

## Cyclosporin Neurotoxicity with Epstein-Barr virus-associated Hemophagocytic syndrome

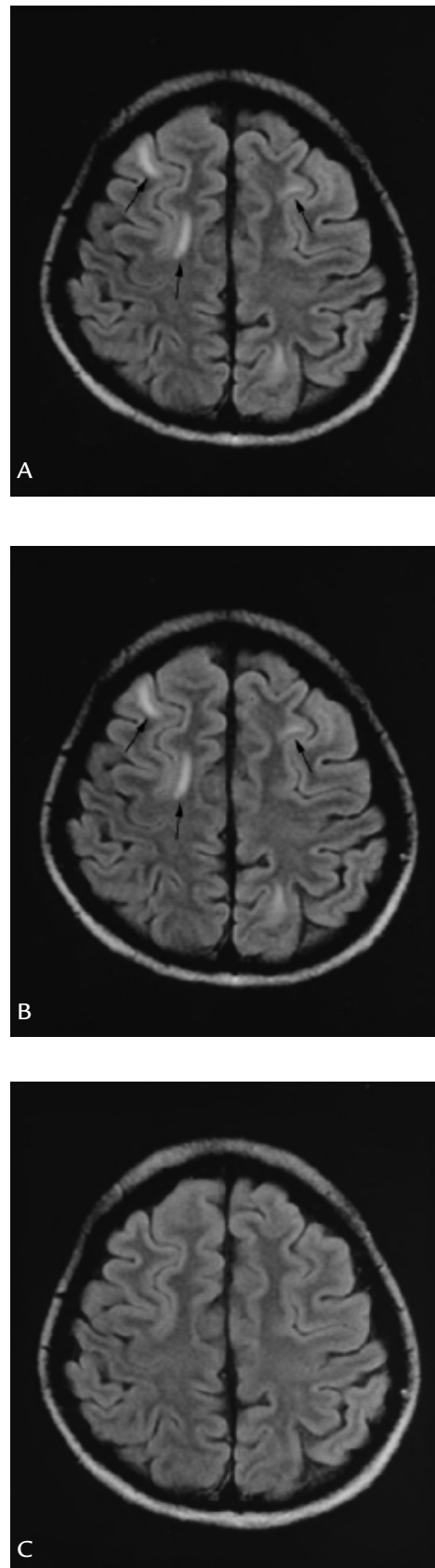
In September 2000, a 22-year-old female was admitted to our hospital due to high grade fever, liver enzymes elevation and pancytopenia. Bone marrow aspiration was performed, and hemophagocytosis was present. Epstein-Barr virus (EBV) DNA was positive in her peripheral blood, and we diagnosed the case as EBV-associated hemophagocytic syndrome (EB-VAHS) after excluding other malignancies. The initial therapy including etoposide and dexamethasone was started. As severe leukocytopenia developed, etoposide was stopped and cyclosporin A (CsA) was administered continuously. Four days after administration of CsA, she developed convulsive seizures with loss of consciousness. An MRI demonstrated decreased signal with T1-weighting and high signal with T2-weighting in the subcortical white matter including the posterior lobe. We stopped CsA infusion, and glycerol was administered. Soon the symptom disappeared. When patients developed an episode of convulsive seizure, other diagnostic possibilities were central nervous system (CNS) involvement of hemophagocytosis, EBV encephalitis and acute disseminated encephalomyelitis (ADEM). CsA neurotoxicity must be considered even in the case of EB-VAHS with administration of CsA. As previously reported, Fluid-attenuated Inversion Recovery (FLAIR) imaging improved diagnostic confidence and conspicuity of the T2 hyper intense lesions of CsA neurotoxicity, as well as tacrolimus encephalopathy, typically in the subcortical white matter.

Haematologica 2005; 90(3):e30-e32

Cyclosporin A (CsA) is widely used as the immunosuppressive agent for bone marrow transplantation, solid organ transplantation, aplastic anemia, and hemophagocytic syndrome. One of adverse side effects of CsA is neurotoxicity. Many cases of CsA neurotoxicity after transplantation have ever been reported. It ranges from the most common findings of tremors to the most severe, sometimes fatal, syndrome of seizures, visual disturbances, and radio graphically characteristic cortical white matter lesions often involving occipital lobes.<sup>1-4</sup> Nontransplant patients or those conditioned with total-body irradiation develop white matter lesions, whereas those conditioned with chemotherapy develop mixed cortical and white matter lesions.<sup>4</sup> Here, we present previously undescribed case of CsA neurotoxicity after treatment for Epstein-Barr virus-associated hemophagocytic syndrome (EB-VAHS).

### Case Report

In September 2000, a 22-year-old female was admitted to the hospital due to high grade fever. Liver enzymes gradually elevated and pancytopenia progressed. Methylprednisolone (1 g/day) was administered for 3 days, but symptoms did not improve. Then she was referred to our hospital. On admission on September 20, her body temperature was 39.2°C, and her conjunctiva appeared anemic and icteric. Liver was palpable about 3.5 cm below right costal margin with mild splenomegaly. Systolic murmur was present because of anemia. Cervical and inguinal lymphadenopathy was



**Figure.** Brain MRI with FLAIR images. **A.** On MRI of the next day, there are multiple high signal areas in the subcortical white matter including the posterior lobe (arrows). **B.** On MRI 7 days later, these abnormalities were gradually decreased. **C.** On MRI 1 month later, there were no abnormalities in the brain.

present. Pitting edema was found on both of her legs. There was no abnormal symptom in the neurological examination. Blood examination showed a white blood cell count of  $5.8 \times 10^9/L$  including 2% of atypical lymphocyte, a hemoglobin level of 6.7g/dl, and a platelet cell count of  $12.6 \times 10^9/L$ . Coagulation examination showed fibrinogen of 135mg/dl, and fibrin degradation product of 32.9  $\mu\text{g/mL}$ . Other laboratory findings were as follows: total bilirubin 8.4mg/dl (direct bilirubin 7.7 mg/dL), aspartate aminotransferase (AST) 348 IU/l, alanine aminotransferase (ALT) 179 IU/l, lactate dehydrogenase (LDH) 2799 IU/l, blood urea nitrogen (BUN) 27.8 mg/dL, creatinine 1.69 mg/dL, ferritin 43285 ng/ml, soluble interleukin 2 receptor 18000 U/mL, EB virus capsid antigen (VCA) IgM 40 titer, EBVCA IgG 320 titer and EB virus associated nuclear antigen (EBNA) negative. The bone marrow aspiration at initial diagnosis showed hypoplastic marrow with marked hemophagocytosis. Cytogenetic analysis of the bone marrow showed 46, XX [20/20]. EBV DNA was positive in her peripheral blood ( $3.8 \times 10^4$  copies/ $10^6$  cells), and we diagnosed the case as EB-VAHS after excluding other malignancies.

The initial therapy of HLH-94 protocol, aiming at inducing a resolution of the disease, included etoposide and dexamethasone, and we used granulocyte-colony stimulating factor (G-CSF) for prevention of leukocytopenia and secondary bacterial infection. On day 8, hemoglobin and platelet count were low and AST, ALT, LDH and ferritin were high, yet. However, as white blood cell count decreased to  $0.2 \times 10^9/L$ , etoposide was stopped and CsA (1.5 mg/kg/day) was administered continuously. Four days after continuous administration of CsA, lymphadenopathy disappeared, but she developed convulsive seizures with loss of consciousness for a few minutes. Anticonvulsants such as diazepam and Phenobarbital were administered. Lumbar puncture was carried out, but there was no abnormality in cerebrospinal fluid. Electroencephalogram showed no apparent findings for localization of the lesions. An MRI demonstrated decreased signal with T1-weighting and high signal with T2-weighting in the subcortical white matter including the posterior lobe. Fluid-attenuated Inversion Recovery (FLAIR) imaging improved diagnostic confidence and conspicuity of the T2 hyperintense lesions in the subcortical white matter (Figure 1A). The concentration of CsA was in the normal range (CsA 178 ng/mL), and hypomagnesaemia (Mg 1.4 mg/dL) and hypertension (160/80 mmHg) were present. These findings indicated a diagnosis of CsA neurotoxicity. We stopped CsA infusion, and glycerol was administered. The symptom completely disappeared after 3 days. MRI performed after 1 week from convulsion showed significant improvement (Figure 1B). After a month, there were no abnormalities in the MRI of the brain (Figure 1C). Gradually bone marrow recovered, and the initial therapy of HLH-94 protocol was finished in eight weeks without twice administration of etoposide in the second week. After 9 weeks, bone marrow aspiration showed no hemophagocytosis. EBV DNA was not also detected in peripheral blood. She discharged in November 2001.

### Discussion

In some cases of virus-associated hemophagocytic syndrome, the combination of CsA and G-CSF is effective.<sup>5</sup> The continuation therapy of HLH-94 Study Group of the Histiocyte Society includes CsA.<sup>6</sup> CsA is thought to be effective for the treatment of hypercytokinemia such as VAHS. Incidence of neurotoxicity in HLH-94 protocol is

not high, but CsA neurotoxicity is very important.

When patients developed an episode of convulsive seizure, diagnosis must be carefully made. In such cases, diagnostic possibilities were central nervous system (CNS) involvement of hemophagocytosis, EBV encephalitis, acute disseminated encephalomyelitis (ADEM), opportunistic infection and etc. CsA neurotoxicity must be considered even in the case of EB-VAHS with administration of CsA.

Of the neurological side effects of CsA, less serious ones consist of tremor, agitation, insomnia, anxiety, amnesia, headache, and dysesthesia. More severe complications include confusion, disorientation, decreased responsiveness, hallucinations, delusions, seizures, cortical blindness, pyramidal motor weakness, aphasia, and ataxia.<sup>7</sup> CsA neurotoxicity is thought to be a manifestation of a more widespread vasculopathy.<sup>4</sup> CsA causes endothelial cell damage that can induce vascular spasm, which might initiate mild reversible ischemia.<sup>2</sup> Lesion location in CsA neurotoxicity may depend on the kind of immunosuppression. Non transplant patients or those conditioned with total-body irradiation develop white matter lesions, whereas those conditioned with chemotherapy developed mixed cortical and white matter. In our case of the nontransplant patient, the main lesions were in the subcortical white matter, but a small area of gray matter was also involved. These findings of MRI are almost compatible. It is recommended that patients on CsA should be followed for neurotoxicity irrespective of CsA level and that MRI and CT are of significant value.<sup>7</sup>

As previously reported, FLAIR imaging improved diagnostic confidence and conspicuity of the T2 hyperintense lesions of CsA neurotoxicity, as well as tacrolimus encephalopathy, typically in the subcortical white matter.<sup>8,9</sup> In our case, it is also of diagnostic value.

In summary, we report a rare case of CsA neurotoxicity after treatment for EB-VAHS, though CsA is often used as the immunosuppressive agent for EB-VAHS. When patients developed an episode of convulsive seizure, CsA neurotoxicity must be considered. As previously reported, MRI, especially FLAIR imaging is a great diagnostic value.

Kimikazu Yakushijin,<sup>1</sup> Ishikazu Mizuno,<sup>1</sup> Akiko Sada,<sup>1</sup> Shion Imoto,<sup>1</sup> Tamio Koizumi,<sup>1</sup> Shinsaku Imashuku,<sup>2</sup> Tohru Murayama<sup>1</sup>  
<sup>1</sup>Hematology/Oncology Division, Department of Medicine, Hyogo Medical Center for Adults

<sup>2</sup>Kyoto City Institute of Health and Environmental Sciences, Kyoto, Japan

Correspondence: Tohru Murayama, M.D., Ph. D., FJSIM, FACP  
Hematology/Oncology Division,  
Department of Medicine, Hyogo Medical Center for Adults, 13-70,  
Kita-oji, Akashi, Hyogo 673-8558, Japan  
Tel 81-78-929-1151 - Fax 81-78-929-2395  
E-mail: tmurayam@hp.pref.hyogo.jp

### References

1. Reece DE, Frei-Lahr DA, Shepherd JD et al. Neurologic complications in allogeneic bone marrow transplant patients receiving cyclosporin. *Bone Marrow Transplant* 1991;8: 393-401.
2. Truwit CL, Denaro CP, Lake JR, DeMarco T. MR imaging of reversible cyclosporin A-induced neurotoxicity. *Am J Neuroradiol* 1991; 12: 651-9.
3. Gopal AK, Thorning DR, Back AL. Fatal outcome due to cyclosporine neurotoxicity with associated pathological find-

- ings. Bone Marrow Transplant 1999; 23, 191-3.
4. Bartynski WS, Zeigler Z, Spearman MP, Lin L, Shaddock RK, Lister J. Etiology of cortical and white matter lesions in Cyclosporin-A and FK-506 Neurotoxicity. Am J Neuroradiol 2001;22: 1901-14; 1998;31: 131-7.
  5. Tsuda H, Shirono K. Successful treatment of virus-associated haemophagocytic syndrome in adults by cyclosporine A supported by Granulocyte colony-stimulating factor. Br J Haematol 1996;93, 572-75.
  6. Henter JI, Arico M, Egeler RM, Elinder G, Favara BE, Filippovich AH, Gadner H, Imashuku S, Janka-Schaub G, Komp D, Ladisch S and Webb D. HLH-94: A Treatment protocol for hemophagocytic lymphohistiocytosis. Med Pediatr Oncol 1997;28: 342-7.
  7. Gijtenbeek JM, van den Bent MJ, Vecht CJ. Cyclosporine neurotoxicity: a review. J Neurol. 1999; 246: 339-46.
  8. Casey SO, Sampao RC, Michel E, Truwit L, Posterior reversible encephalopathy syndrome: utility of fluid-attenuated inversion recovery MR Imaging in the detection of cortical and subcortical lesions. Am J Neuroradiol. 21:1199-1206, 2000
  9. Furukawa M, Terae S, Chu BC, Kaneko K, Kamada H, Miyasaka K, MRI in seven cases of tacrolimus(FK-506) encephalopathy: utility of FLAIR and diffusion-weighted imaging. Neuroradiol 2001; 43:615-21.