Scrub Typhus Encephalomyelitis With Prominent Focal Neurologic Signs

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Background: Encephalomyelitis with prominent focal neurologic signs and associated neuroradiologic abnormalities has not been previously described in scrub typhus.

Case Description: A 22-year-old woman was admitted because of fever and an altered mental state. Neurologic examination revealed bilateral sixth and seventh nerve palsies, bilateral gaze evoked nystagmus, anarthria, dysphagia, quadripareisis, and sensory level at T1. Serum and cerebrospinal fluid samples were positive for tsutsugamushi antibody. The patient’s magnetic resonance images demonstrated the lesions responsible for the neurologic dysfunctions: in the lower brainstem, cerebellar peduncles, and spinal cord. It was interesting that the gray matter of the spinal cord was predominantly involved.

Conclusions: The recognition of unusual manifestations and the clinical suspicion of this treatment-responsive disease may be important, particularly in the face of increasing international and intranational travel.

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Scrub typhus is a rickettsial disease characterized by fever, myalgia, headache, rash, eschar formation, interstitial pneumonia, and meningoencephalitis. Fortunately, its incidence today is not as high as it was in the past; during World War II, 18000 cases of scrub typhus occurred among allied military personnel. However, rickettsioses continue to constitute major health problems in many parts of the world, and their prompt recognition is becoming more important to physicians because of increased international travel. Another important reason for the early diagnosis of rickettsioses is their excellent response to treatment. Neurologic involvement is quite common; the greatest degree of central nervous system involvement in rickettsial diseases occurs in Rocky Mountain spotted fever and epidemic typhus, followed closely by scrub typhus. Thus, the topic is also of importance to neurologists.

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A 22-year-old woman was admitted because of fever and an altered mental state. Four weeks before admission, she had visited her hometown and had helped on the family farm. One week later, she developed a headache, fever, and generalized malaise. Four days before admission, she visited a local hospital because of nausea, vomiting, and an aggravated headache. She was drowsy and needed assistance to walk. The next day, she developed dysarthria and quadripareisis, followed by voiding difficulties. She had persistent fever, with a peak temperature of 38.6°C, and her white blood cell count was 15.6 × 10⁹/L. After doxycycline hyclate therapy (200 mg/d) was started empirically, her body temperature normalized. However, she became drowsier and was transferred to our hospital.

On admission, her temperature was 36.3°C; blood pressure, 122/76 mm Hg; and pulse rate, 76/min. The findings of the rest of the physical examination were normal. On neurologic examination, she was deeply drowsy but could be aroused. Cranial nerve examination revealed bilateral abducens nerve palsies, facial diplegia, anarthria, dysphagia, and bilateral gaze evoked nystagmus. Motor power was decreased in the upper (grade 3/5) and lower (grade 0/5) extremities. Hypesthesia was detected for all sensations below T1. Deep tendon reflexes were 3+ and symmetrical. Plantar responses were flexor. The neck was supple.
The results of urinalysis and routine hematologic testing were normal except for an elevated erythrocyte sedimentation rate (66 mm/h). Serum aspartate aminotransferase (191 IU/L), alanine aminotransferase (462 IU/L), creatine kinase (987 IU/L), and lactate dehydrogenase (398 IU/L) levels were elevated. Serologic tests were negative for hepatitis B surface antigen and IgM antibodies against hepatitis A virus. Widal and polymerase chain reaction test results and tests for antibodies against various microorganisms—Hantaan virus, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, human immunodeficiency virus, *Listeria*, *Mycoplasma*, *Leptospira*, and *Legionella*—were all negative. However, serum IgM and IgG antibody titers against *Orientia tsutsugamushi*, which were measured using immunofluorescent antibody assays, were 1:5120 and 1:10240, respectively. Cerebrospinal fluid analysis showed mononuclear pleocytosis (25 white cells per cubic millimeter), mildly elevated protein content (0.49 g/L), and normal glucose levels (3.2 mmol/L [57 mg/dL]). The cerebrospinal fluid sample was positive for tsutsugamushi antibody (IgG, 1:160).

The chest radiograph revealed no abnormalities. Magnetic resonance images (MRIs) were obtained on the third day of admission. T2-weighted MRIs (1.5-T system, repetition time [TR], 4000 milliseconds [ms]; echo time [TE], 98 ms; and 3 excitations) and fluid-attenuated inversion recovery images revealed hyperintense lesions in the dorsolateral pontomedullary region, cerebellar peduncles bilaterally, and cervical spinal cord. The spinal cord lesion mainly involved the central gray matter (Figure). These lesions were slightly hypointense on T1-weighted MRIs (TR, 450 ms; TE, 10 ms; and 2 excitations) and were not enhanced after the intravenous injection of contrast material. T2-weighted gradient-echo MRIs (TR, 500 ms; TE, 15 ms) showed no abnormal signal loss lesions. A recording of brainstem auditory evoked potentials showed a delayed peak latency of wave V and a delayed interpeak latency of wave III-V.

The patient was treated with doxycycline hyclate for 2 weeks. On day 4, she was only slightly drowsy and could move her lower extremities. Superficial sensation was decreased to below the T5 level. The Babinski sign was noted bilaterally. On day 7, she became alert, and her ocular excursion was full, without nystagmus. On day 15, she could walk with assistance and void voluntarily. There was no dysarthria or dysphagia. On day 24, motor power of all 4 limbs became grade 5/5. Follow-up T2-weighted MRIs revealed decreased extent of abnormal hyperintensities (Figure).

**COMMENT**

Scrub typhus is an acute febrile zoonosis caused by *O. tsutsugamushi*, which is transmitted to humans by the bite of the trombiculid mite at the larval stage. It occurs in persons who engage in occupational or recreational behavior that brings them in contact with mite-infested grassy and brushy habitats in rural areas of Asia or South Pacific. It occurs throughout the year in tropical areas, and in temperate areas is most common in spring and summer.1,2,3

The diagnosis of scrub typhus was a challenge to us, since our patient did not have an eschar, the presence of which is a useful differential sign, although it is not always observed.1,4,5 Chest radiographs, which were reported to show abnormalities in about 70% of patients, revealed no abnormalities in our case.10 Furthermore, focal neurologic signs of encephalomyelitis, which were prominent in our patient, are known to be uncommon in scrub typhus.1,6,7 Scrub typhus may be characterized as an acute generalized inflammation of the vascular lining, vascular wall, and perivascular tissue. An exhaustive study of 200 cases of scrub typhus in Assam and Burma revealed that the central nervous system was involved at least slightly in almost all patients. However, focal central nervous system damage was rare, and no definite spinal cord lesion was seen.7 Thus, during the encephalitis stage, few objective neurologic signs are apparent, other than those suggesting more generalized cerebral involvement, such as confusion, tremor, and restlessness.1,2,7,8 In 1 series of rickettsial meningitis and encephalitis, only 1 of 72 patients with scrub typhus had focal neurologic signs, of cerebellitis.6 Accordingly, our patient’s prominent focal neurologic signs—bilateral sixth and seventh nerve palsies, bilateral gaze evoked nystagmus, anarthria, dysphagia, quadriparesis, and sensory level at T1—may be very unusual manifestations.
The patient’s MRIs clearly demonstrated the lesions responsible for the neurologic dysfunctions that had been revealed by neurologic examination and brainstem auditory evoked potentials in the lower brainstem, cerebellar peduncles, and spinal cord (Figure). It was interesting that the gray matter of the spinal cord was predominantly involved, because the most common location of miliary or microscopic focal nodules in scrub typhus is known to be in the gray matter. Although punctate focal hemorrhages are often reported to be observed at autopsy,7,8 our patient’s gradient-echo MRIs showed no abnormal signal loss lesion.

We considered the possibilities of postinfectious encephalomyelitis as well as of various infections that may take the form of a rhombencephalitis, such as Mycoplasma, Listeria, herpes, and human immunodeficiency virus infections. Because our hospital is a referral hospital, and located far from the endemic area, we might not have suspected rickettsiosis without knowledge of her traveling to an endemic area and the laboratory abnormalities, which suggested multiorgan involvement, as indicated by elevated levels of liver and heart enzymes. Although scrub typhus can be associated with significant morbidity,1,7,8 the patient recovered completely from the encephalomyelitis by taking doxycycline, aimed at the specific etiologic agent, tsutsugamushi.11 Therefore, the recognition of unusual manifestations and the clinical suspicion of this disease may be important, particularly in the face of increasing international and intranational travel.3

In summary, we describe a patient with scrub typhus encephalomyelitis. To our knowledge, encephalomyelitis with prominent focal neurologic signs and associated neuroradiologic abnormalities has not been previously described in scrub typhus.

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