

## Differentiating scrub typhus meningoencephalitis, from tuberculous meningitis: Two case reports and a review

De Silva CM<sup>1</sup>, Fonseka CL<sup>1,2</sup>, Nanayakkara SD<sup>1</sup>, Singhapura SDAL<sup>1</sup>, Palangasinghe DR<sup>1</sup>, Hewawithana Js<sup>1</sup>, Pathirana KD<sup>1,2</sup>, Bodinayake CK<sup>1,2</sup>

<sup>1</sup>University Medical Unit, Teaching Hospital Karapitiya, Galle, Sri Lanka.

<sup>2</sup>Department of Internal Medicine, Faculty of Medicine, University of Ruhuna, Galle, Sri Lanka.

**Correspondence:** Dr. C.L Fonseka

e-mail: [fonseka.lakmal@gmail.com](mailto:fonseka.lakmal@gmail.com)

<https://orcid.org/0000-0003-3364-6257>

### Introduction

Scrub typhus is a zoonotic disease where currently about one million new cases are identified annually and one billion people may be at risk of this disease (1-3). The infection is acquired through agricultural activities in the rice fields, oil palm, rubber plantation and during recreational activities in the woods or mountainous areas which are common in Southeast Asia (4). Scrub typhus is underdiagnosed due to its nonspecific clinical presentation and lack of diagnostic facilities. The clinical manifestations of the disease range from sub-clinical disease to fatal organ failure (5) and it is commonly observed in endemic areas as one of the causes of fever of unknown origin (6). The pathognomonic clinical sign of scrub typhus is the presence of an eschar (60%) (7-9), which may be hidden and painless as it is often present in areas like breast folds, groin, external genitalia and gluteal folds which may go unnoticed in dark-skinned individuals.

The complications of scrub typhus usually develop after the first week of illness where jaundice, renal failure, pneumonitis, ARDS, septic shock, myocarditis and meningoencephalitis are all described. Central nervous system (CNS) involvement is a well-known complication of scrub typhus ranging from aseptic meningitis to frank meningoencephalitis (10). Patients with scrub typhus with meningitis and/or encephalitis present as confusion, agitation or seizures. Focal neurological signs are rare but are known to occur (11). Cranial nerve deficits are seen in ~25% of patients with the

sixth being the most commonly involved (12). Unilateral or bilateral abducent palsies occur with or without meningitis and facial palsies ensue singly or in association with Guillain Barre Syndrome (13). Although focal CNS damage is rare complications like cerebellitis (14), myelitis (12), and cerebral hemorrhage (15) are reported during the encephalitis stage. Generalized cerebral vasculitis caused by scrub typhus (*Orientia tsutsugamushi*) can present as meningitis or meningoencephalitis in 5.7 - 13.5% of patients. Cerebrospinal fluid (CSF) profile may show changes similar to viral meningitis such as mild leukocytosis, slightly increased protein content, and normal glucose levels (6). It should be included in differential diagnosis of aseptic meningitis and encephalitis in patients in endemic areas especially when alternative diagnoses are uncertain (5,11,16). In some instances features similar to tuberculous meningoencephalitis (TBM) such as cranial nerve palsies with CSF showing lymphocytic pleocytosis, moderately elevated protein levels, low glucose and elevated CSF adenosine deaminase (ADA) levels have been described (10).

To confirm the diagnosis, Weil-Felix test can be used with the Proteus OXK strain with a minimum positive titer of 1 : 80 or a fourfold rise over previous levels. Several studies have shown that the Weil-Felix test has a high specificity. It was found that at a cut-off value of  $\geq 1 : 320$ , OXK had a specificity of 97% but it was less sensitive. Other tests that can be used to diagnose scrub typhus with higher specificity include indirect immuno-

fluorescence test (IFA), immunoperoxidase test (IPT) and complement fixation test (CFT). Also detection of scrub typhus IgM by ELISA method also has a high specificity (~90%) and sensitivity (~90%) when compared with IFA and IPT (13).

This paper describes two cases of scrub typhus presented as isolated meningoencephalitis with significantly elevated CSF proteins and completely recovered with appropriate antibiotics.

### Case report - 01

A 47 year-old previously healthy male presented with generalized severe headache associated with photophobia and vomiting for 2 weeks. Initially he had high grade fever lasting for 7 days with arthralgia and myalgia. He did not have a history of altered sensorium, seizures. On examination, there was conjunctival congestion and neck stiffness but there was no mucosal pallor, jaundice, lymphadenopathy, rashes or oedema. Vitals were stable with respiratory and cardiovascular system examination being normal and he didn't have hepatosplenomegaly. Optic fundi were normal. Investigations showed a total white cell count of  $6700 \text{ cell/mm}^3$  with normal haemoglobin, and platelets. His ESR was 36 mm and CRP was 4 mg/L. His renal and liver profiles and chest radiograph were normal and the peripheral smear for the malarial parasite was negative.

A lumbar puncture revealed a significantly elevated protein level of 153 mg/dL with 5 polymorphs and 30 lymphocytes per  $\text{mm}^3$  with glucose of 68 mg/dL (plasma glucose 110 mg/dL). His CSF culture and bacterial antigen tests for pneumococcal, meningococcal and haemophilus spp. were negative. A clinical diagnosis of partially treated bacterial meningitis was made and patient was started on intravenous ceftriaxone. Despite continuation of ceftriaxone for more than 48 hrs the patient had continuous headache and fever reappeared during hospital stay. MRI brain was normal and CSF PCR for mycobacterium tuberculosis was negative. Upon further questioning patient revealed that he had been working in his lands visiting wooded areas prior to the onset of current illness. A through physical examination revealed a healed eschar in his groin that was unnoticed even by the patient until then (Figure 1).

A clinical diagnosis of typhus meningitis was made and patient was promptly commenced on oral doxycycline which resulted in dramatic symptomatic improvement resulting patient being afebrile and headache free within 48 hrs of treatment. Weil-Felix agglutination test was positive (PROTEUS OX 19 - 1/160, PROTEUS OX 3 - 1/160, PROTEUS OX K - 1/640). Repeat lumbar puncture performed after one week showed dramatic reduction of protein to 58 mg/dL and clearance of cells with normal glucose levels. Patient recovered completely and was discharged after completion of ten days of antibiotics.



**Figure 1:** Eschar found in left groin (Case 1)

### Case report - 02

Previously healthy, 23 year-old male presented with history of fever for nine days and acute confusion with change in behavior. He was suffering from a dull aching type headache associated with vomiting without photophobia. One week prior to the admission he had participated in a mountain hike. On admission he was disoriented with a GCS of 14 (E - 4/4, M - 6/6, V 4/5). He was febrile (102 °F), tachycardic (pulse rate 108/min) with a blood pressure 110/70 mmHg. Neck was supple. On careful examination a maculopapular rash involving upper limbs, back and chest was noted. No eschar could be detected. On clinical suspicion of meningoencephalitis intravenous ceftriaxone was initiated. Full blood count showed elevated white cell count with neutrophil predominance. (WBC  $11,300/\text{mm}^3$ , Neutrophils 65%). CRP was 97.4 mg/L while ESR was 41mm. Blood cultures were negative.

Patient underwent lumbar puncture which showed CSF proteins of 157.5 mg/dL with a lymphocyte count of  $2/\text{mm}^3$ . Polymorphs were not seen. CSF sugar was 60 mg/dL. (Random blood sugar 98 mg/dL). CSF culture, gram stain and antigen for common bacterial pathogens (pneumococcal, meningococcal and haemophilus spp.) were negative.

After 48 hours, patient continued to be symptomatic with high fever and the possibility of typhus meningoencephalitis was considered. Weil-Felix agglutination test showed positive results with PROTEUS OX 19 - 1/80, PROTEUS OX 3 - 1/160 and PROTEUS OX K - 1/320. Rapid test for scrub typhus antibody (IgM ELISA) also was positive. Oral doxycycline was initiated, with resultant dramatic clinical improvement within 24 hours and subsequently patient was discharged after 10 days of antibiotics.

## Discussion

In the two cases reported we faced a diagnostic dilemma due to the elevated CSF proteins with lymphocytic pleocytosis and poor response to conventional antibiotics. Literature mentions that CSF in typhus meningoencephalitis can show a spectrum of changes. It may show leukocytosis, elevated protein, and slightly reduced glucose resembling viral meningoencephalitis, leptospirosis, and in certain instances tuberculous meningitis (6). Pai Het *et al*, reported a series of 25 patients with scrub typhus without signs of overt CNS involvement and showed that 48% had a reactive CSF showing mild mononuclear pleocytosis and PCR for *O. tsutsugamushi* was positive in 24% of cases. CSF white cell count ranged from 0 to 110, and the mean lymphocyte proportion was 51.9%. The CSF protein level was high ( $>50$  mg/dL) in seven patients in this case series but only one patient had protein level more than 100 mg/dL (15). Another case series of 13 patients with suspected typhus meningitis / meningoencephalitis, mean CSF protein of  $152 \pm 66.88$  mg/dL, glucose concentration of  $55.23 \pm 12.7$  mg/dL and cell count of  $46.07 \pm 131$  cells/ $\text{mm}^3$  were seen. Most patients had lymphocytic pleocytosis and mean lymphocyte percentage was  $98.66\% \pm 3.09\%$  (17). Abhilash *et al*, reported a series of 189 patients with scrub typhus admitted

with meningitis / meningoencephalitis (with IgM-ELISA positivity and/ or the presence of a pathognomonic eschar with PCR confirmation) (17), where mean CSF white cell count was  $80 \pm 120/\text{mm}^3$  (range 5 - 900 cells) and  $> 60\%$  patients showing counts up to 100 cells/ $\text{mm}^3$ . Only 10.5% (20/189) patients had counts exceeding 200 cells/ $\text{mm}^3$  with lymphocyte predominance in 87.6%. The mean CSF protein level in this study group was  $105.9 \pm 80.9$  (range 13 - 640 mg/dL) and was more than 100 mg/dL in 38% (72/189) of patients. This makes differentiating tuberculous meningitis (TBM) from typhus meningoencephalitis on CSF findings difficult. TBM is known to have high CSF proteins ( $>100$  mg/dL) with lymphocytic predominance.

Although we have not performed, CSF Adenosine Deaminase (ADA) is another investigation that can be used in this setting. Some studies looked at ADA to differentiate TBM from typhus meningoencephalitis. CSF ADA  $>10$  U/L increases the post-test probability of TBM, especially in a setting where TB prevalence is low. CSF-ADA sensitivity as high as 92.5% and specificity of 97% for the diagnosis of TBM at the cut-off at  $> 10$  U/L has been observed (18). In a retrospective study in India (12) involving 65 cases of scrub typhus of which 17 had meningitis, CSF ADA levels were  $>10$  U/L. In another study by Jamil *et al* (16), where CSF analysis was done in 13 patients of scrub typhus with clinical suspicion of meningitis / meningoencephalitis, 9 had ADA levels  $> 10$  U/L. Mean CSF ADA was  $16.98 \pm 7.37$  U/L with the highest ADA level of 33.25 U/L.

Other investigations which may be beneficial in these patients would be the detection of acid-fast bacilli (AFB) in CSF and Xpert-TB-PCR. Staining for AFB in CSF has low sensitivity and CSF culture for AFB take up to 8 weeks and is positive only in 50 - 75% of cases (19). Most studies on TB PCR (Xpert) found low sensitivity in detecting TBM (about 50%) and specificity was as high as 98% (20-23).

Scrub typhus meningitis can also be differentiated from TBM by the shorter period taken for the normalization (24) of CSF and the dramatic response to doxycycline. Rifampicin is also used to treat severe scrub typhus and in fact gives rise to better inhibitory concentrations in CSF (24) than doxycycline so that improvement following anti-

tuberculous therapy (ATT) may mask the diagnosis of scrub typhus.

We used doxycycline in both our patients and observed a marked improvement of symptoms within 24 - 48 hours. Rapid defervescence after antibiotics is so characteristic that it is used as a diagnostic clue for typhus as seen in our patient. Usually, the neurological abnormalities recover within 2 - 5 days of doxycycline therapy (13). In instances where doxycycline cannot be used other antibiotics such as tetracycline, azithromycin and rifampicin can be considered. Tetracycline 500 mg qid or doxycycline 200 mg once daily for 7 days is the treatment of choice. Azithromycin has been proven to be more effective than doxycycline in doxycycline-susceptible and doxycycline-resistant strains causing scrub typhus and can be used in pregnancy and in renal failure (11). Suggested mechanism for doxycycline resistance include poor CNS penetration with 15 - 30% of drug reaching the CNS, resistance, bacteriostatic nature, immune mediated injury etc. (16,25,26). Chloramphenicol 500 mg qid, is an alternative and as mentioned above rifampicin, 900 mg per day for a week has been found effective in patients who respond poorly to conventional therapy (27). Patients can be additionally given dexamethasone and mannitol if they have altered sensorium or cranial nerve deficits. In some instances, progressive neurological damage has been observed despite treatment calling for alternative medications (13).

### Conclusions

Significantly elevated CSF protein levels with lymphocytosis can be observed in Scrub Typhus meningoencephalitis which can be confused with tuberculous meningitis. Recognition of an eschar or appropriate serological investigations will guide treatment specific for typhus. Rapid defervescence and faster normalization of CSF after doxycycline may be a clue to diagnosis.

### References

1. Isaac R, Varghese GM, Mathai E, Manjula J, Joseph I. Scrub typhus: prevalence and diagnostic issues in rural Southern India. *Clinical Infectious Diseases*, 2004; **39**(9): 1395-6.
2. Chaudhry D, Garg A, Singh I, Tandon C, Saini R. Rickettsial diseases in Haryana: not an uncommon entity. *J Assoc Physicians India*, 2009; **57**(4): 334-7.
3. Ittyachen AM. Emerging infections in Kerala: a case of scrub typhus. *National Medical Journal of India*, 2009; **22**(6): 333-4.
4. Mahajan SK. Scrub typhus. *JAPI*, 2005; **53**(955): 269.
5. Silpapojakul K, Ukkachoke C, Krisanapan S, Silpapojakul K. Rickettsial meningitis and encephalitis. *Archives of Internal Medicine*, 1991; **151**(9), 1753-7.
6. Drevets DA, Leenen PJ, Greenfield RA. Invasion of the central nervous system by intracellular bacteria. *Clinical Microbiology Reviews*, 2004; **17**(2): 323-47.
7. Warrell DA, Benz EJ, Cox TM, Firth JD, eds. Oxford Textbook of Medicine (Vol. 1). Oxford University Press, USA. 2003; **1**: 629-31.
8. Walker D, Raolt D, Dumler JS. In Harrison's Principles of Internal Medicine Braunwald E, Fauci AS, Kasper DL, et al (Edi.) 15<sup>th</sup> Edi. New York. McGraw Hill Companies Inc, 2001; **1**: 1070.
9. Cracco C, Delafosse C, Baril L, Lefort Y, Morelot C, Derenne JP, Bricaire F, Similowski T. Multiple organ failure complicating probable scrub typhus. *Clinical Infectious Diseases*, 2000; **31**(1), 191-2.
10. Garg RK. Tuberculous meningitis. *Acta Neurologica Scandinavica*, 2010; **122**(2): 75-90.
11. Jamil MD, Hussain M, Lyngdoh M, Sharma S, Barman B, Bhattacharya PK. Scrub typhus meningoencephalitis, a diagnostic challenge for clinicians: A hospital based study from North-East India. *Journal of Neurosciences in Rural Practice*, 2015; **6**(4), 488.
12. Kim DE, Lee SH, Park KI, Chang KH, Roh JK. Scrub typhus encephalomyelitis with prominent focal neurologic signs. *Archives of Neurology*, 2000; **57**(12): 1770-2.
13. Viswanathan S, Muthu V, Iqbal N, Remalayam B, George T. Scrub typhus meningitis in South India - a retrospective study. *PLoSone*, 2013; **8**(6): p.e66595.
14. Yang SH, Wang LS, Liang CC, Ho YH, Chang ET, Cheng CH. Scrub typhus complicated by intracranial haemorrhage - A case report. *Tzu Chi Med J*, 2005; **17**: 111-4.
15. Pai H, Sohn S, Seong Y, Kee S, Chang WH, Choe KW. Central nervous system involvement in patients with scrub typhus. *Clinical Infectious Diseases*, 1997; **24**(3): 436-40.

16. Ben RJ, Feng NH, Ku CS. Meningo-encephalitis, myocarditis and disseminated intravascular coagulation in a patient with scrub typhus. *Journal of Microbiology, Immunology, and Infection*. 1999; **32**(1): 57-62.
17. Abhilash KPP, Gunasekaran K, Mitra S, Patole S, Sathyendra S, Jasmine S, Varghese GM. Scrub typhus meningitis: An under-recognized cause of aseptic meningitis in India. *Neurology India*, 2015; **63**(2): 209.
18. Rana SV, Chacko F, Lal V, Arora SK, Parbhakar S, Sharma SK, Singh K. To compare CSF adenosine deaminase levels and CSF-PCR for tuberculous meningitis. *Clinical Neurology and Neurosurgery*, 2010; **112**(5): 424-30.
19. Thwaites GE, Chau TTH, Stepniewska K, Phu NH, Chuong LV, Sinh DX, White NJ, Parry CM, Farrar JJ. Diagnosis of adult tuberculous meningitis by use of clinical and laboratory features. *The Lancet*, 2002; **360**(9342): 1287-92.
20. Chaidir L, Ganiem AR, vander Zanden A, Muhsinin S, Kusumaningrum T, Kusumadewi I, van der Ven A, Alisjahbana B, Parwati I, van Crevel R. Comparison of real time IS6110-PCR, microscopy, and culture for diagnosis of tuberculous meningitis in a cohort of adult patients in Indonesia. *PLoS One*, 2012; **7**(12): e52001.
21. Haldar S, Sharma N, Gupta VK, Tyagi JS. Efficient diagnosis of tuberculous meningitis by detection of Mycobacterium tuberculosis DNA in cerebrospinal fluid filtrates using PCR. *Journal of Medical Microbiology*, 2009; **8**(5): 616-24.
22. Patel VB, Theron G, Lenders L, Matinyena B, Connolly C, Singh R, Coovadia Y, Ndung'u T, Dheda K. Diagnostic accuracy of quantitative PCR (Xpert MTB/RIF) for tuberculous meningitis in a high burden setting: a prospective study. *PLoS Medicine*, 2013; **10**(10): e1001536.
23. Nagdev KJ, Kashyap RS, Deshpande PS, Purohit HJ, Taori GM, Dagainawala HF. Comparative evaluation of a PCR assay with an in-house ELISA method for diagnosis of Tuberculous meningitis. *Medical Science Monitor*, 2010; **16**(6): CR289-CR295.
24. Yum KS, Na SJ, Lee KO, Ko JH. Scrub typhus meningoencephalitis with focal neurologic signs and associated brain MRI abnormal findings: literature review. *Clinical Neurology and Neurosurgery*, 2011; **113**(3): 250.
25. Vivekanandan M, Mani A, Priya YS, Singh AP, Jayakumar S, Purty S. Outbreak of scrub typhus in Pondicherry. *J Assoc Physicians India*, 2010; **58**(1): 24-8.
26. Kim DM, Kim YS, Cho HY, Lee YB. Scrub typhus meningoencephalitis occurring during doxycycline therapy for Orientia tsutsugamushi. *Diagnostic microbiology and infectious disease*, 2011; **69**(3): 271-4.
27. Strickman D, Sheer T, Salata K, Hershey J, Dasch G, Kelly D, Kuschner R. In vitro effectiveness of azithromycin against doxycycline-resistant and-susceptible strains of Rickettsia tsutsugamushi, etiologic agent of scrub typhus. *Antimicrobial Agents and Chemotherapy*, **39**(11): 2406-10.