가피를 동반하지 않은 쯔쯔가무시 수막뇌염 1례

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A Case of Scrub Typhus Meningoencephalitis without Eschar

Scrub typhus caused by *Orientia tsutsugamushi* manifests as fever, headache, myalgia and sometimes central nervous system dysfunction after mite bite. Eschar is an important diagnostic factor for scrub typhus but can be absent in about 30% of cases. We report a 6-year-old boy with scrub typhus meningoencephalitis, in whom diagnosis was late due to absence of eschar and direct exposure history. He was transferred to our hospital due to altered mental status and seizures following sustained fever. Previously, he had been diagnosed with aseptic meningitis as cerebrospinal fluid examination showed pleocytosis with normal range of glucose and protein. No pathogen had been proven and no abnormalities had been found in brain magnetic resonance imaging. On admission to our hospital, electroencephalography showed diffuse delta slowing with bilateral frontal sharps and scrub typhus antibody was positive, although the patient had no eschar. Family history-taking revealed his grandmother had been recently treated for scrub typhus and his father helping her farm and often cared for the patient wearing his working pants, as a possible vehicle of infection. Recovery was gradually upon treatment with clarithromycin, intravenous methylprednisolone and immunoglobulin. As scrub typhus can be present without eschar and can be transmitted through contaminated clothes, it needs to be considered for patients presenting with meningoencephalitis in a vulnerable season.

Key Words: Scrub typhus, Meningoencephalitis, Child

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Introduction

Scrub typhus is an acute febrile disease caused by rickettsial infection after the bite of chigger larvae infected with *Orientia tsutsugamushi*¹⁾. It is prevalent in a wide area of eastern Asia and the western pacific region¹⁾. Persons doing occupational or recreational behavior who come in contact with mite-infested habitats, such as bush and grass, are most susceptible to infected¹⁾. Scrub typhus has a wide spectrum of clinical manifestations within 7-10 days after mite bite, which include fever, rash, eschar, and gastrointestinal, pulmonary, renal, or hematological symptoms^{1,2)}. Some patients with scrub typhus can display central nervous system (CNS) dysfunction evident as altered mental status or sensorium, seizure, aseptic meningitis, and encephalitis²⁻⁴⁾.

The classic case description of scrub typhus includes an eschar at the site of

chigger feeding, regional lymphadenopathy, and a maculopapular rash^{5,6)}. The presence of an eschar is an important diagnostic sign of scrub typhus, but may not be found in up to 30% of cases^{5,7,8)}. We report a patient with scrub typhus meningoencephalitis, in whom diagnosis was late due to absence of eschar and direct exposure history to mites.

Case report

A 6-year-old boy who was previously healthy was transferred to our hospital due to stuporous mental state following fever and generalized tonic-clonic seizure. Five days before, he had visited another clinic due to a 5-day history of fever and subsequent seizures. He was diagnosed with aseptic meningitis as cerebrospinal fluid (CSF) examination showed only increase of CSF white blood cells (WBCs, 292 cells/mm³) with normal CSF protein, CSF glucose and serum C-reactive protein (CRP). No pathogen was isolated and no abnormalities were seen in enhanced brain magnetic resonance imaging (MRI) (Fig. 1). On admission to our hospital, his vital sign was stable without fever. Physical exami-

nation revealed an enlarged right cervical lymph node but demonstrated no skin lesion including rash or eschar. He could open and focus his eyes when experiencing pain, and sometimes uttered inappropriate words. Electroencephalography showed diffuse dysmorphic and slow delta background activities with bilateral independent frontal sharps (Fig. 2).

CSF analysis on admission showed evidence of improvement, with a WBC count of 5/mm³ with normal level of CSF glucose and protein. Laboratory investigations for usual pathogens of meningoencephalitis in the previous clinic and our hospital included CSF Gram stain, acid fast bacilli stain, and potassium hydroxide mount; CSF latex particle agglutination test for bacteria; CSF multiplex polymerase chain reaction (PCR) test for bacteria (e.g., *Streptococcus pneumoniae*, *Haemophilus influenza*, *Neisseria meningitis*, *Listeria monocytogenes*, and group B streptococcus) and viruses (e.g., herpes simplex virus type 1, herpes simplex virus type 2, human herpes virus 6, cytomegalovirus, ebstein-barr virus, and varicella zoster virus); enterovirus PCR test of CSF and stool; anti-Japanese encephalitis virus antibody in serum; CSF PCR test for tuberculosis; and bacterial culture of CSF, blood, and urine. All failed to reveal the causative pathogen.

Fig. 1. Result of enhanced brain magnetic resonance imaging. T1-weighted sagittal (A), T2-weighted axial (B), diffusion-weighted axial (C), and T1-weighted axial enhanced (D) images demonstrate no abnormal findings in parenchyma with abnormal signal intensity or enhancement.

Fig. 2. Electroencephalography of the patient on admission showed diffuse dysmorphic and slow delta background activities with bilateral independent frontal sharps (A and B with sharps from the right and left frontal areas, respectively).

Further serologic tests for fever of unknown origin included: 1) serum antibodies against cytomegalovirus, Epstein-Barr virus, herpes virus, surface antigen test for hepatitis B virus and *Mycoplasma pneumoniae*; 2) multiplex PCR test for throat-dwelling viruses including influenza virus; and 3) rapid immunochromatographic test (ICT) for hantaan virus, *leptospira* and *O. tsutsugamushi*. Although the patient showed no eschar or direct exposure history to mites, ICT for *O. tsutsugamushi* was positive, with an antibody titer in a passive hemagglutination assay (PHA) of 1:80. No abnormal findings were seen in the other tests for other pathogens. Urine analysis, other basic laboratory tests including thyroid function test, chest X-ray, and electrocardiography showed no abnormal results.

In family history, his grandmother had complained of fever, rash, and general weakness, and was recently diagnosed as scrub typhus with a clue of eschar on her vulva. She recovered on doxycycline therapy. Although our patient had no history of exposure to the grandmother's vegetable garden, where his father also worked, his father often cared for his son while wearing his working pants. The clothing was a possible vehicle of infection to our patient. The patient was treated with clarithromycin (30 mg/kg/day for 14 days), intravenous methylprednisolone (15 mg/kg/day for 5 days), and immunoglobulin treatment (1g/kg/day for 2 days). Generalized tonic-clonic seizures recurrently appeared for the first 3 days despite fosphenytoin, valproic acid and topiramate treatment. On day 5 of admission, seizures disappeared and he improved to an alert mental state. On day 13, he could walk alone and was discharged next day on valproic acid and topiramate.

Discussion

Scrub typhus is a febrile endemic disease in Asian-Pacific areas including Korea^{3,7)}. It is prevalent in autumn and has been reported from June to November in South Korea (from rainy months to the time of harvest)⁹⁾. It is a clinically important, as it can cause many serious complications including CNS symptoms³⁾. A study of 189 patients with scrub typhus reported that 79 patients (41.8%) had CNS symptoms³⁾. Among them, headache was the most common (100.0%), followed by altered sensorium (53.2%), neck stiffness (48.1%), and seizure (15.2%)³⁾. Misra et al. reported that among 37 scrub typhus patients, headache occurred in 33 patients (89.2%), altered sensorium in 32 patients (86.5%), neck stiffness in 18 patients (48.6%), and seizure in 8 patients (21.6%)⁴⁾. In addition to these symptoms, ataxia, delirium, cranial nerve palsy, quadriplegia, hypesthesia, motor weakness, and diplopia have

been reported¹¹⁾. Palanivel et al. reported that among 67 pediatric scrub typhus patients, 58.2% had altered sensorium and 28.4% showed seizures⁸⁾. However, headache, which is the most common neurologic symptom of patients with scrub typhus, was not investigated in the study⁸⁾.

Brain or spinal MRI lesions in patients with scrub typhus have been reported only in some patients, which are usually limited to the gray matter^{1,4,6,10)}. This might be because scrub typhus involves invasion of small vessels^{1,4,10)}. Among 25 patients who received brain MRIs (consisting of scrub typhus meningoencephalitis, encephalitis, and encephalopathy) in the study of Mirsa et al., only one patient showed an abnormal finding of leptomeningeal enhancement⁴⁾. Two case reports have described spinal cord lesions: one in the thoracic spine and another in the cervical spine and the brainstem^{1,11)}. Recently, a few cases of scrub typhus were reported with periventricular and/or deep white matter lesion^{1,10)}.

CSF examinations in patients with scrub typhus meningitis or meningoencephalitis have revealed the mild-to-moderate increase of CSF WBC with lymphocyte dominance in addition to mild increase of CSF protein^{2,3)}. WBC in CSF usually normalizes in a shorter period^{2,3)}. Pai et al. reported that CSF WBC counts were elevated from 5 to 110/mm³ with lymphocyte dominance in 12 of 25 patients with CNS symptoms²⁾. Boorugu et al.'s study of 39 patients with CNS symptoms showed similar results: mean CSF WBC count was 47.3/mm³ (range: 2–450/mm³) with lymphocyte dominance, and mean CSF protein was 90.6 mg/dL (range: 14–360 mg/dL)³⁾.

For diagnosis of scrub typhus, the eschar is the single most useful clue^{5,7)}. The eschar begins as a small papule, which enlarges, undergoes central necrosis, and eventually acquires a blackened crust with an erythematous halo resembling a cigarette burn⁶⁾. An eschar usually occurs at sites where skin surfaces meet (e.g., axilla and groin) or where clothes bind (e.g., neck and waist)^{5,6)}. However, as it can be absent in 30% of patients with scrub typhus, clinical suspicion and early request for an appropriate laboratory investigation are very important in a prevalent season^{5,7)}. As the levels of hepatic enzymes or alkaline phosphatase frequently elevated, patients with hepatitis and CNS symptoms need to be screened for scrub typhus^{6,7)}.

The main stay in scrub-typhus diagnostics remains serology^{5,6,12)}. The indirect fluorescent antibody (IFA) test that is the most sensitive method is known as the gold standard^{5,13)}. However, the IFA is still expensive, needs several days to get a result, and requires experts with considerable training to perform it^{5,13)}. Therefore, the alternative diagnostic method of PHA has been used widely for recent two decades; nevertheless it has a lower sensitivity, especially in the acute phase^{5,13)}. Recently, the ICT was

introduced as a rapid diagnostic test to replace the PHA¹²⁾. Previous studies found that the sensitivities and specificities of ICT were ranged from 46.3% to 67.9% and 67.9% to 95.1%, respectively¹²⁾.

The drug of choice for scrub typhus treatment is doxycycline and chloramphenicol in adult patients⁷⁾. However, these are not appropriate for children due to their adverse effects^{14,15)}. Doxycycline is not recommended in children under 8 years of age as it can result in teeth staining¹⁵⁾. Chloramphenicol can cause gray baby syndrome and irreversible bone marrow toxicity of fatal aplastic anemia¹⁶⁾. Therefore, macrolides are recommended as alternative antimicrobials for children especially under 8 years of age¹⁴⁻¹⁶⁾. Several studies showed they were not less effective for treatment of scrub typhus and can be better tolerated in children than doxycycline¹⁴⁻¹⁶⁾.

Most patients showing neurologic symptoms associated with scrub typhus have good prognosis. Misra et al. reported that all 31 patients with impaired consciousness were completely recovered within 1 month⁴⁾. However, rare complication such as cerebral infarction, polyneuropathy, and transverse myelitis have been reported in other literature^{3,11)}.

As scrub typhus meningoencephalitis can be seen without eschar and can be caused by indirect exposure through contaminated clothes, serum antibody test targeting *O. tsutsugamushi* should be considered in patients with meningoencephalitis who seek treatment between June and November in Korea. Our patient with altered mental state, seizure, and prolonged fever showed positive result for antibodies against *O. tsutsugamushi*, although he had no eschar and no previous history of recreational behavior in contact with mite-infested habitats, such as bush and grass. His CSF pleocytosis was improved in a week and he had recovered in 14 days without sequelae.

요약

쯔쯔가무시병은 *O. tsutsugamushi*에 감염된 털진드기의 유충에 물려 발생하는 질환으로 발열, 두통, 근육통 등의 증상을 보이며, 신경학적 증상이 나타나기도 한다. 가피는 쯔쯔가무시 진단에 중요하지만 30% 정도에서는 관찰되지 않는다. 저자들은 가피 및 직접 노출된 병력이 없어 진단이 늦어졌던, 쯔쯔가무시 수막뇌염 환자 증례를 경험하였기에 보고하고자 한다. 타병원에서 무균성 뇌수막염 진단을 받고 5일간 치료한 6세 남자 환자가 지속되는 발열과 이후 발생한 의식의 저침, 반복되는 경련을 주소로 전원되었다. 타병원에서 시행한 뇌척수액 검사에서 백혈구 증가(292개/mm³)를 보였으나 척수액 당과 단백은 정상 이었고, 세균 및 바이러스는 검출되지 않았으며, 뇌 자기공명영상은 정상이었다. 입원 후 시행한 뇌파검사에서 전반적으로 느

린 서파와 양쪽 전두엽 쪽의 예파가 관찰되었고, 불명열에 대해 시행한 혈액검사에서 쯔쯔가무시 항체가 양성이었다. 환아는 피부 가피가 없고, 직접적으로 노출된 병력도 없었지만 할머니가 2주 전 쯔쯔가무시로 진단받아 치료받았고, 자주 환아와 접촉하였던 아버지도 같이 농장 일을 했었다고 했다. 따라서, 아버지의 오염된 옷이 환아에게 쯔쯔가무시병을 옮긴 매개체로 생각된다. 환아는 clarithromycin, methylprednisolone, immunoglobulin 치료 후 호전되어 14일째에 퇴원하였다. 쯔쯔가무시병은 가피가 없이 발생하기도 하며, 오염된 옷이 매개체가 될 수 있으므로 유행하는 시기에 수막뇌염으로 내원하는 환아에서는 진단에 고려해야 할 것이다.

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