

A Case of Biopsy Proven Acute Demyelinating Encephalomyelitis (ADEM) with Haemorrhagic Leucoencephalitis

Dear Editor,

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated inflammatory disorder of the central nervous system. It has a monophasic course which occurs after viral infection or vaccination.^{1,2} Acute haemorrhagic leucoencephalitis (AHLE) is considered to be a hyperacute form of ADEM which is fulminant and is frequently fatal.³

There are only a few cases of biopsy-proven AHLE in the current literature. This case emphasises the importance of early recognition by magnetic resonance imaging (MRI) for institution of medical therapy.

Case Report

A 23-year-old man was admitted with a 7-day history of fever and headache. It was associated with lethargy, myalgia, arthralgia, retroorbital pain and loss of appetite. Physical examination revealed that the patient was dehydrated and febrile. He was conscious with the glasgow coma score of 15/15 during admission. There were no signs of meningism and both pupils were equal and reactive to light. Fundoscopic examination was normal. There were no focal neurological signs initially. Examination of the lung, heart and abdomen were normal. Four hours after admission, he became confused and agitated. His glasgow coma score dropped to 13/15. He was treated empirically as viral meningoencephalitis with intravenous acyclovir.

Laboratory testing performed at admission revealed a white cell count of $7.2 \times 10^9/L$, with normal differential count. The thrombocytopenia was $117 \times 10^9/L$, haemoglobin was 16.0 g/dL and haematocrit was 48.6%. The blood urea was raised by 7.8 mmol/L, creatinine by 120 $\mu\text{mol/L}$, sodium by 138 mmol/L and potassium by 3.8 mmol/L. The liver function test, urine analysis and serum ferritin were normal. Chest radiograph was normal. Contrast-enhanced brain CT did not show any abnormalities.

A lumbar puncture was performed with the opening pressure of 160 mmH₂O. The cerebrospinal fluid (CSF) was clear with lymphocytes of 20/cmm. The protein level in the CSF was 696 mg/L, and the glucose level was 2.1 mmol/L with random blood glucose of 4.6 mmol/L. The cryptococcal antigen was not detected in the CSF.

The blood and urine cultures were negative. Serology for varicella zoster and measles IgG were positive. The screen for herpes simplex, enterovirus, tuberculosis, leptospira,

chlamydia, legionella and dengue infection were negative. Drug toxicology, CSF lactate and connective tissue screen were also negative.

An electroencephalogram showed generalised theta wave activity that was consistent with mild to moderate diffuse cerebral disturbance.

On the fourth day of admission, the patient's conscious level deteriorated and he required elective ventilation. He developed neurogenic pulmonary oedema and was managed with intravenous frusemide and intravenous mannitol.

A MRI of the brain showed an enlarged and abnormal pons. The medulla oblongata and proximal spinal cord also showed abnormal signal changes with the evidence of acute petechiae haemorrhages (Figs. 1A and 1B). Based on the rapid progression of the disease reflected by the imaging findings, a diagnosis of acute disseminated encephalomyelitis with haemorrhagic leucoencephalitis was made.

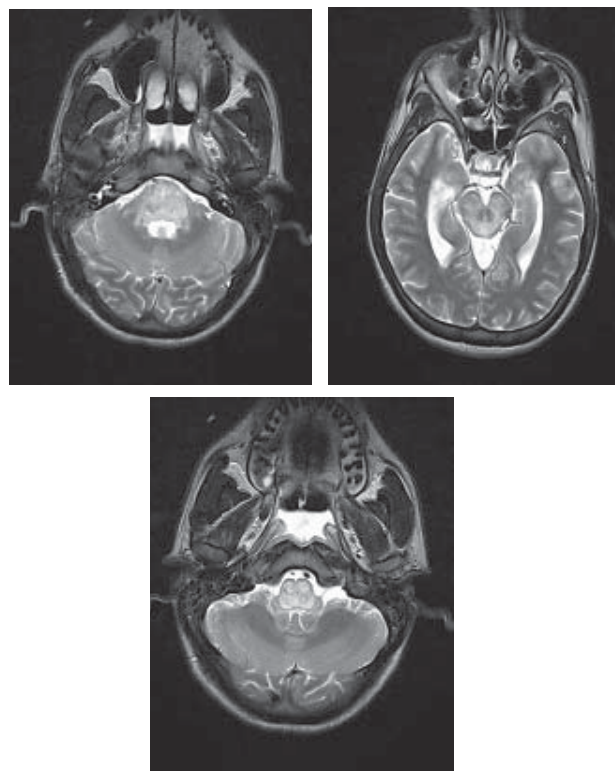


Fig. 1A. Axial T2W1 magnetic resonance images showed hyperintense changes in the brainstem.

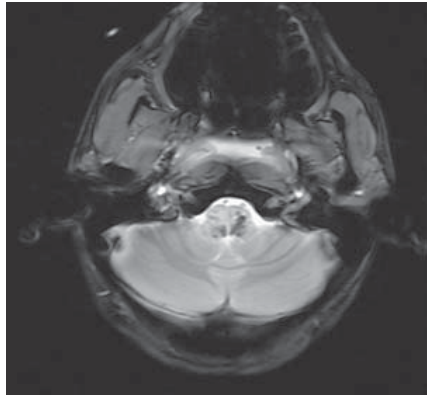


Fig. 1B. Axial GRE sequence showing hypointense signal within the medulla in keeping with the blood product.

He was given intravenous methylprednisolone 250 mg 4 times daily for 3 days followed by oral prednisolone 40 mg daily. Despite optimal medical treatment, patient did not recover and finally succumbed after 2 weeks.

An autopsy was performed where gross examination showed that the brain was edematous with diffuse petechial haemorrhages within the brainstem (Fig. 2A). Microscopic examination of the brain post mortem showed infiltration of lymphocytes and plasma cells in the pons, cerebellum, parasagittal gyrus, corpus callosum, internal capsule and hypothalamus. There were focal areas of haemorrhage in the pons (Fig. 2B) and hypothalamus (Fig. 2C). The viral and immunofluorescence studies were negative.

Discussion

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated inflammatory disorder of the central nervous system (CNS) characterised by a widespread demyelination that predominantly involves the white matter of the brain and spinal cord.¹ It predominantly affects children and young adults.^{1,2} The estimated incidence is 0.8 per 100,000 population per year.²

Acute disseminated encephalomyelitis and acute haemorrhagic leukoencephalitis are similar in many ways and may be part of a spectrum of CNS demyelinating disease with the same fundamental process resulting from an autoimmune process. Currently, MR imaging is frequently used to differentiate between acute disseminated encephalomyelitis and acute haemorrhagic leukoencephalitis.

Haemorrhage is not seen on MR imaging in patients with acute disseminated encephalomyelitis, while mass effect and hemispheric oedema are rare and tend to be smaller compared to the lesions seen in acute haemorrhagic leukoencephalitis.³

Acute haemorrhagic leukoencephalitis produces a predominantly neutrophilic infiltrate whereas lymphocytic infiltrates and macrophages are abundant in acute disseminated encephalomyelitis. Perivascular haemorrhage and vascular necrosis are not seen in acute demyelinating encephalomyelitis.³

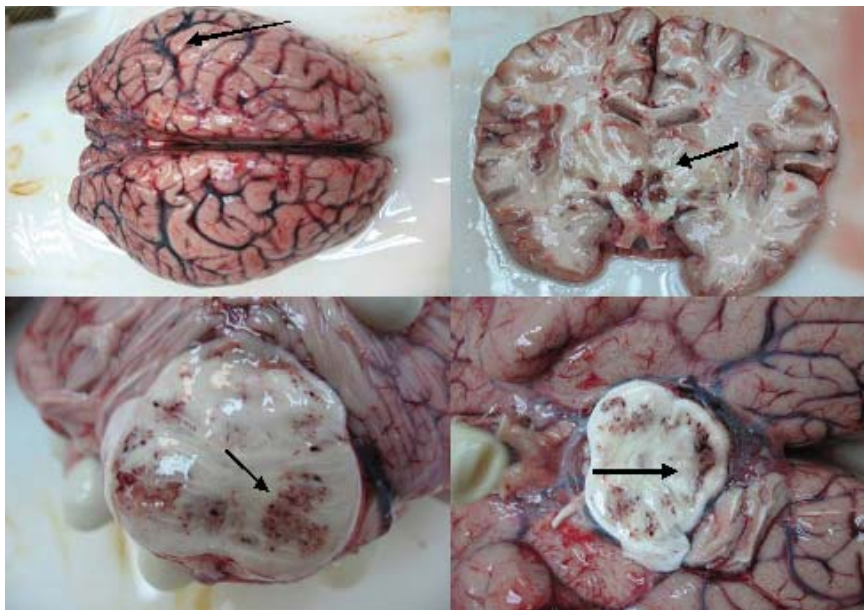


Fig. 2A. Gross autopsy of patient's brain showing congested superficial vein of cerebral hemisphere and indicating cerebral oedema and multiple haemorrhagic necrotic areas in hypothalamus and pons (arrows).

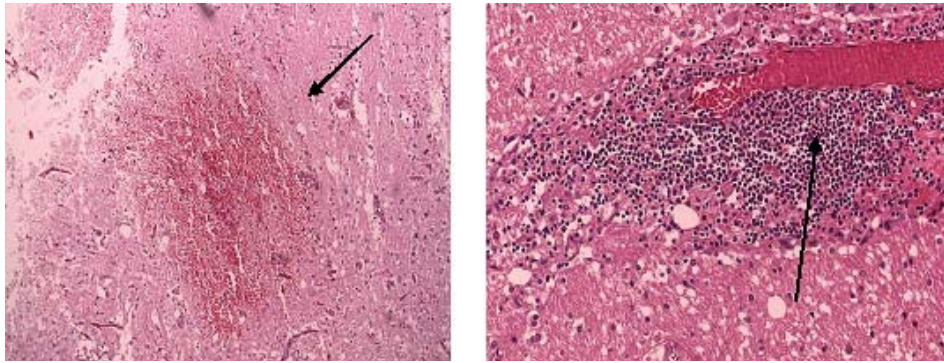


Fig. 2B. Microscopic examination of patient's pons showing multiple foci of haemorrhage with lymphocyte infiltration surrounding the vessel (perivascular cuffing). Fig. on the left: 40 x hpf stained with hematoxylin eosin. Fig. on the right: 100 x hpf stained with hematoxylin eosin.

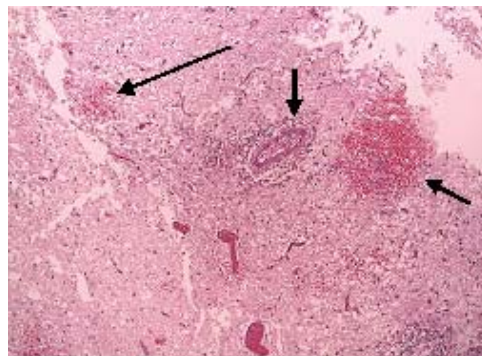


Fig. 2C. Microscopic examination of hypothalamus showing multiple foci of haemorrhage with lymphocyte infiltration (perivascular cuffing). 40 x hpf stained with hematoxylin eosin.

The combination of clinical, laboratory and imaging findings validates the diagnosis of ADEM in this patient, but the aggressive course of the disease with the presence of cerebral oedema and foci of haemorrhage in the brainstem on magnetic resonance images are consistent with the severe form of acute haemorrhagic leucoencephalitis. Autopsy findings, which showed lymphocytic infiltration and foci of haemorrhage, were in keeping with the clinical diagnosis.

The differential diagnosis of acute necrotizing encephalitis and macrophage activation syndrome were considered. Both diseases can have similar neurological presentation with comparable MRIs. However, in the absence of hyperferritinaemia which is an important laboratory hallmark of macrophage activation syndrome and without past medical history of rheumatological disease, the diagnosis of macrophage activation syndrome seemed to be unlikely in our patient. As cerebrospinal fluid (CSF) polymerase chain reaction (PCR) for herpes simplex virus (HSV) was negative, the diagnosis of HSV was ruled out as the CSF PCR has high sensitivity (98%) and specificity for the diagnosis of HSV.⁴ Furthermore, the brain biopsy confirmed the diagnosis of acute haemorrhagic leucoencephalitis.

The treatment for AHLE is still not well established. So far, 2 case reports recorded that early administration of high

dose corticosteroids resulted in complete recovery of the patients.⁵ Despite the commencement of corticosteroids in this patient, he succumbed to the disease, perhaps because of late administration of the corticosteroid. The aggressive treatment combined with corticosteroids, cyclophosphamide and plasmapheresis has been reported to cure the disease.⁶ Therefore, we encourage clinicians to be more prompt and aggressive in treating AHLE patients as it may lead to favourable outcome⁶ despite the aggressiveness of the disease.

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