

## Scrub Typhus for the Neurologist: Forget Me Not

Scrub typhus is an important yet underrecognized cause of acute febrile illness in India. In a multicentric study done at seven community hospitals located in six different states, 10% of patients with undifferentiated acute febrile illness had serological evidence of scrub typhus.<sup>[1]</sup> Given that this illness derives its name from the Greek word *typhos*, which means smoke or fog, alluding to the clouding of sensorium,<sup>[2]</sup> it is not surprising that scrub typhus commonly affects the central nervous system. In fact, outbreaks of acute encephalitis syndrome among children in some geographical regions are epidemiologically linked with serological evidence of *Orientia tsutsugamushi* infection.<sup>[3]</sup> What is rather interesting is the frequent occurrence of neurological manifestations such as opsoclonus-myoclonus, cranial nerve palsies including neural deafness, and status epilepticus as a manifestation of scrub typhus.

Notwithstanding its clinical relevance and importance, comprehensive reviews on neurological manifestations of scrub typhus are very few.<sup>[4,5]</sup> A recent issue of the *Journal* carried an important article on the neurological manifestations of scrub typhus.<sup>[6]</sup> The authors, Garg and Manesh, presented a succinct, up-to-date description of various neurological manifestations among adults with scrub typhus. Although their review was primarily narrative, inclusion of studies and reports into this narrative synthesis was informed by a fairly systematic search of literature published in English. Notably, the authors presented a conceptual timeline of various neurological manifestations and also provided valuable insights into the possible pathogenetic mechanisms responsible for these manifestations.

A few points from this review are worth highlighting. First, cerebrospinal fluid (CSF) glucose levels are typically normal or only slightly decreased in scrub typhus meningitis, as opposed to tuberculous meningitis which is characterized by low CSF glucose levels. Overlooking this important clue, clinicians often initiate tuberculosis treatment and feel vindicated by the clinical response brought about by rifampicin, which is also effective against scrub typhus. As rightly pointed out by the authors, presence of thrombocytopenia, elevated liver enzymes, and acute kidney injury should alert the clinician to the possibility of scrub typhus when there is lymphocytic pleocytosis with normal CSF glucose level.

Second, many of the neurological manifestations improve without adjunctive immunosuppressive treatment. Rickettsial meningoencephalitis is characterized by the presence of typhus nodules—focal perivascular mononuclear cell infiltrates—in the brain parenchyma and meninges.<sup>[7]</sup> Similar pathological changes have been noted to involve the VIII nerve and inner ear in British soldiers who succumbed to epidemic typhus in South East Asia during the World War II.<sup>[8]</sup> All of them had hearing loss as an early manifestation of typhus. *O. tustsugamushi*

directly infects endothelial cells of various organs including the brain.<sup>[9]</sup> Typhus nodules probably represent sites of active rickettsial multiplication, and this may explain why many of the neurological manifestations of scrub typhus improve with antibacterial treatment alone.

Third, prognosis of patients with multiorgan dysfunction associated with scrub typhus is distinctly better compared to other bacterial infections, if treated appropriately.<sup>[10]</sup> Given that scrub typhus is fairly common and that the sensitivity of point-of-care tests is suboptimal,<sup>[11]</sup> should professional society guidelines include doxycycline in their empiric treatment recommendations for acute meningitis and meningoencephalitis in endemic regions? Indeed, many clinicians would presumptively add doxycycline while treating patients with acute meningoencephalitis in such settings.<sup>[12]</sup> I believe, they are correct in doing so. While doxycycline and azithromycin are equally effective,<sup>[13]</sup> the optimal treatment strategy in those with severe scrub typhus is yet unknown. Particularly, it is unclear at present whether a combination of doxycycline and azithromycin would be superior to monotherapy in patients with severe disease. Ongoing clinical trials are expected to clarify this issue.<sup>[14,15]</sup>

Finally, it is worthwhile to ask the question “Does scrub typhus have long-term health consequences?” Many rickettsial pathogens, including *O. tsutsugamushi*, are known to persist in animals for prolonged periods of time.<sup>[16]</sup> Viable *O. tsutsugamushi* has been isolated on several occasions from asymptomatic humans several months after recovering from scrub typhus.<sup>[17,18]</sup> It has been suggested that such latent infection could have health consequences.<sup>[18]</sup> At least two population-based cohort studies indicate an increased risk of acute coronary syndromes among adults who had recovered from scrub typhus.<sup>[19,20]</sup> Although no excess of strokes was observed in one of these studies,<sup>[19]</sup> there is no reason why there should be a discordant association. Long-term health consequence of scrub typhus remains an understudied area.<sup>[21]</sup> No doubt, more research is needed to explore this interesting aspect of scrub typhus, and this could be of particular interest to neurologists.

**Tamilarasu Kadiravan**

Department of Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India

**Address for correspondence:** Dr. Tamilarasu Kadiravan, Department of Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research, Dhanvantri Nagar, Puducherry - 605 006, India. E-mail: kadir@jipmer.edu.in

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