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Scrub Typhus in India-An Impending Threat!

*Sneha K Chunchanur**

Department of Microbiology, Bangalore Medical College and Research Institute, India

Editorial

Scrub typhus, a rickettsial infection caused by *Orientia tsutsugamushi*, a gram-negative obligate intracellular coccobacillus is transmitted to humans by the bite of larval stage (chigger) of trombiculid mite. The disease has been reported from all over the world, but it is endemic in terrains of the *tsutsugamushi* triangle, a geographical region comprising of South and East Asia and the Southwest Pacific.

In India, studies in the 1960s and 1970s have shown the endemic nature of Scrub typhus in many states and union territories, the first reported cases were from Himachal Pradesh [1,2]. However, in later years, the disease virtually disappeared, probably because of widespread use of insecticides to control other vector borne diseases, empiric treatment of febrile illnesses with Tetracyclines and Chloramphenicol by practitioners then or due to changes in lifestyle [3].

There seems to be a resurgence of the disease now. Recent reports from India suggest that there is a resurgence of scrub typhus and that the resurgence is associated with considerable morbidity and mortality [3,4]. This is a cause of concern. Though considered as disease of rural areas, this disease has been urbanized and the prevalence has broadened further. Increasing prevalence of scrub typhus may be attributed to combination of climate change and expansion of humans into previously uninhabited areas and widespread use of Beta-lactam Antibiotics [3,5]. Interest in this infection is also rekindled because of report of strains of *O. tsutsugamushi* with reduced susceptibility to antibiotics [6]. *O. tsutsugamushi* expresses a type-specific protein (56-kDa protein), which is unique and contains cross-reacting epitopes, variations in this have resulted in the genetic diversity of *O. tsutsugamushi*. The prototype strains of *O. tsutsugamushi* Kato, Karp, Gilliam and Boryong are reported from all over the world, also strains closely related to these prototype strains are being frequently reported from endemic areas. 56kDa protein has also been explored in the development of vaccines [7].

According to the World Health Organization, "Scrub typhus is probably one of the most underdiagnosed and under-reported febrile illnesses requiring hospitalization" [1,8,9]. Scrub typhus accounts for up to 23% of all febrile episodes, with an estimated 1 million cases occurring annually, in endemic areas. Scrub typhus is an important cause of acute febrile illness in India [7]. Prevalence is found to be more during rainy and winter seasons. The seasonality of scrub typhus depends on the climate, temperature and degree of rainfall in a particular region [10]. In India, after the rainy season, increased humidity favors hatching of mite eggs into chiggers which leads to transmission of Scrub typhus [11]. Knowledge of seasonality may help in undertaking preventive measures.

Clinical spectrum of Scrub typhus can range from a self-limiting disease to multiorgan dysfunction resulting in death. Prompt diagnosis and appropriate treatment is therefore very important [12]. Patients with scrub typhus often present with fever, headache, myalgia, malaise, rash and lymphadenopathy, which are commonly seen in other acute febrile illnesses as well. An eschar may develop at the site of chigger bite, which is highly suggestive of scrub typhus but is reported to occur in a variable proportion of patients (from 7% to 97%). Eschar may be inconspicuous and may go unnoticed unless looked for carefully. In the absence of an eschar, presenting features are often indistinguishable from those of other acute febrile illnesses like malaria, dengue, typhoid, leptospirosis, and viral hemorrhagic fevers [13-15]. The clinical course and prognosis may vary depending on the type of endemic strain of *O. tsutsugamushi*. Case fatality rate may be as high as 30% if left untreated [16].

Once diagnosed, treatment with Doxycycline is affordable and mostly successful with dramatic clinical response within 48 hours [17]. Infact rapid defervescence on treatment with Doxycycline can be taken as diagnostic of scrub typhus. Alternatively, Azithromycin can also be used in treatment.

Such being the scenario, it is important to get familiar with the diagnostic tests available for

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Correspondence:
Sneha K Chunchanur, Department of Microbiology, Bangalore Medical College and Research Institute, Bengaluru, Karnataka, 560002, India, E-mail: drsnehakc@gmail.com

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scrub typhus, so as to differentiate it from other etiologies of acute febrile illness. An early diagnosis and prompt treatment will reduce morbidity and mortality due to this infectious disease [18]. Mainstay of scrub typhus diagnosis is serology. There is variety of tests available namely Weil-Felix test, Immunofluorescence Assay (IFA), latex agglutination, indirect hemagglutination, immunoperoxidase assay, complement fixation test, Enzyme Linked Immunosorbent Assay (ELISA), western immunoblot and line probe assay. In most of the laboratories in India, Weil Felix test is used which is a heterophile agglutination test. Traditionally, Weil-Felix test is not considered very useful in the diagnosis of Scrub typhus. However, comparative evaluation of Weil-Felix test and IgM ELISA for diagnosis of Scrub Typhus carried out at National Centre for Disease Control (NCDC), India, showed that Weil Felix test is equally sensitive with specificity of 89% [19]. Utility of Weil Felix test is acceptable in conditions where definitive investigations are not possible, but it has to be interpreted in the correct clinical context [20].

IFA, incorporating the four prototype strains of *O. tsutsugamushi* is considered "gold standard" and is used as a reference technique in most laboratories. This has been modified to allow the use of smaller volumes of serum and antigens (Micro Immuno Fluorescence/MIF) [21]. Fourfold rise in antibody titre by IFA is considered diagnostic of scrub typhus. But, due to high cost and need for specialized equipment they are out of reach in our country for routine diagnostic purpose.

The definitive diagnosis of scrub typhus by isolation of *O. tsutsugamushi* from blood by culture is not practical for routine diagnosis due many reasons [22]. Performing a Polymerase Chain Reaction (PCR) assay on the blood sample or eschar has proven useful for the early diagnosis of scrub typhus. PCR for detecting the DNA from *O. tsutsugamushi* is both sensitive and specific [23]. Studies have shown utility of various molecular methods such as PCR, nested PCR, real-time polymerase chain reaction and Polymerase Chain Restriction Analysis (PRA). Various targets used for PCR techniques are genes coding for antigens of 58-kDa, 56-kDa, 47-kDa and a region of the 16S rRNA gene [13,24-26].

Though there is whole armamentarium of tests available for diagnosis of scrub typhus, lack of access to specific and sensitive diagnostic tests in most places and low index of suspicion among the clinicians has led to underdiagnosis of scrub typhus in India [17]. In addition, antigenic heterogeneity of *O. tsutsugamushi* and short-lived immunity in scrub typhus has resulted in a substantial number of primary infections and reinfections leading to its reemergence [27].

Scrub typhus, a long forgotten and neglected infectious disease, with no licensed vaccines is undoubtedly a reemerging disease. With improvements in approaches to estimating the burden of febrile illnesses, it is important to reevaluate the burden of scrub typhus [28]. DHR-ICMR, India in 2015, issued guidelines for diagnosis and management of Rickettsial diseases including Scrub typhus in India [29]. This shows the importance, scrub typhus has gained off late in India.

However, more research (both basic research and epidemiological studies) on this treatable infection in Indian perspective is required to give inputs for health policy. Indisputably, its time scrub typhus received its due attention.

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