Scrub Typhus-Associated Acute Disseminated Encephalomyelitis

Pei-Hao Chen, Kuo-Hua Hung, Shih-Jung Cheng, and Kuang-Nan Hsu

Abstract-

Background: Acute disseminated encephalomyelitis (ADEM) is a monophasic demyelinating disease of the central nervous system, typically occurring after infections or vaccinations. To our knowledge, scrub typhus has not been described in association with ADEM.

Case report: A 77-year-old man was admitted with fever, convulsions and an altered level of consciousness. On neurological examination, the patient was stuporous and had nuchal rigidity and left hemiparesis. A generalized tonic-clonic seizure was observed. Serum and cerebrospinal fluid samples were positive for anti-Orientia tsutsugamushi antibody. Despite a 10-day course of parenteral minocycline, his clinical condition deteriorated. Serial cranial magnetic resonance images demonstrated progressively extensive areas of signal hyperintensity on conventional T2-weighted and fluid attenuated inversion recovery sequence images, mainly affecting the periventricular white matter. After administration of intravenous high-dose corticosteroids, the patient had limited improvement.

Conclusions: This is the first identifiable case of ADEM temporally associated with scrub typhus alone.

Key Words: Scrub typhus, Orientia tsutsugamushi, Acute disseminated encephalomyelitis, Postinfectious encephalitis

Acta Neurol Taiwan 2006;15:251-254

INTRODUCTION

Acute disseminated encephalomyelitis (ADEM) is an uncommon, acute demyelinating disorder of the central nervous system (CNS). The pathophysiology is obscure, but it has been postulated to result from an autoimmune response to myelin basic protein triggered by infection or immunization[1]. A number of infectious agents, mainly viruses, have been associated with ADEM[2]. In this article, we reported a patient with laboratory-confirmed scrub typhus who then developed clinical and imaging characteristics of ADEM.

CASE REPORT

A 77-year-old man who lived alone in a rural area and collected junk for a living presented with a 5-day history of fever, altered mental status and abdominal pain. He was seen at a small hospital and found to be lethargic and dyspneic. Electrocardiograms showed

From the Department of Neurology, Mackay Memorial Hospital, Taitung, Taiwan.
Received March 8, 2006. Revised April 7, 2006.
Accepted May 3, 2006.

Reprint requests and correspondence to: Pei-Hao Chen, MD. Department of Neurology, Mackay Memorial Hospital, Taitung Branch, No. 1, Lane 303, Changsha St., Taitung, Taiwan.
E-mail: a766288.chen@msa.hinet.net

transient atrial flutter. A chest radiograph showed only mild cardiomegaly. One day before transfer to our hospital, he became drowsier and developed dysarthria and left hemiparesis.

On admission to our hospital, he had a temperature of 39°C, pulse of 120 beats/min, and blood pressure of 120/70 mmHg. There was no eschar on the skin nor lymphadenopathy. On neurologic examination, he was stuporous with meningismus, left facial palsy, left hemiplegia, and a left extensor plantar response. He was also observed to have a generalized tonic-clonic seizure.

The results of routine urinalysis, hematologic and biochemical testing were normal except for leukocytosis (16.4×10^9/L) and an elevated erythrocyte sedimentation rate (50 mm/h). Cranial magnetic resonance (MR) images showed signal hyperintensity of the right parietal white matter on conventional T2-weighted and fluid attenuated inversion recovery sequence (FLAIR) images (Figure). A lumbar puncture yielded yellowish cerebrospinal fluid (CSF) at an opening pressure of 170 mm H_2O. The white blood cell (WBC) counts of 230 cells/mL (84% lymphocytes), glucose 41 mg/dL (170 mg/dL in the serum), and protein 219 mg/dL. Empirical parenteral antibiotics were given, including acyclovir, minocycline, and ceftriaxone. Studies of the CSF sample, including a test for cryptococcal antigen, India ink and Gram stains, polymerase chain reaction for tuberculosis and herpes simplex virus, a test for syphilis, and cultures for bacteria or fungus, all had negative results. Serologic tests were negative for hepatitis A, B or C viruses; Epstein-Barr, herpes simplex, and human immunodeficiency viruses; and for Mycoplasma, Leptospira, Chlamydia, and Legionella. However, IgG antibody titers against Orientia tsutsugamushi, measured by immunofluorescent antibody assay, were >4-fold increase in titers between acute- and the convalescent-phase for both serum (1:>10000) and CSF (1:320) samples, confirming a diagnosis of scrub typhus.

The patient developed acute respiratory failure on day 14 of his illness requiring mechanical ventilation. By day 25, he was in deep coma with quadriplegia. A second cranial MR imaging scanning showed extensive white matter lesions in the right cerebral hemisphere and few deep white matter lesions in the left cerebral hemi-

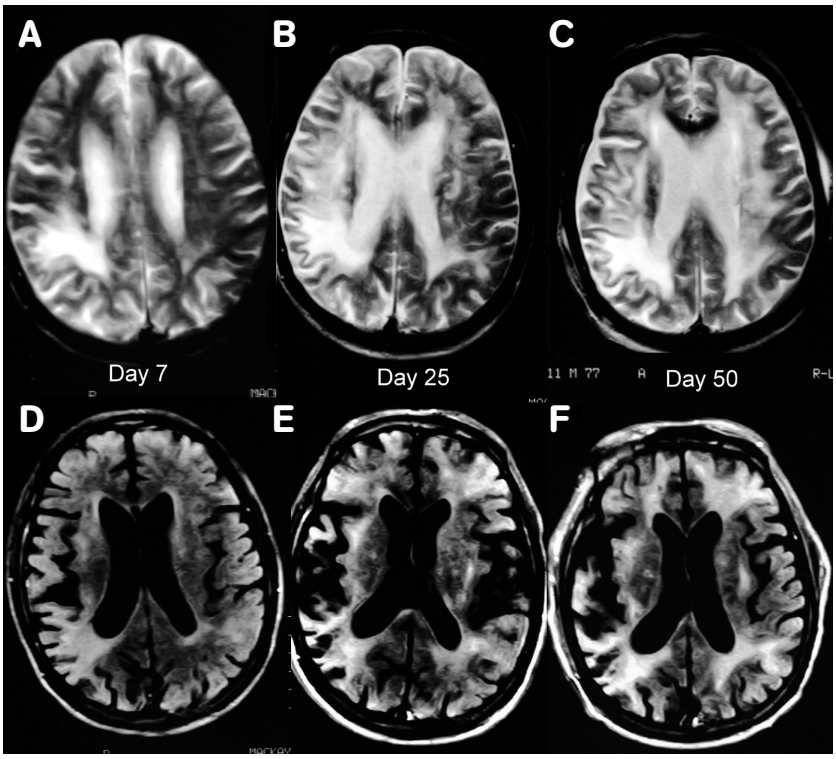

Figure. Axial T2 weighted (A) and fluid attenuated inversion recovery sequence (FLAIR) (D) images obtained on day 7 showed focal lesions of increased signal intensity mainly in the right parietal white matter. Repeated T2 weighted (B and C) and FLAIR (E and F) images on day 25 and 50 , respectively, showed progressively extensive signal hyperintensities in the subcortical and periventricular white matter areas.

sphere (Fig.), consistent with ADEM. Gadolinium contrast enhancement was not found on conventional T1 weighted images and no obvious abnormality was found on MR angiography. A second lumbar puncture yielded yellowish CSF at an opening pressure of 160 mm H_2O and with a white cell count of 243 cells/mL (64% neutrophils, 6% lymphocytes, and 30% eosinophils), glucose 59 mg/dL, and protein 203 mg/dL. Oligoclonal bands were not detected on electrophoresis. The results of tests of stool and urine for parasites, CSF for Angiostrogylus catonesis, and serum for Lyme disease were negative. The patient was given high-dose corticosteroids intravenously, after which he improved slightly with eye opening to verbal commands.

A third cranial MR imaging scanning on day 50 revealed extensive subcortical white matter lesions in both cerebral hemispheres (Fig.). Lumbar puncture yielded clear CSF (an opening pressure 140 mm H_2O) with a white cell count of 57 cells/mL (96% lymphocytes), glucose 103 mg/dL, and protein 91 mg/dL. The patient was weaned from the ventilator. He appeared alert but did not respond verbally, and he had persistent quadriplegia. He was transferred to a long-term care unit.

DISCUSSION

Scrub typhus is a zoonosis of the western Pacific islands and rural Asia. It is caused by Orientia tsutsugamushi and transmitted to humans by the bite of a larval thrombiculid mite, known commonly as a chigger[3]. The pathogen is an obligate intracellular Gram-negative bacterium. Infection with it involves multiple organs including the lung, heart, and CNS and is characterized by focal vasculitis or perivasculitis[4]. The main clinical features are high fever, rash, lymphadenopathy, and characteristic eschar formation. Although our patient did not have an eschar or lymphadenopathy, he lived in a rural area where the chance of exposure to infected chiggers is high. Parenteral minocycline, the drug of choice for severely ill patients in our hospital, was started on the day following admission. His initial CSF findings showed lymphocytic pleocytosis, elevated protein and decreased glucose levels, which raised the possibility of CNS infection due to scrub typhus. In most previously reported cases, the patients improved dramatically after appropriate antibiotics. In 2004, the Center for Disease Control, Taiwan recorded 369 confirmed cases of scrub typhus, with only 1% of patients dying from the disease[5]. Our patient's course was therefore very unusual in that his condition rapidly deteriorated and he had severe neurologic deficits. Besides, repeated cranial MR images showed progressively extensive lesions in the subcortical white matter, which was very unusual for scrub typhus encephalitis alone. Parainfectious encephalitis or co-infection with another pathogen was suspected. The combination of the cranial MR imaging findings plus the lack of evidence for any infection other than scrub typhus led us to the conclusion that the patient had ADEM temporally associated with scrub typhus.

ADEM, which has also been called post- or parainfectious encephalitis, has been found in association with a number of infectious agents, mainly viruses. Less commonly, bacteria or other pathogens have been reported, including Borrelia burgdorferi, Chlamydia, Legionella, Mycoplasma pneumoniae, Rocky Mountain spotted fever, streptococci, and Plasmodium vivax[6]. There are currently no generally accepted diagnostic criteria for ADEM, so it is largely a diagnosis of exclusion. The diagnosis of ADEM is usually made in the setting of a recent infectious illness on the basis of clinical findings with the aid of MR images and CSF examination. CSF findings include a mononuclear pleocytosis and elevated protein levels. Typical MR imaging findings are multiple areas of increased signal intensity throughout the CNS on T2 weighted images, most of the lesions being located in the subcortical white matter of both hemispheres. Besides, there may be a delay of over a month between the onset of symptoms and the appearances of new lesions on conventional MR images[7]. This time lag was also observed in our patient. The most important entity to differentiate it from is infectious meningoencephalitis of viral, bacterial or parasitic origin. These infections can be diagnosed through specific antibody testing, microbial culture, or PCR. Other diagnoses included

ischemic strokes, first manifestation of multiple sclerosis, and primary isolated CNS angiitis. Although they are difficult to differentiate from ADEM by clinical presentations, serial cranial MR images, MR angiography and CSF findings help us exclude them. Regarding primary isolated CNS angiitis, typical MR imaging findings revealed asymmetrical cortical, subcortical and deep white matter lesions, areas of bleed and heterogeneous parenchymal, pial or leptomeningeal enhancement[8]. Initial cranial MR images of our patient showed lesions in the right parietal white matter, relatively sparing the gray matter. In addition, the followed images revealed progressively extensive white matter lesions, which helped us to exclude the diagnosis of ischemic strokes or primary isolated CNS angiitis. As for multiple sclerosis, the patient was too old for the first attack, he had severe widespread neurological symptoms, and the followed cranial MR images showed large multiple lesions located subcortically. Due to a lack of informed consent, we did not perform invasive procedures, such as a conventional cerebral angiography or even a stereotactic brain biopsy for a definite diagnosis.

First-line treatment for ADEM is usually high dose glucocorticoids. Prognosis and response to glucocorticoids were generally good, except for some patient subgroups[9]. In our patient, he showed minimal improvement after treatment. As this is a case of laboratory-confirmed scrub typhus alone followed by neurologic deterioration in spite of appropriate treatment, we believe he had ADEM in association with O. tsutsugamushi infection. Progressively extensive white matter lesions as showed in the serial MR images further support the diagnosis. To our knowledge, ADEM has not previously been reported in association with scrub typhus.

ACKNOWLEDGEMENTS

A word of thanks goes to Dr. MJ Buttrey for her revision of the English manuscript.

REFERENCES

1. Schwarz S, Mohr A, Knauth M, et al. Acute disseminated encephalomyelitis: a follow-up study of 40 adult patients. Neurology 2001;56:1313-8.
2. Garg RK. Acute disseminated encephalomyelitis. Postgrad Med J 2003;79;11-7.
3. Watt G, Parola P. Scrub typhus and tropical rickettsioses. Curr Opin Infect Dis 2003;16:429-36.
4. Silverman DJ, Bond SB. Infection of human vascular endothelial cells by Rickettsia rickettsii. J Infect Dis 1984;149:201-6.
5. National Notifiable Disease Surveillance System [database on the Internet]. Center for Disease Control, Taiwan, R.O.C. c2006 - [cited 2006 Feb 20]. Available from: http://www.cdc.gov.tw/WebSite_En/Statistics%20&%20Analysis/Surveillance%20System/National%20Notifiable%20Disease%20Surveillance%20System2.htm
6. Menge T, Hemmer B, Nessler S, et al. Acute disseminated encephalomyelitis: an update. Arch Neurol 2005;62:1673-80.
7. Honkaniemi J, Dastidar P, Kahara V, et al. Delayed MR imaging changes in acute disseminated encephalomyelitis. Am J Neuroradiol 2001;22:1117-24.
8. Singh S, John S, Joseph TP, et al. Primary angiitis of the central nervous system: MRI features and clinical presentation. Australas Radiol 2003;47:127-34.
9. Marchioni E, Ravaglia S, Piccolo G, et al. Postinfectious inflammatory disorders: Subgroups based on prospective follow-up. Neurology 2005;65:1057-65.