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Review Article

A Review of Epidemiology of Scrub Typhus

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Abstract:
Scrub typhus is a life-threatening public health problem in the Asia- pacific region. It is a serious disease where the case fatality rate can increase up to 30% when left untreated. Also the antigenic heterogenecity of Orientia tsutsugamushi allows reinfection. There are no licensed vaccines or vector control efforts currently in place pointing that it has long been a neglected infectious disease. Even though it is widely prevalent in Indian subcontinent, there is lack of specific prevalence data. Also lack of awareness, paucity of confirmatory diagnosis and clinical symptoms mimicking other febrile illness a low index of suspicion is prevailing among clinicians. There is still a large gap in our knowledge, as seen in the sporadic epidemiologic data, in so many aspects including diagnosis to prevention. This review article was designed to provide a comprehensive view of the epidemiology, diagnosis, prevention and control of scrub typhus.
Keywords: Epidemiology, Prevention, Diagnosis, Control.

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Introduction

Scrub typhus is a vector-borne rickettsial zoonotic disease caused by Orientia tsutsugamushi, an obligate intracellular bacteria, transmitted by the bites of chigger mites [1]. In Asia, where one million new cases are reported yearly and 1 billion could be at risk for the disease, scrub typhus is a major public health concern. [2] During the pre-antibiotic era, Scrub typhus was a dreaded disease with case fatality reaching 50%. In many geographic areas, lack of laboratory methods and difficulties with the clinical diagnosis has underestimated the public health importance of this disease.

In order to better understand the vectors, outbreaks, and pathogenesis associated with this potentially fatal organism that has been linked to human cases/outbreaks both within and beyond its previously recognized areas of endemicity the World Health Organisation (WHO) has designated Scrub Typhus as one of the most underdiagnosed/underreported diseases that frequently requires hospitalization.

Awareness of the epidemiology, clinical profile, and common laboratory parameters in combination with early initiation of treatment with doxycycline gives a complete cure for scrub typhus. Hence in this study, we will discuss the geographical distribution, pathogenesis, clinical manifestations, and treatment of Scrub typhus in view of South India to help clinicians in the periphery to identify scrub typhus early in the course and manage them effectively.

Methodology

A literature search was performed using PubMed and Google scholar websites, and we accessed published literature, newspaper articles, and other internet resources. Our study included articles published between 2000 and 2022

Pathogenesis

Orientia tsutsugamushi is transmitted by the bite of the larval stage of infected Leptotrombidium mites. The Life cycle of mites in the family Trombiculidae consists of an egg, two six-legged stages, and four eight-legged stages. The two six-legged stages include pre-larval and larval stages while, the four eight-legged stages include protonymph, deutonymph, tritonymph, and adult. The Larval mites (chiggers) are the only parasitic stages whereas, the pre-larval, proto-, and tritonymphal stages are inactive and nonfeeding while deuteronymph and adult stages are non-parasitic and feed on small arthropods.

The mites are both the vector and the natural reservoir for Orientia tsutsugamushi. Unscreened blood transfusions and unhygienic needles are other possible routes of transmission. But there is no chance of person-to-person transmission. Man gets infected accidentally mainly during the rainy

season while encroaching on a zone of infected mites. Secondary scrub growth makes up the whole vegetation in these zones after clearance of primary forest hence termed as 'Scrub Typhus'. Once the chiggers have grasped on a passing host, they do not pierce the skin but prefer to insert their mouthparts down hair follicles or pores. On attachment, they release a liquid that dissolves the tissue around the feeding site and the liquefied tissue is then sucked up by chiggers for their living. Orientia tsutsugamushi which are found in large numbers in the salivary glands of mites are injected into the host while feeding. Endothelial cells of most of the organs including skin, heart, kidney, and pancreas have been presented as the target cells. The organism proliferates on the endothelium of blood vessels and releases cytokines which damage endothelial integrity, causing fluid leakage, platelet aggregation, polymorphs and monocyte proliferation leading to occlusive end angiitis causing microinfarcts. A study conducted in among Thai patients suggested that Orientia tsutsugamushi induces a type 1 Immune response associated with the elevation of interferon alpha, IL-18 and IL 15 levels. Due to the additional research changes associated with researching exclusively intracellular bacteria, there are still many unanswered questions regarding the processes of pathogenicity and the cell biology of this bacterium's relationship with its host cell.

Geographical distribution

The endemic area of scrub typhus i.e., tsutsugamushi triangle, covers 8 million km2, extending between Russia in the north to Pakistan in the west, Australia in the south, and Japan in the east. Advancements in Globalization and related travel resulted in the exportation of infected persons to non-endemic areas. The epidemiological investigation of scrub typhus is complicated by the antigenic and genetic variety of O. tsutsugamushi strains and their unclear correlation with virulence in humans. Understanding the epidemiology of scrub typhus in detail will help to prevent and control the disease. Climate changes and man's behaviour combine to influence the occurrence of this disease. The season of scrub typhus starts in May, while the maximum number of cases was reported in June and July months. The age group affected by the disease varies with country. The age distribution which was largely affected by the disease in South Korea and Japan was found to be 60-69 years and 51-75 years respectively. Outdoor Activity, Working in Farms and forestry, being uneducated, and lifestyle are some of the main reasons for the cause of scrub typhus disease. Studies have shown that rural populations are affected more than people staying in urban areas.

In 1917, Scrub typhus was recognized as a typhus-like fever. It was the major cause of fever among military people during World War II along the Assam-India-Myanmar border and during the Indo-Pak war in 1965. A decline in the incidence was noticed with the widespread use of insecticides and empirical treatment of febrile illness. However, scrub typhus still remains an underdiagnosed disease in India.

Studies indicate that the disease occurs throughout the country, from South India to Northeast and Northwest India. Studies done by Vaz et al in Jammu, 2002; Sharma et al in Himachal Pradesh, 2003; Kumar et al in Chandigarh, 2012; Borkakoty et al in Arunachal Pradesh, 2013 had 12, 52, 49, and 31 patients with Scrub typhus respectively [3,4,5. In South India, Outbreaks and Increased incidence of Scrub typhus were seen in Pondicherry, Goa, Kerala, and Vellore. In Pondicherry outbreaks have been reported between 2008 and 2009, by Vivekanandan et al [6]. Outbreaks in South India have been shown in table 1.

Table 1: Scrub typhus Outbreak in South India (2000-2020)

Author	Region	Year	Patients with Scrub Typhus
Kamarasu [7]	Tamil Nadu	2004-2005	204
Vivekanandan [6]	Pondicherry	2006-2008	50
Chrispal [8]	Vellore	2007-2008	189
Narvencar [9]	Goa	2009-2010	15
Krishnan [10]	South Kerala	2011-2015	108
Kayanaduth [11]	North Kerala	2012	26
Roopa [12]	Pondicherry	2012-2015	225
Trowbridge [13]	Tamil Nadu	2016	231

Clinical Manifestations and Diagnosis

Scrub typhus is an acute febrile illness and is one of the major causes of "fever of unknown origin". It was often misdiagnosed as many acute febrile illness, like malaria, leptospirosis, other rickettsioses, meningococcal disease, typhoid fever, infectious mononucleosis and HIV. The incubation period ranges from 6 to 20 days (an average of 10 days). From subclinical illness to organ failure to deadly illness, this disease's clinical presentations span the spectrum. Deaths are caused mainly due to delayed presentation, late diagnosis, and drug resistance.

The clinical picture includes nonspecific flu-like symptoms, like, fever, rash, eschar at the bite site, headache, myalgia, cough, generalized lymphadenopathy, nausea, vomiting, and abdominal pain. About 95-100% of confirmed cases were found to have a fever in several studies. In a study done by Vivekanandan et al in Pondicherry, among the 55 cases of scrub typhus, all (100%) had a fever, 58% had nausea and vomiting, 38% had myalgia, 52% had a headache, 40% had a cough, 26% had breathlessness, 20% had abdominal pain and 16% had diarrhea. [6]

In another study done by Kayanaduth et al in North Kerala among 26 cases, all had fever, 885% had a headache, 77% had myalgia and only 3 cases had eschar as their symptoms [11]. A necrotic eschar at the inoculation site is the pathognomic sign of scrub typhus. It begins as a papule at the bite site and later ulcerates and forms a black crust similar to cigarette burn. Eschar is commonly seen in East Asian patients as compared to dark-skinned South Asian patients. Studies showed that the site of Eschar varies with gender. The most prevalent site among male patients are sites within 30 cm below the umbilicus [14]. In the case of female patients, the most prevalent sites are the anterior chest, head, and neck, whereas in children axilla is found to be the most prevalent site [15,16,17].

Multiorgan dysfunction is a commonly seen life-threatening complication of scrub typhus. Jaundice, Acute renal failure, pneumonitis, acute respiratory distress syndrome, myocarditis, septic shock, pericarditis, and disseminated intravascular coagulation (DIC) are some of the features of severe multiorgan failure due to scrub typhus. Respiratory dysfunction is the commonest followed by haematological and cardiovascular complications. Varied case fatality rates have been noted across different countries as well as different studies. The median case fatality rate of untreated and treated patients is 6% and 1.4% respectively. Hence, the creation of efficient methods to treat, manage and prevent illness is a major public health concern. [18]

Diagnosis of scrub typhus is an integrated approach of clinical suspicion and appropriate laboratory investigation. Failure to do so will result in complications and death. The mainstay in the diagnosis remains serology. The oldest test is the 'Weil Felix OX-K agglutination reaction, which is inexpensive but lacks specificity and sensitivity. In a study done by CMC, Vellore has found that the sensitivity of the Weil Felix OX-K strain was 30% at a titre of 1:80.

Also the test tends to be negative during the early stages of the disease as the agglutinating antibodies are detectable only during the second week of illness. [19] The Indirect Fluorescent Antibody is the Gold standard test in serology, is both specific and sensitive, and is available in less time but the test is highly expensive and requires specialized training for its use. However Indirect Immunoperoxidase is another gold standard serology test that has high specificity and sensitivity, available in less time while the cost of the test is low and no specialized training is essential. Enzyme immunoassays and PCR amplification of Orientia from eschar and blood are the other tests available for detection. These molecular biologic method can detect the infection in blood even when there is no obvious clinical symptoms or signs seen [19].

Treatment and Prevention

Orientia infection can be treated with appropriate antibiotics. For mild cases, oral treatment is sufficient while for severely ill patients parenteral treatment is required. Doxycycline is one of the most effective antibiotics for treating scrub typhus. Antibiotics are usually able to reduce patient's fever rapidly and this outcome is used as an outcome indicator. In patients who were responding poorly to doxycycline, rifampicin was shown to be more effective than tetracycline. Randomised control trials have shown that there was no significant difference in outcomes among tetracycline, doxycycline, and azithromycin. As per WHO guidelines, pregnant women and children were advised to use azithromycin or chloramphenicol. Even though antibiotic resistance was noted in few articles, there is much unknown regarding the same. [10]

Prevention of scrub typhus mainly depends on prophylactic treatment and general protective measures as there is no vaccine available for any rickettsial infections including scrub typhus. The main hinderance to vaccine development is the antigenic variations in different O. tstsugamushi strains. The prophylactic treatment suggested by WHO includes a single oral dose of doxycycline, chloramphenicol or tetracycline every 5 days for a total of 35 days provides protection against Orientia infection. A weekly dose of doxycycline was used by US military to prevent scrub typhus. [13] General protective measures for people living or visiting endemic areas include-

⇒ Avoiding areas known for focal outbreaks
⇒ Avoid Exposures like siting on bare ground or grass. Person must wear long sleeved shirts, long pants and closed shoes to reduce exposure
⇒ Application of insect repellent like benzyl benzoiate, diethyl tolumide to prevent chigger bites
⇒ Thorough cleaning of skin and clothes with detergent after work can reduce the risk of infection [20]

Conclusion

The re-emergence of scrub typhus explains us the urgent need of developing effective control and preventive measures. For effective implementation of the measures, public education on case recognition and personal protection is a must. Advocacy awareness and educational activities must be targeted against teachers, school children, field workers and outdoor travellers in endemic areas. Also development of new diagnostic tools

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