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Euro Neuropharmacology 2018 - Scrub typhus meningoencephalitis, a diagnostic challenge for clinicians: A hospital based study from North- East India - Masaraf Hussain - North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences

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Scrub typhus is a zoonotic disease, which is also known as 'tsutsugamushi disease' This disease was first mentioned in Japanese folklore which was named 'dangerous bug'. Tsutsugamushi is derived from two Japanese words, 'tsutsuga' means something small and dangerous, and 'mushi' which means creature. 'Typhus' has been derived from the Greek word 'typos' which means 'fever with stupor'. As the name itself indicates a clinical aspect of the disease. Scrub typhus caused by an obligate intracellular gram-negative bacterium known *Orientia tsutsugamushi*. Ogata in 1931 seperated the bacterium and named it as *Rickettsia* tsutsugamushi. The organism is in lack of cell wall. There are six serotypes of *O. tsutsugamushi*—Gilliam, Karp, Kato, Shimokoshi, Kawasaki and Kuroki. *O. tsutsugamushi* invades the central nervous system. The CNS is affected in 20–33% of patients infected by the *Rickettsia* that causes Rocky Mountain spotted fever, identified *O. tsutsugamushi* DNA using nested PCR in the CSF in 6 of 25 patients with scrub typhus. Results have been proved that mild pleocytosis with lymphocyte dominance and protein levels ≥ 45 mg/dL is present in the CSF in 48% of patients. Studies reveal that WBC counts in the CSF were ≤ 250/mm^3, which points to mild pleocytosis; lymphocytes were dominant in six patients, and polymorphonuclear cells in another nine of 16 patients with CSF > 10. The identifications of mild leukocytosis (≤ 250/mm^3 in most cases), slightly increased protein content, and normal glucose levels resemble those in viral meningoencephalitis, leptospirosis, and tuberculous meningitis, which must be differentiated from scrub typhus meningitis or meningoencephalitis. Most of the latter patients undergo changes of mentation and/or behavior, indicating generalized involvement of the CNS. A new strain has been isolated from in Australia which was different from the classic strains and named it as Litchfield. The bug has four stages: egg, larva, nymph and adult. The larval forms transfer the disease to humans. The larvae feed on rodents specific wild rats of subgenus Rattus. The infection in humans is acquired agricultural activities, by the bite of the larval stage of mites. The areas are generally secondary scrub growth which grows after the removal of primary forest hence the term scrub typhus. Humans are accidental hosts for the pathogen. Vertical transovarial transmission can occur in mites. In humans, it spreads by the blood and lymphatics, with clinical involvement such as fever, generalized lymphadenopathy, liver function impairment, pneumonitis, gastric ulcer, meningitis, meningoencephalitis, renal failure, and septic shock. The pathogen multiplies at the site of bite and produces both systemic and local manifestation. Typhus Infection spreads through both haematogenous and lymphatic routes.

The severity of the illness depends on pathogen-related factors and host-related factors. Pathogen-related factors relates to the different strains of *O. tsutsugamushi*. Host-related factors relates to humans with G6PD deficiency who has a worse prognosis also play a key role. Target cells for multiplication are the endothelial cells of the several systems. The immune response produced by the pathogen is a combination of humoral and cell-mediated immunity. There occurs an increase in cytokines during an acute infection. There also occurs a rise in macrophage colony stimulating factor, interferon gamma and granulocyte colony stimulating factor. Autopsy specimens shown that central nervous system pathology in scrub typhus cases in the form of diffuse of leptomeninges, presence of typhus nodules (clusters of microglial cells) and haemorrhages of the brain substance. The incubation period of *O. tsutsugamushi* in humans is around 10–12 days. The clinical manifestations vary from a mild to a severe potentially disease. The systemic features of the infection include fever, gastrointestinal disturbance, malaise, cough, myalgia and headache. A maculopapular rash starting from the trunk and spreading to the limbs is seen towards the end of the first week of the fever. Diffuse lymphadenopathy is commonly observed. Neurological manifestations in scrub typhus does not occur in isolation but are accompanied by systemic features like jaundice, breathlessness, cough, renal impairment and in some cases, with multiorgan dysfunction. Studies revealed that neurological manifestations were associated with lymphadenopathy (46.15%), jaundice (53.85%), pulmonary oedema (23.08%), oliguria (15.38%), hepatomegaly (38.46%) and splenomegaly (7.69%). Multi-organ dysfunction was found in 15.38% patients of scrub typhus with neurological manifestation. Cranial nerve deficits are seen in 25% patients. Sixth nerve involvement is seen, which maybe unilateral or bilateral. Facial palsy may occur in association with Guillain Barre syndrome. Cochlear nerve involvement occurs in about 19% patients and cause sensorineural hearing loss, otalgia and tinnitus. This is due to direct invasion by the pathogen. Doxycycline is the drug of choice for treating this disease. Appropriate antimicrobial agents were administered at an early stage in this study, meningitis or meningoencephalitis occurred in some of the patients during the doxycycline therapy. Studies failed to explain its therapeutic actions as its bacteriostatic action difficulty in penetrating through the blood brain barrier and the resulting low concentrations in the CNS and resistance to the drug. Headaches did not occur with increased frequency in the scrub typhus patients with meningoencephalitis. Similar results were reported in a study of mortality rates which found that only four of seven

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patients (57.1%) who died of scrub typhus meningoencephalitis complained of headaches, whereas 29 of 43 (67.4%) survivors did so. This also explains by the loss of pain sensation in patients with meningitis or meningoencephalitis. However, the time to resolve headache was significantly prolonged. The minimum inhibitory concentration for *O. tsutsugamushi* is 0.0625–0.5 μg/mL, rifampin is a more effective. Randomized controlled trials of doxycycline and rifampin for meningitis and meningoencephalitis patients, and further systematic studies of the concentrations of doxycycline and rifampin achieved in brain tissue and CSF required determining whether increasing the doxycycline dosage or using rifampin instead, is more effective. And, scrub typhus causes profound disturbances in T cell homeostasis. This opens the possibility that mechanisms other than antibiotic resistance/failure are causes of meningeal presentations. Age and occupation (farmer) were significant risk factors for the occurrence of meningoencephalitis. there are more farmers in the rural population, as a result of the aging of rural communities, it is conceivable that being a farmer by occupation is a risk factor for the occurrence of meningitis. Meningoencephalitis is a common manifestation of scrub typhus and diagnosis requires high degree of clinical suspicion which if diagnosed early and specific treatment started, patients usually recover completely with few complications.

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