve metabolic suppression and neuronal preservation in therapeutic coma is claimed not to have been supported by scientific rationale. Vasopressor dependency, increased risk of infection which are the complications of therapeutic coma discourage its use [18].

Learning Points

Acute disseminated encephalomyelitis associated with vaccination is an entity that should be a differential in the event of ascending type of paralysis post vaccination with anti rabies vaccine. Several options are available which are methylprednisolone pulses, IV immunoglobulin and plasmapheresis and the patient usually responds quite well to these. In rabies corticosteroids and therapeutic coma should be avoided as the risks outweigh the benefits.

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