

Acute Disseminated Encephalomyelitis (ADEM) Presenting With Seizures Secondary to Anti-tetanus Toxin Vaccination

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Summary

Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disease of the central nervous system (CNS) that is known to occur spontaneously in association with specific and non-specific viral illnesses and after vaccination against various pathogens. Although it is often a self-limited monophasic illness, the fatality rate is estimated to be as high as 20%, and many patients suffer residual neurologic impairment¹. The diagnosis is mainly based on clinical and radiological findings. The clinical presentation varies from merely an asymptomatic condition to loss of consciousness, seizures, ataxia, optic neuropathy, cranial nerve palsies, and motor dysfunction. MRI of the brain is the single most important diagnostic radiological investigation and can facilitate early diagnosis and prompt treatment. This case report describes a patient with ADEM presenting with only seizures after vaccination with anti-tetanus toxin.

Case report

A 28-year-old housewife gave birth to a baby boy via Caesarean section at 36 weeks gestation (for foetal distress) with an otherwise uneventful antenatal period. She was discharged four days later. She was given routine antenatal anti-tetanus toxin injections at 26 and 32 weeks of gestation. One week after her discharge from hospital, she developed an episode of generalised tonic-clonic convulsion while she was sleeping at 2.00am, which was witnessed by her husband. A similar seizure occurred at 6.00am and she was immediately sent to our hospital. The patient's previous medical history was unremarkable.

On admission to our institution, the patient was unresponsive to verbal commands, moved all extremities spontaneously, showed appropriate withdrawal to painful stimuli, had roving eye movements, and blinked to pain. Her pupils were 4mm

in diameter, regular, and reactive. Corneal reflexes were symmetric bilaterally. Fundoscopic examination was normal. Deep tendon reflexes were present and symmetric, and plantar reflexes were extensor bilaterally. Muscle tone was normal and signs of meningeal irritation were absent. Her blood pressure was 130/80 mmHg, and pulse rate 88/minute (regular). She was afebrile. She had mild bilateral ankle oedema and examination of the abdomen revealed that her surgical scar had healed and the uterus had contracted to a 12-week size. Examination of the lungs and heart was normal.

Her serum potassium was 4.3 mmol/l, sodium 138 mmol/l, urea 4.0 mmol/l, random glucose 6.5 mmol/l and creatinine 67 μ mol/l. The haemoglobin was 11.2g%, white cell count $22.3 \times 10^9/l$ and platelet count $226 \times 10^9/l$. Her arterial pH was 7.49, bicarbonate 26 mmol/l, pCO₂ 20 mmHg, pO₂ 98 mmHg, and oxygen saturation was 98%. The liver function test was normal.

This article was accepted: 17 June 2003

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Urine examination showed a pH of 5.0, proteinuria (3+) and no haematuria. The chest radiograph was normal. Cerebrospinal fluid (CSF) examination revealed no white or red blood cells, level of protein 373 mg/l and glucose content of 3.4 mmol/l. An urgent brain CT (plain) showed multiple hypodense lesions in the temporo-parietal areas bilaterally, involving mainly the subcortical white matter. Magnetic resonance imaging (MRI) of the brain was subsequently done and showed that these areas were hypointense on T1-weighted images and hyperintense on T2-weighted images and FLAIR (fluid attenuated inversion recovery) images. EEG on the third day of admission showed that generalised slow activity formed the background. Antinuclear antibody and HIV serology were negative.

Although a diagnosis of ADEM was made based on the clinical and radiological findings, intravenous steroid was not instituted because the patient did not have any neurological deficit and the drowsiness (24 hours) was attributed to the post-ictal state. She was discharged well after one week of hospitalisation. She was seen again three months later and a repeat brain MRI showed resolution of the lesions. After 2 years of follow-ups, there were no recurrences.

Discussion

Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disease of the central

nervous system, principally affecting the white matter. It is most often seen in children or young adults. It is typically a monophasic disease associated with preceding infection or immunization, both of which preceded our patient's illness. Investigators of most series have reported a short latent period (1 to 20 days) of onset to illness due to a wild virus infection. In post-vaccinal ADEM, the latency from time of injection to the onset of illness is between 4 to 24 weeks¹. Therefore, looking at the onset of the illness in our patient, the vaccination (7 weeks- first vaccination and 5 weeks- second vaccination) can be implicated as the cause of the disease. The agents which have been implicated to cause ADEM were infections such as cytomegalovirus, Epstein-Barr virus, Herpes simplex virus, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Salmonella typhi*, streptococcal exotoxins, and *Campylobacter jejuni*, and infections such as Rocky Mountain spotted fever and Pontiac fever. To our knowledge, there was only one case report of ADEM associated with tetanus vaccine¹. Other vaccines which have been implicated include rubella, rabies, Japanese B virus, diphtheria-tetanus-pertussis, pertussis, mumps-measles-rubella, measles, oral polio, *Haemophilus influenzae* B, hepatitis A, and meningococcal A and C vaccines. Another possibility is ADEM occurring after pregnancy. Nonetheless, there were no such reports previously.

The clinical spectrum is wide, ranging from subclinical episodes diagnosed incidentally by brain MRI showing multifocal white matter lesions, to a fulminant, rapidly

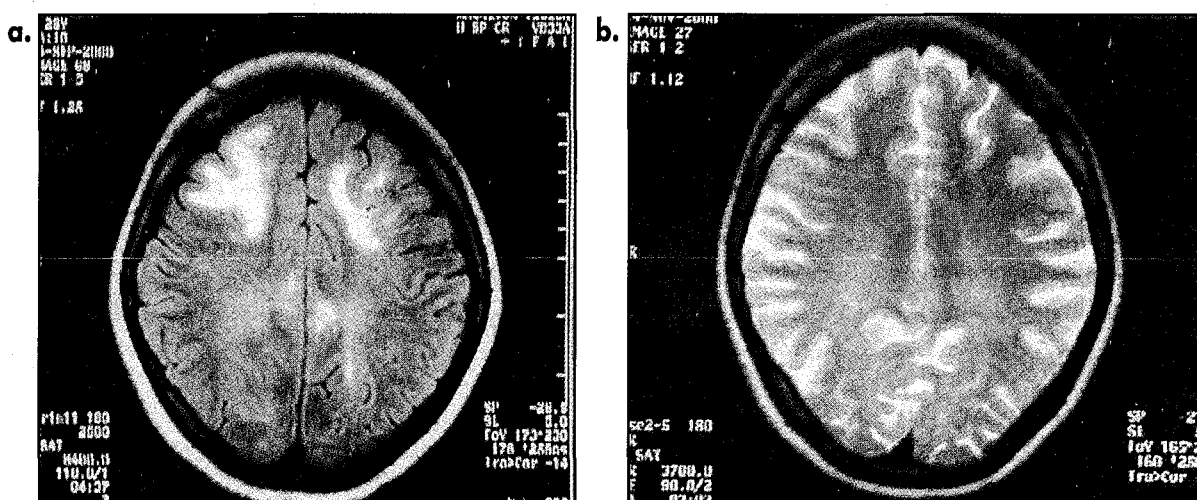


Fig 1: Magnetic resonance imaging (MRI) of the brain showing the lesions which were hyperintense; seen clearly in the FLAIR image (a). The lesions disappeared three months later (b) in the T2 weighted image..

CASE REPORT

progressing course with coma and death². The specific neurologic syndromes reflect multifocal lesions involving the cerebral white matter, cerebellum, brain stem, and spinal cord². Magnetic resonance imaging (MRI) has been proven to be far superior to computerized tomography (CT) in the diagnosis of ADEM and is considered the imaging modality of choice in detecting the lesions of the disease. ADEM lesions are best seen on long TR (time of repetition) images and multifocal subcortical hyperintense foci are found on T2-weighted images. Most of the time, the diagnosis of ADEM is frequently established on the basis of characteristic findings on MRI of the brain³. Without MRI, a diagnosis of ADEM is merely presumptive and sometimes almost impossible to arrive at. The lesions on the MRI should resolve in conjunction with clinical improvement.

Our patient fulfilled the following conditions leading to a diagnosis of ADEM; a single clinical episode, widespread encephalopathic disturbance or neurological deficits due to CNS involvement, and typical MRI findings. The disease manifested as a single episode illness and our patient recovered fully both clinically and radiologically at the last follow up. The generalised seizures and dominant theta waves on EEG even after the post-ictal drowsiness period had passed point towards a widespread encephalopathic disturbance. The MRI findings in this patient were strikingly classical of ADEM and together with the typical clinical features make the diagnosis of ADEM highly likely.

One might argue that CNS vasculitis should be considered as a possible alternative diagnosis as negative screening tests do not rule out the disease. Repeat vasculitis screening might be useful later especially if the disease recurred. Nonetheless the MRI lesions disappeared three months after the onset of illness without any treatment, making the diagnosis of vasculitis unlikely. Multiple sclerosis and other demyelinating diseases were also less likely based on

the patient's clinical, neuroimaging and CSF findings. In progressive multifocal leucoencephalopathy (PML), the CT and MRI findings are almost similar to our patient's, but in the absence of HIV infection, this condition is also unlikely. Another possibility is eclampsia especially when there is proteinuria, ankle oedema and seizures. However the seizures only occurred 11 days after the delivery (7 days after the discharge). The criteria for eclampsia is seizures occurring less than 7 days. Moreover, the seizures and mental status changes of eclampsia are related to hypertensive encephalopathy. In this patient, she was normotensive and had an uneventful antenatal period. Therefore, the diagnosis of eclampsia is less likely.

Most authors suggest that ADEM is a cell-mediated auto-immune disease. Lesions in ADEM have striking similarities to those of experimental allergic encephalomyelitis. It has also been shown that the human immune response would change with age. Therefore, the age-related alteration of cell-mediated immunity might partly explain the fact that the majority of patients are children or young adults. Mostly the disease seems to be self-limiting, but in untreated patients, the mortality rate may be as high as 20% and the risk of permanent neurological deficits 10-33%.

Owing to the suggestion that ADEM may be an auto-immune disease, corticosteroids are used despite the lack of controlled studies. Currently, the accepted mode of treatment of patients diagnosed as having ADEM is early high dose steroids. An urgent MRI is therefore an indispensable tool in the diagnosis and management of ADEM. On the other hand, as ADEM is a self-limiting disease, supportive treatment is also imperative to make sure that the patient survives the episode with minimal or no disability. The learning point from this case report is that ADEM should be considered in patients presenting with seizures especially when there was a history of receiving vaccination and MRI is mandatory to ascertain its diagnosis.

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