

# Acute encephalitis syndrome following scrub typhus infection

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## Abstract

**Objective:** The aim was to find the incidence of acute encephalitis syndrome (AES) secondary to scrub infection and to observe the clinical, biochemical, radiological profile, and outcomes in these patients. **Materials and Methods:** A total of 20 consecutive patients of AES were evaluated for scrub infection using scrub typhus immunoglobulin M enzyme linked immuno-sorbant assay positivity along with the presence or absence of an eschar. Clinical profile, routine laboratory tests, cerebrospinal fluid (CSF) analysis, and neuroimaging were analyzed. Patients were treated with doxycycline and followed-up. **Results:** Among 20 consecutive patients with AES, 6 (30%) were due to scrub infection. They presented with acute onset fever, altered sensorium, seizures. "Eschar" was seen in 50% of patients. CSF done in two of them was similar to consistent with viral meningitis. Magnetic resonance imaging brain revealed cerebral edema, bright lesions in the putamen and the thalamus on T2-weighted and fluid-attenuated inversion recovery sequences. Renal involvement was seen in all patients. All patients responded well to oral doxycycline. **Conclusion:** AES is not an uncommon neurological presentation following scrub typhus infection. It should be suspected in all patients with fever, altered sensorium, and renal involvement. Oral doxycycline should be started as early as possible for better outcomes. **Keywords:** Acute encephalitis syndrome, multidisciplinary care, renal involvement, scrub typhus

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## Introduction

Scrub typhus or bush typhus caused by *Orientia tsutsugamushi* is a common, zoonotic disease in South East Asia and due to rapid urbanization of rural and forested areas, it has become an emerging public health problem in India.<sup>[1-3]</sup> Its commonly presents as fever, headache, inoculation eschar, and lymphadenopathy. In severe forms, pneumonia, myocarditis, azotemia, shock, gastrointestinal bleed, and meningoencephalitis are known to occur.<sup>[4,5]</sup> Although available medical literature mentions many of these complications, central nervous system involvement, in the form of acute encephalitis syndrome (AES), has seldom been highlighted.<sup>[5,6]</sup>

Relative unawareness of this type of presentation of scrub typhus makes a prompt diagnosis difficult, resulting in significant morbidity and mortality.<sup>[6]</sup> Here, we describe six patients with scrub typhus presenting as an AES.

## Materials and Methods

This is a prospective observational study conducted in a tertiary care hospital, over a period of 9 months from November 2011 to June 2012. AES is defined as a short duration febrile illness associated with convulsion, altered sensorium, and focal neurological deficits such as aphasia, hemiparesis, involuntary movements, ataxia, or cranial nerve palsies.<sup>[7]</sup> Adult patients (age >18 years) who presented with an AES were evaluated. On admission, every patient was subjected to thorough examination including search for an inoculation eschar and relevant blood investigations such as complete blood counts, blood and urine cultures, hepatic and renal function tests, serum electrolytes and serologies for dengue, malaria, leptospirosis and

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scrub typhus were done to rule out common infective causes. This was followed by neuroimaging (magnetic resonance imaging/computed tomography [MRI/CT] scan). Cerebrospinal fluid (CSF) was analysed for the routine cytology, biochemistry, Gram-stain, cultures, herpes simplex, Japanese encephalitis, Enterovirus, and tuberculosis (using tuberculosis-polymerase chain reaction). Immediately after admission all patients received broad spectrum antibiotics, including doxycycline and antiviral therapy which was modified later, based on subsequent culture reports and serologies. Apart from this, all patients who presented with seizures underwent an electroencephalogram (EEG) study. A diagnosis of scrub typhus was made on the basis of scrub typhus immunoglobulin M enzyme linked immuno-sorbant assay positivity and/or presence of eschar, in the absence of other demonstrable cause (s) of infection.<sup>[8]</sup> Once the diagnosis of scrub typhus was established, patient was continued only on doxycycline 100 mg twice daily for a period of 7-10 days. For patients who showed inadequate response to doxycycline alone, azithromycin was added. During their stay in the hospital, all patients were given supportive management, intensive care including ventilatory support and dialysis if warranted. After discharge, patients were regularly followed-up.

## Results

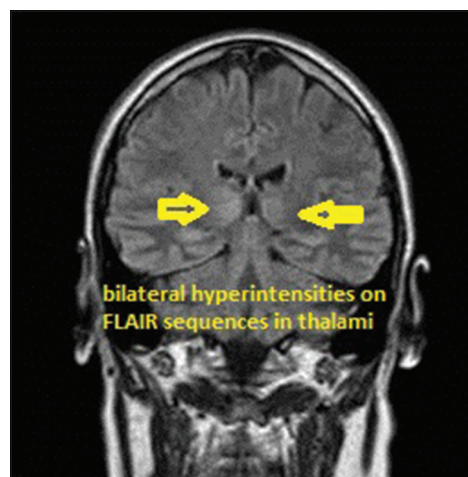
During the study period, 20 cases of AES were encountered and evaluated by a single neurologist. Among them six were found to have scrub typhus, accounting for 30% of the study group. Of the rest 14, the different etiologies were: Dengue encephalitis (1), leptospirosis (2), systemic sepsis associated encephalopathy (2), cerebral malaria (1), Japanese encephalitis (1), tuberculous meningoencephalitis (1) herpes encephalitis (2), unknown viral encephalitis (4). The six comprised of one female and five males, the age group was 35-62 years and they were predominantly from suburbs of Tamil Nadu and Andhra Pradesh. Only one patient was from the metropolis of Chennai. Demographically three out of the six cases were from near and around the town of Nellore in Andhra Pradesh. Of the six, four were farmers, and one a wildlife enthusiast with history of significant exposure and recent history of travel to forested areas in the north east and one a housewife who lives in the city. They all presented with history of fever of 2-4 days (mean: 3 days) abrupt in onset, with history of altered sensorium by day 3 or 4 of fever. Generalized tonic clonic seizures were present in three patients (50%) and neck stiffness in one. Initial neurological evaluation of these patients revealed a fall in sensorium with a Glasgow coma scale of 2T (T = intubated) to eight in all the patients. The characteristic inoculation "eschar" was seen in 3 (50%) of the patients. None of

the patients had objective focal signs like hemiplegia or cranial nerve palsies. CSF study was done in four patients. One patient refused a lumbar puncture and in another it could not be done due to technical difficulties. The CSF analysis was abnormal in two patients and showed raised protein with normal glucose with lymphocytosis varying between 150 and 200 cells/cumm. Brain imaging was done in five of patients in this study. MRI brain in four, CT brain in one and in the sixth person it could not be done, as he was critically ill. MRI pictures showed diffuse cerebral edema, hyperintense lesions in the putamen and thalamus in T2-weighted and fluid-attenuated inversion recovery (FLAIR) images [Figure 1]. CT scan done in one patient also showed cerebral edema. EEG study was carried out on three patients, showed bilateral diffuse cerebral dysfunction with epileptiform discharges with no specific lateralization. All these patients received levetiracetam intravenously for 3 days followed by oral therapy. These patients received empirical acyclovir, ceftriaxone, doxycycline of which only the latter was continued once the diagnosis was made.

All patients suffered from multi-organ dysfunction syndrome (MODS) (>2 organ involvement) and required multidisciplinary intensive care. Three patients required ventilatory support. Five patients (71%) had significant acute kidney injury requiring dialysis and recovered completely from it over the next 10 days. All patients required intensive care for a minimum of 5 days before they could be shifted out to the wards. One among the six succumbed to his illness due to MODS.

## Discussion

Acute encephalitis syndrome is characterized by rapid onset of febrile illness associated with convulsion,



**Figure 1:** Magnetic resonance imaging brain, fluid-attenuated inversion recovery sequences showing hyperintensities in bilateral thalami with features of cerebral edema

altered sensorium and focal neurological deficit such as aphasia, hemiparesis, involuntary movements, ataxia or cranial nerve palsies.<sup>[7]</sup> It is generally caused by various neurotropic viruses. In a recent study from India on acute febrile encephalopathy comprising of 120 patients, the common causes were acute viral encephalitis, acute bacterial meningoencephalitis, cerebral malaria, and sepsis related encephalopathy.<sup>[9]</sup> On the contrary in the present study of 20 cases of AES in as many as 30% of them the etiology was scrub typhus. Although it is difficult to explain such diverging reports, it could be attributed to the varying geographical prevalence of the virulent form of the disease or a hospital based bias. Analysis of available literature related to febrile encephalopathy and scrub typhus show that, the alteration of sensorium and convulsions occurred following a fever of more than a week's duration.<sup>[4,5]</sup> On the other hand, in the present series symptoms of AES were preceded by fever of 3 days only, mimicking an acute viral encephalitis. This unusual presentation of scrub typhus can be easily overlooked, resulting in delay in initiating life-saving treatment.

The important neurological manifestations of scrub typhus observed in the previous studies were mainly meningitis, meningoencephalitis, seizures, and altered sensorium. Focal neurological signs were seldom reported.<sup>[5]</sup> In the current study also, all the six had diffuse encephalopathy like picture with convulsions in three, signs of meningeal irritation in one and conspicuous absence of focal signs. Of the four CSF studies done only two were abnormal and showed features mimicking viral meningitis. Earlier studies have also observed a similar pattern of CSF results with some showing reduced sugar levels, consistent with a sub-acute tubercular meningitis like picture.<sup>[4,5]</sup> There is limited literature on the neuroimaging finding of scrub encephalitis, with the exception of a single case report of MRI brain showing small ring enhancing lesions in the corpus callosum and hyperintensities on FLAIR and T2-weighted sequences in periventricular and deep white matter regions of the brain.<sup>[10]</sup> In this study, all the five who underwent neuroimaging, showed abnormalities like diffuse cerebral edema along with T2-weighted and FLAIR hyper intensities in the putamen and thalamus, indicating primary involvement of the brain parenchyma. This study is limited by its size, hence it is difficult to say that the imaging findings mentioned above is pathognomonic of scrub as it is seen in other encephalitis too, hence larger studies on neuroimaging in scrub infections is warranted.

Multiple organ involvement in the form of acute respiratory distress syndrome (ARDS), azotemia,

deranged liver enzymes and thrombocytopenia is common and is secondary to diffuse vasculitis.<sup>[6]</sup> Similarly in this study, all six patients with AES had multi-organ dysfunction like ARDS, acute kidney injury and deranged liver enzymes. Kidney involvement in the background of central nervous system complications of scrub typhus has been reported in earlier studies also.<sup>[4,5]</sup> On the basis of this study, we would want to emphasize the need to consider the possibility of scrub typhus in all patients of AES with renal involvement. This report also highlights the need to involve a multidisciplinary team in the treatment of these patients as most of the complications are reversible with early and aggressive treatment.

## Conclusion

Among patients presenting with AES Scrub typhus is not uncommon. An AES presenting with kidney involvement warrants urgent evaluation for scrub typhus and early initiation of appropriate treatment on an empirical basis.

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