Clinical Spectrum and Outcome of Acute Encephalitis Syndrome in Children with Scrub Typhus: A Series of Eight Cases from India

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ABSTRACT
Scrub typhus has reemerged with a different geographical distribution and varied clinical presentation like acute encephalitis syndrome (AES), which is a less known entity in scrub typhus. In this case series, we studied the clinical profile and outcome of eight patients who presented with AES and a positive scrub serology without any other identifiable cause of encephalopathy. All these patients had fever, altered sensorium, and nuchal rigidity, while seizures were present in six (75%) patients and papilledema in two (25%) patients. Complications like shock, pulmonary edema, and gastrointestinal (GI) bleed were observed in three (37%) patients. All patients except for one responded well to the treatment and recovered completely. Scrub typhus should be suspected early in patients presenting with AES.

Keywords: Doxycycline, Meningoencephalitis, Orientia tsutsugamushi.

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INTRODUCTION
Scrub typhus caused by Orientia tsutsugamushi is a reemerging disease in India, which is affecting the urban population also and presenting with varied symptoms.1–5 It commonly presents with undifferentiated fever, headache, inoculation eschar, and lymphadenopathy along with multi-organ dysfunction, which is known to occur in scrub typhus.4,5 Also, various neurological manifestations like meningitis, meningoencephalitis, encephalopathy, seizures, stroke, neuropathy, and myelitis have been defined in the literature.6,7 The neurological manifestations may also be accompanied with systemic features as hepatitis, bleed, difficulty in breathing, renal involvement, and multi-organ dysfunction. But, very less has been studied and reviewed about its presentation as acute encephalitis syndrome (AES). In this series, we studied the clinical profile and outcome of AES in scrub typhus infected children. Doxycycline is the drug of choice and in case of non-responders azithromycin can be used as a second-line therapy.

CASE DESCRIPTIONS
Eight consecutive patients (<12 years) who presented in emergency during rainy season with clinical features of AES, and showed serum scrub typhus IgM positivity [enzyme-linked immunosorbent assay (ELISA)] were studied. Along with routine investigations [like complete blood count, liver function test (LFT), renal function test (RFT), prothrombin time (PT)/International Normalized Ratio (INR), chest X-ray (CXR), blood culture], fundus examination, lumbar puncture, and neuroimaging were performed for the patients. Also, many serological tests were performed to rule out other causes of AES [namely herpes simplex virus (HSV), Japanese encephalitis (JE), dengue, malaria, and enteric]. After taking informed consent, demographic profile, signs and symptoms, course of hospital stay, and outcome of all these patients were documented. All these patients (age group 1.5–12 years) presented with fever (mean duration 7.5 ± 2.6 days) and altered sensorium. Six patients (75%) had seizures and seven patients (87%) showed signs of meningitis.

Cerebrospinal fluid (CSF) analyzes was performed in six patients and all showed high protein (mean 67 mg/dL), three showed hypoglychorhachia, and one had pleocytosis. The neuroimaging [computed tomography (CT) head] was performed in five patients and only one showed cerebral edema while rest were normal. Three patients developed complications like shock requiring inotropic support, gastrointestinal (GI) bleed, and pulmonary edema. All patients were treated with doxycycline alone after confirming the diagnosis and ruling out other causes. Seven patients responded well, became afebrile after 4–5 days and recovered completely except for one patient who succumbed to death because of refractory shock (Table 1).

DISCUSSION
In last two decades, scrub typhus has shown a resurgence pattern in India, infecting people living in hilly as well as urban sectors.1–3 Recent studies have shown scrub typhus as an important cause of AES other than the etiologies like HSV encephalitis, JE, malaria, and dengue. Acute encephalitis syndrome is defined as rapid onset of febrile illness associated with convulsion, altered sensorium, and focal neurological deficit, such as aphasia, hemiparesis, involuntary movements, ataxia, or cranial nerve palsies.8 The burden of

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AES caused by scrub typhus has been studied previously and documented to be 13.6% in one study and 30% in another.\textsuperscript{6,9} In this case series, we observed the clinical spectrum and outcome of such patients.

All patients in our study presented during rainy and post-rainy season suggesting the seasonal habitation of the vector as documented previously.\textsuperscript{7} Out of eight patients, five presented with less than 1 week of fever and other three presented later because they were referred from other hospitals. However, all patients developed the neurological symptoms like altered sensorium (100%) or seizure (87%) or nuchal rigidity (87%) within 3–6 days of onset of fever. Neurological deficit or cranial nerve palsies were not observed in any patient. Laboratory findings of patients revealed thrombocytopenia (100%), elevated transaminases (87%), and coagulopathy (12.5%), which are also known to occur in scrub but on the contrary none had deranged RFTs. Complications such as shock requiring inotropes, GI bleed, and pulmonary edema were observed in three patients, similar to other studies.\textsuperscript{5,7,9}

Cerebrospinal fluid analysis in scrub meningoencephalitis shows low-to-normal sugars, mild-to-moderate rise in proteins, and presence of lymphocytes. Cerebrospinal fluid examination of our patients showed elevated protein (mean 67) and low glucose levels (mean 47), and pleocytosis in one patient. The above-mentioned pattern of CSF results is consistent with a subacute tubercular meningitis like picture, which is therefore, is an important differential of scrub typhus meningoencephalitis. Some studies have reported usefulness of CSF adenosine deaminase for the differentiation but its definite role is not proven.\textsuperscript{9,10}

Neurological involvement in scrub typhus is associated with different neuroimaging findings ranging from normal imaging to abnormalities like cerebral edema, features of ischemic changes, small ring enhancing lesions in the corpus callosum, and hyperintensities in periventricular and deep white matter regions of the brain.\textsuperscript{8–10}

### Table 1: Clinical and biochemical profile of all patients

| Symptoms | Case 1 | Case 2 | Case 3, 9 years/F | Case 4, 6 years/M | Case 5, 7 years/F | Case 6, 12 years/M | Case 7, 3 years 6 months/F | Case 8, 1 year 6 months/M |
|----------|--------|--------|------------------|------------------|------------------|------------------|--------------------------|--------------------------|
| Fever    | 12 days| 5 days | 6 days          | 6 days          | 4 days          | 12 days         | 5 days                   | 10 days                  |
| Headache | +      | –      | –               | –               | +               | –               | –                        | –                        |
| Vomiting | –      | +      | +               | –               | –               | –               | –                        | +                        |
| Seizures | GTCS   | –      | Focal           | –               | GTCS            | GTCS            | Focal                    | GTCS                    |
| Altered sensorium | + | + | + | + | + | + | + | + |
| Periorbital swelling | – | – | + | + | – | + | – | – |

### Signs

| Altered GCS | + | + | + | + | + | + | + | + |
| Nuchal rigidity | + | + | + | + | – | + | + | + |
| Hepatomegaly | – | + | + | + | + | – | + | – |
| Splenomegaly | – | – | + | – | – | – | – | – |
| Papilledema | – | – | – | – | – | + | – | + |
| Eschar | – | – | – | – | – | + | – | – |

### Lab findings

| TLC | 26,000 | 7,400 | 5,700 | 6,700 | 8,800 | 7,500 | 6,200 | 10,900 |
| Platelet count | 1.2 lac | 0.47 lac | 0.60 lac | 1.1 lac | 1.43 lac | 1.0 lac | 1 lac | 0.18 lac |
| SGOT/SGPT (>2 UL IJ) | + | + | + | + | – | + | + | – |
| BUN/creatinine | 12/0.7 | 14/0.6 | 18/0.7 | 12/0.6 | 9/0.2 | 11/0.6 | 10/0.3 | 15/0.6 |
| PT/INR | Normal | Normal | Normal | Normal | Normal | Normal | Normal | 26 seconds/1.98 |

### CSF findings

| TLC | Acellular | Acellular | 500 cells | Acellular | Not done | Acellular | Acellular |
| Sugar | 56 | 43 | 43 | 24 | | 62 | 68 |
| Protein | 74 | 90 | 66 | 61 | | 52 | 60 |
| Neuroimaging | Normal CT | Normal CT | Normal CT | Not done | Raised ICP features | Normal CT | Not done | Not done |
| Other complications | Nil | Nil | Shock | Nil | Shock, pulmonary edema | Nil | Nil | GI bleed, Shock |

### Outcome

| 6 months | Recovered | Recovered | Recovered | Recovered | Recovered | Recovered | Recovered | Recovered | Expired |
|----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|---------|

\textsuperscript{>2 UL, >2 times upper limit; CSF, cerebrospinal fluid; GCS, Glasgow Coma Scale; GTCS, generalized tonic–clonic seizures; INR, International Normalized Ratio; PT, prothrombin time; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; TLC, total leukocyte count}
**Conclusion**

Scrub typhus infection is usually suspected in patients presenting with prolonged undifferentiated fever with eschar and other commonly defined signs and symptoms, in rural and suburban areas. But recently, it has reemerged as an important cause of AES in addition to other etiologies namely neurotropic viruses (HSV, JE), bacterial, cerebral malaria, and dengue. Hence, scrub typhus should be suspected in patients presenting with AES along with thrombocytopenia and elevated transaminases even in uncommon geographical areas, so that treatment can be started early. Clinical picture along with serology and CSF analysis is helpful in diagnosis. Doxycycline is the drug of choice with good outcomes.

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