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Acute disseminated encephalomyelitis treated with plasmapheresis

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ABSTRACT

Accepted modes of therapy in acute disseminated encephalomyelitis include intravenous methyl prednisolone, intravenous immunoglobulin or a combination of both. Effectiveness of plasmapheresis has been demonstrated by previous case reports. We report two patients with steroid non-responsive acute disseminated encephalomyelitis in which plasmapheresis resulted in complete clinical and radiological recovery, though the therapy was initiated in the fifth week of illness. A total of 45-50ml/kg body weight of plasma was removed in six equal exchanges over a period of two weeks. This report highlights that plasmapheresis could be of use even in the early second month of illness.

Keywords: acute disseminated encephalomyelitis, demyelinating disease, encephalomyelitis, immunotherapy, plasmapheresis

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INTRODUCTION

Acute disseminated encephalomyelitis (ADEM) is an acute inflammatory demyelinating disease of the central nervous system, characterised by multifocal neurological deficits days to weeks after an episode of viral illness or vaccination[1]. Accepted methods of treatment include intravenous methyl prednisolone (IVMP), intravenous immunoglobulin (IVIG) or a combination of both[2]. Few reports highlight the importance of plasmapheresis in ADEM[3-7]. We report two cases of ADEM in adults treated effectively with plasmapheresis.

CASE REPORTS

Case 1

A 25-year-old woman had headache, vomiting, altered sensorium and progressive right hemiparesis ten days following an upper respiratory tract infection. On the fifth day of illness, she lapsed into a coma after an episode of right focal motor seizure. She had a Glasgow Coma Scale (GCS) score of seven. She had palmo-mental reflex and bilateral pyramidal signs (more prominent on the right side) and no papilloedema. The following tests were negative or normal: haemogram, renal and liver functions, chest radiograph, electrocardiogram, blood and urine cultures, Widal test, peripheral smear for malarial parasite, serum HIV-ELISA, serum antibody test for Ebstein-Barr, measles, mumps, rubella, herpes simplex and Japanese encephalitis viruses, Brucella and mycoplasma.

Electroencephalogram showed diffuse slowing without epileptiform discharges. Cerebrospinal fluid (CSF) study revealed 26 white blood cells/mm^3 (80% lymphocytes), protein 55mg/dL and glucose 72mg/dL. CSF PCR for Herpes simplex virus and antibody for Japanese encephalitis virus were negative. Magnetic resonance (MR) imaging of the brain done on the sixth day of illness showed multiple hyperintense lesions, predominantly involving subcortical white matter in T2-weighted images, suggestive of demyelination (Fig. 1). She was treated with IVMP from the sixth day at a dose of 1g per day for five days, followed by 1mg/kg body weight of oral prednisolone for two weeks.

On the 30th day of illness, she was still bed-bound with a GCS of nine. Starting on day 31 of the illness, six plasma exchanges were done over a period of two weeks, removing a total of 270ml/kg body weight of plasma. Clinical improvement began after the second exchange. At the end of six exchanges, she had a mild pyramidal weakness on the right side. One month after the procedure, she had no neurological deficit. Repeat MR imaging of the brain at 12 months showed total clearance of the brain lesions. There were no neurological or cognitive deficits at one year.

Case 2

A 55-year-old woman was admitted to the neurology ward with ataxia, right hemiparesis and bilateral ptosis, which began one week following a short febrile illness. Physical examination showed bilateral pyramidal signs (right>left), bilateral cerebellar signs,

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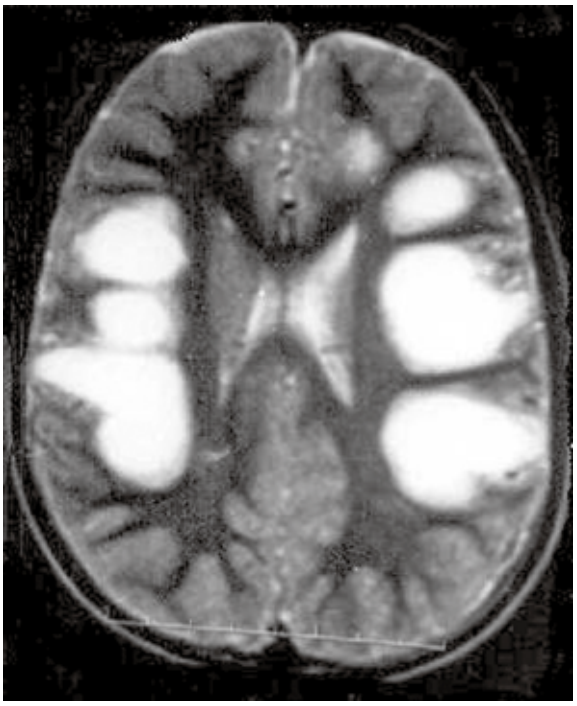

Fig. 1 Patient 1. Axial T2-W MR image of the brain (TR 2600, TE 100) shows multiple hyperintense lesions, predominantly involving subcortical white matter suggestive of demyelination.

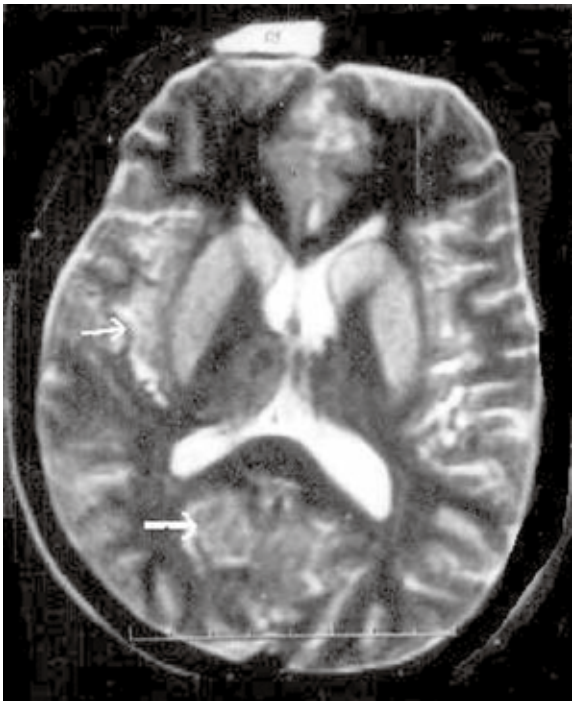

Fig. 2 Patient 2. Axial T2-W MR image of the brain (TR 2600, TE 100) shows multiple hyperintense lesions (arrows), involving subcortical white matter and basal ganglia.

bilateral upward gaze restriction and ptosis. CSF examination showed 50 white blood cells/mm^3 (60% lymphocytes), protein 55mg/dL and glucose 60mg/dL. Laboratory tests were normal as in the first case. MR imaging on the sixth day of illness showed multiple hyperintense lesions involving subcortical white matter and basal ganglia (Fig. 2). She was treated with IVMP from the sixth day at a dose of 1g per day for five days, followed by oral prednisolone (1mg/kg body weight) for two weeks. She remained quadriplegic with a GCS of 11 at the end of steroid therapy.

Starting on the 33rd day of illness, six exchanges over two weeks removed a total of 300ml/kg body weight of plasma. After the six exchanges, she had only mild ataxia, which cleared one month later. Repeat MR imaging of the brain at 12 months showed radiological clearance. There were no neurological or neuropsychiatric deficits at one year.

DISCUSSION

Diagnosis of ADEM was made on the basis of clinical picture, CSF findings and MR imaging features. There has been no randomised controlled clinical trial to establish the efficacy of steroids in ADEM[1,2]. Impressive response to steroid therapy had been reported[2,8]. Our patients had no significant clinical improvement after steroid therapy. But clinical response to plasmapheresis was remarkable. 45-50ml/kg body weight plasma was removed in each of six equal exchanges over two weeks. In steroid-resistant ADEM, the currently-used therapies include plasmapheresis and IVIG[2,9]. These two patients could not afford IVIG.

Keegan et al reviewed 59 patients treated with plasmapheresis for acute severe demyelinating disease of the central nervous system, which included ten patients each with ADEM and neuromyelitis optica. In this group, 50% had moderate or marked improvement[10]. Favourable therapeutic response was obtained, even when plasmapheresis was initiated 60 days after the onset of neurological symptoms. However, it was not clear whether these patients had ADEM or other acute severe demyelinating diseases. In a randomised double-blind study involving 22 patients with acute CNS demyelinating disease, 42% of patients treated with plasmapheresis improved[11]. In contrast, only 6% receiving placebo treatment improved. There was only one case of ADEM in this study and that patient received placebo treatment. Plasmapheresis was used after a course of steroid in all the series and case reports. Plasmapheresis in our patients was initiated in the fifth week, possibly to exclude the delayed steroid effect.

Effectiveness of plasmapheresis could be due to its ability to remove offending circulating antibodies[3]. The exact pathogenesis of ADEM is not clear. There could be humoral mechanisms as well[12]. In the acute phase of ADEM, cytokines such as tumour necrosis factor, soluble tumour necrosis

factor receptor 1, interleukin-6, and interleukin-10 are elevated[13]. Antibodies to gangliosides, such as GM1 and GD1a, and myelin basic protein-reactive T helper 2 cells, may be present in some patients with ADEM[11].Goto et al postulated that plasmapheresis not only removes humoral factors but also affects the balance of T helper type 1 and T helper type 2 cells circulating periphereal lymphocytes in patients with neuroimmunological diseases[14]. Experimental autoimmune encephalomyelitis (EAE) is a good model for ADEM[12]. If ADEM is considered as a cell-mediated immune-mediated disease, it would be difficult to explain the use of plasmapheresis. In one model of EAE, transfer of sensitised myelin basic protein (MBP)-specific T cells resulted only in perivenular inflammatory infiltrates, with little demyelination. However, when antiserum to myelin oligodendrocyte glycoprotein is simultaneously given with MBP-sensitised T cells, severe demyelination results[12].

Lin et al analysed 14 patients who were treated with plasmapheresis for ADEM (the literature review included their own two patients). Plasmapheresis was initiated 9.6 days (mean; SD 4.8) after the onset of illness (range 3-18 days). Improvement began three days after initiating plasmapheresis[5]. There is no consensus regarding the total volume of plasma to be removed in ADEM. Keegan et al used 1.1-1.4 volume plasma exchange per session. Their patients received 2-20 exchanges (median of seven exchanges)[10]. Tselis had suggested a total of six or seven exchanges every two days, each plasma exchange consisting of removal of approximately one-plasma volume[2].

We used a lower volume of plasma, but the effect was significant and sustained. There could be individual variation in the frequency, duration and volume of plasma exchange. There are only a few reports, which had shown the effect of plasma exchange even late in the illness[5]. Delayed effect of steroid treatment and the natural course of disease might have contributed to the recovery in our patients. In conclusion, these two cases demonstrate that plasmapheresis could be useful even in the fifth week of severe ADEM not responding to steroid therapy. A randomised controlled trial is needed to prove the effect of plasmapheresis in ADEM, and to address issues of volume, frequency, duration and timing of plasmapheresis in ADEM.

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