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Research Article

A REVIEW OF CLINICAL INDICATORS AND LAB INVESTIGATIONS FOR ASSESSING SEVERITY IN SCRUB TYPHUS

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ABSTRACT

Scrub typhus is an infectious disease caused by the bacteria Orientiatsutsugamushi from chigger bites. Early diagnosis and treatment may prevent complications including multi-organ dysfunction and death. Many studies have been conducted to analyse the co-relation between clinical characteristics and lab investigations and their effect on outcome; and better prognosis with early initiation of treatment. On reviewing multiple articles, it was observed that the signs and symptomsthat served as independent risk factors for developing severe disease included dyspnoea, altered sensorium, tachypnoea. Elevated liver and renal parameters, albuminuria, Chest X-ray and ABG suggestive of ARDS and CSF analysis suggestive of meningitis were the lab investigations that were observed to be associated with a severe form of the illness.

INTRODUCTION

Scrub typhus is an infectious disease caused by the bacteria *Orientiatsutsugamushi* from chigger bites.Scrub typhus is endemic to the part of world known as the 'tsutsugamushi triangle' which extends from northern Japan and far eastern Russia in the north to northern Australia in the South and to Pakistan in the West(1).

An indirect immunofluorescence antibody test is the standard diagnostic test. The rapid immunochromatographic test is used to help in making prompt treatment decisions.

Patients respond rapidly with early diagnosis and treatment, but when the diagnosis and treatment are delayed, complications are common and death may follow. Studies of risk factors for severe scrub typhus reported somewhat similar results such as leukocytosis, thrombocytopenia, hyperbilirubinemia, hypoalbuminemia, elevated transaminase, elevated serum creatinine levels and abnormal chest X-ray(2). Non-laboratory risk factors related to severity were dyspnoea, altered sensorium, absence of eschar and age more than 60 years.
The present study aims to explore clinical risk characteristics that may be used to forecast disease severity under routine clinical practice. The findings may be incorporated into clinical evaluation, awareness, and prevention of disease complications, which may reduce case fatality.

METHODS

In this article, we reviewed various observational and clinical studies. Electronic databases like Pubmed and Cochrane central register of controlled trials were used for potentially relevant articles. Keywords used for search included scrub typhus, severity, prognostic indicators.

Background

Scrub typhus is a rickettsiosis caused by an obligate intracellular bacterium – *Orientiatsutsugamushi* which is transmitted by the bite of a chigger. Trombiculid mites are the natural hosts of the pathogen.

History

The disease has been known since ancient times. The first description was documented in 313 ad in China(3). In early 1900s, there were periodic outbreaks of the disease and it was classified as a typhus-like fever in 1917. Fatality rate due to the illness was close to 50 percent before the antibiotic era. Use of

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tetracycline and chloramphenicol subsequently lowered the mortality associated with this infection dramatically. In the subsequent decades, the reported incidence declined possibly due to common use of tetracycline and chloramphenicol for the treatment of febrile illness and pesticide use, and so the interest in this infection also generally reduced (4). However, resurgence of the infection in several states of India and its neighbouring countries has been documented with incidence of considerable morbidity and mortality due to multi-organ involvement.

Orientia tsutsugamushi

Orientiatsutsugamushi is an obligate, intracellular, gram-negative bacterium (0.5 × 1.2–3.0 µm) (5). The genus Orientia belongs to the order Rickettsiales within the family Rickettsiaceae.The term 'tsutsugamushi' is derived from the Japanese 'tsutsuga' meaning illness and 'mushi' meaning insect. Its cell wall structure and genetic makeup is different to other rickettsiae. There is enormous genetic and antigenic variability between strains of *O. tsutsugamushi*. There are three antigenically distinct prototype strains: Karp, Kato and Gilliam, originally isolated from New Guinea, Japan and Burma, respectively(1). DNA analysis along with immunological analysis suggest that the prototype Karp strain and other strains closely related to it are the most common in the endemic regions. Serological analysis revealed that half of the isolates were seroreactive to Karp antisera and about one-quarter of isolates were seroreactive to the Gillian strain antisera (6). Small rodents serve as animal reservoirs for the pathogen, but it can also be maintained within mite colonies through transstadial and transovarial transmission. Transovarial transmission, also called vertical transmission is the process by which the female passes the pathogen to the eggs. Infection rate through this route is almost 100 %, with similar rates through transstadial route. The mite population can be re-infected with the pathogen from mammals and by co-feeding on a host with infected larvae.

Epidemiology

Its distribution is documented in a triangle called the'tsutsugamushi triangle' delimited by northern Japan, western Australia, and central Russia that includes the Indian subcontinent, eastern Russia, China, and the Far East.

One billion people live in the endemic area. Majority of cases are from rural areas as the mites thrive in that environment. In Asia, there was an estimated incidence of one million each year (7) with a case fatality rate of 10 %. Immunity wanes over 1–3 years, and the organism exhibits remarkable antigenic diversity.

Outbreaks generally occur during the cooler months of the year after monsoons. Highest incidence was observed during the months of October, December and January, which coincided with the period after Southeast and northwest monsoons (4). A study conducted at Puducherry had also revealed that there was continued presence of the infection in the relatively cooler months between September and March (8). This could be due to increased exposure to mites during harvesting season and growth of new vegetation which is a suitable habitat for this vector. Scrub typhus has also emerged as an important cause of febrile illness in Pondicherry (9). The disease has been extensively reported in Tamil Nadu especially around Vellore and the state border. The reason for this could be due to dense vegetation near a river in this region. Traditionally, rice farming has been associated with scrub typhus infection, whereas in Taiwan and Korea, there was greater association of the infection with dry farming.

Scrub typhus is no longer restricted to just the tsutsugamushi triangle. New incidence of the infection has been reported from South America, Africa, France and the middle east. This should lead to acknowledgement of the possibility of new *Orientia*species and new vectors for the infection (10).

Pathophysiology

O. tsutsugamushi exists in the wild in a cycle involving trombiculid mites (principal vectors) and other vertebrates. Humans are accidental hosts for the organism. The larval stage of the chiggers harbouring the bacterium bite exposed individuals in mite infested undergrowth during occupational and recreational activities. The chiggers use pores and hair follicles to gain entry into the skin and feed for 3–5 days using a stylostome to inject salivary secretions that lyse host tissue. This dissolved tissue is ingested by larval mites. The bacterium multiplies at the site of infection and causes local and systemic manifestations of infection. The target site of the pathogen are the endothelial cells. They have been found in endothelial cells of the liver, lung, heart, kidneys, pancreas, brain and skin. It was initially thought that the entry of the organism to the target organs was through the lymphatic system but later, the presence of the organism in mononuclear cells in patients with acute infection was demonstrated (11).Different strains of the bacterium contribute in a different way to disease severity and thus both host and pathogen related factors determine disease severity. The immune response induced by *O. tsutsugamushi* is a combination of both humoral and cell mediated immunity. There was a marked rise in macrophage colony stimulating factor (M-CSF), interferon gamma and granulocyte colony stimulating factor (G-CSF).These observations demonstrated that the macrophage and T lymphocyte response may be the driving factor in immunity against infection(12). The parasite has emerged to elude the immune mechanisms of the host. As there is a high mortality rate for untreated disease, these mechanisms are of clinicopathological significance.

Clinical manifestations

The incubation period of the bacterium in humans is around 10-12 days; can last upto 21 days. Initial clinical features are non-specific in the form of headache, malaise, fever, chills, gastrointestinal disturbances and myalgia. Regional lymphadenopathy is commonly observed.

Another characteristic finding which is almost diagnostic is the presence of an eschar at the bite site. There was a 7-80 % prevalence of eschars in patients with scrub typhus. The reason for this difference may be atypical presentation of eschars in moist and damp skin, difficulty in finding small eschars in dark skinned individuals, eschar inducing capacity of different strains of the organism. Eschars are commonly found in the groin, axilla, waist and other exposed parts of the body. In females, the most prevalent area to find an eschar was the front chest above the umbilicus while in males, it was most commonly found within 30 cm below the umbilicus (13). This

difference in eschar site was attributed to differences in skin folds, clothing and pressure points created by undergarments.

Clinical manifestations vary from a mild febrile illness to a potentially fatal disease with multi-organ dysfunction. From the second week, patients may start showing evidence of systemic infection, especially those who were untreated.

It can involve different organ systems including the central nervous system in the form of acute diffuse encephalomyelitis(14), meningoencephalitis, cerebellitis, transverse myelitis, cranial nerve palsies (15).

Cardiovascular system involvement is usually manifested as myocarditis, rhythm abnormalities and acute cardiac failure(16).

Respiratory system involvement can present as bronchitis and interstitial pneumonitis of various grades and progress to acute respiratory distress syndrome (ARDS). It occurs in about 11% of the patients and is one of the serious complications of scrub typhus with mortality rate of about 25%. Initial presentations of dyspnoea and cough with delayed use of antibiotics were significant predictors of ARDS (17). Older age, thrombocytopenia, and the presence of early pneumonitis have been proposed as risk factors for the development of ARDS in scrub typhus patients (18).

Renal system involvement can present as acute renal failure. Older patients with higher total leukocyte counts, hypoalbuminemia and one or more co-morbidities like diabetes and hypertension were found to be more prone for developing AKI (19). As a rare complication, occurrence of acute rhabdomyolysis and acute renal failure has also been reported (20).

Gastrointestinal system involvement occurs in the form of altered liver function tests(21), diarrhoea, acute pancreatitis and cholecystitis (22,23). Gastrointestinal tract involvement in the form of gastric mucosal erosions and ulcerations owing to vasculitis resulting in gastrointestinal bleeding is common.

ometimes, Multi-organ dysfunction (MODS) ensues (24). Due to the wide variation in clinical presentation, the diagnosis of scrub typhus if often made late and it is crucial to reach an early diagnosis to prevent life-threatening complications.

Diagnosis

Diagnosis depends on clinical suspicion and appropriate lab investigations. The diagnosis is supported by the presence of an eschar but it is variably present. Failure to diagnose early can result in severity progression and mortality. The main stay of diagnosis is serology.

The oldest test that is still in use is the Weil-Felix OX-K agglutination reaction which is easy to perform, inexpensive and results are attained overnight. However, the test lacks sensitivity and specificity (25). This test should be carried out only after 5-7 fays of fever. There is sharing of antigens between Rickettsia and Proteus is the basis of this heterophile antibody test. Possible infection should be considered if titre is 1:80 and baseline titre should be standardized for each region.

Another test that is more sensitive with results available in a couple of hours but more expensive is the Indirect fluorescent antibody (IFA) test. It uses fluorescent anti-human antibody to detect specific antibody from patient serum bound to a smear of scrub-typhus antigen and is currently the reference standard. A four-fold rise in IFA titre or a single titre $\geq$ 1:160 was taken as the diagnostic criterion for scrub typhus (26).

Usually IFA uses antigens from just three serotypes: Karp, Kato, and Gilliam. But as enormous antigenic variations have been found, Japan follows a two-pronged approach to diagnosis. Local strains are used in the IFA whereas PCR of blood clot, preferentially the buffy coat is used on all other specimens. This recommendation is not widely followed outside Japan (27). Because of its high cost and need for technical expertise, its use is limited mainly for research and in areas where seroprevalence of the disease is established and necessary expertise available to conduct these tests.

A less expensive test compared to the IFA is the Indirect immunoperoxidase (IIP) which eliminates the need of a fluorescent microscope by substituting peroxidase for fluorescein. The eschar PCR assay is another useful diagnostic tool which is rapid and reliable to confirm the diagnosis of scrub typhus, even if the patients had received treatment with appropriate antibiotics (28).

Though IFA is the gold standard test for the serologic diagnosis of scrub typhus, it is expensive and requires training to perform and interpret results. Alternative diagnostic methods like Passive hemagglutination assay (PHA) have been developed but they have lesser sensitivity, especially during the acute phase of illness.

The immunochromatographic test (ICT) was developed as a rapid diagnostic test to replace passive hemagglutination assay. Commercially available kits were used for early, rapid diagnosis at the time of admission to the hospital. This test employed the 56-kDa major surface protein antigens from representative *O. tsutsugamushi* including Gilliam, Karp, and Kato strains to detect IgG, IgM, and IgA antibodies to *O. tsutsugamushi*. It was found that fever duration before the time of testing affected ICT results. The overall sensitivity of ICT was 72.6 %, with increase in positive rate with increased duration of fever. Therefore, caution should be ensured by clinicians while interpreting results as a false negative result could be attained during the early days of illness which was the same with Passive hemagglutination assay (29). Validation of the rapid ICT kit for serodiagnosis of scrub typhus was done recently with a sensitivity of 99.25 % and a specificity of 93. 02 % (30).

Polymerase chain reaction (PCR) is another test used for diagnosis that is both rapid and specific. Rickettsial DNA can be detected in whole blood, buffy coat fraction or tissue specimen. Results are best within the first week for blood samples because of presence of rickettsemia in initial 7-10 days (31).

ELISA techniques, particularly immunoglobulin M capture assays are probably the most sensitive tests available for rickettsial diagnosis and the presence of IgM antibodies, indicates recent infection with Rickettsia. Significant IgM antibody titres are observed in case of infection with *O. tsutsugamushi* at the end of first week and IgG antibodies appear at the end of second week. Optical density of 0.5 is taken as the cut-off value. As in the case of Weil-Felix,

baseline titres have to be established with regard to regional variations. One of the drawbacks of IgM ELISA is that it is a qualitative test and is suited for testing in batches (8).

In Chest X-ray, the most frequent abnormal finding was bilateral parenchymal infiltration with predilection to lower lung. Chest X-ray abnormality was observed more than 50% during the first week of illness (32).

Prognostic Indicators

Various studies have used various parameters with respect to clinical presentation and lab investigations for assessing severity in scrub typhus. A study done by PamornsriSriwongpan *et al* included symptoms and signs of rapid pulse rate, low body temperature, presence of crepitation and lab reports showing low serum albumin, positive urine albumin, low percentage of lymphocytes, elevated serum creatinine and elevated aspartate aminotransferase as indicators for severity progression (2).

Another study conducted by Varghese *et al* found that elevated creatinine had a relative risk of 43.99 for death (33).

Lee CS *et al* conducted a study to investigate the clinical significance of hypoalbuminemia to disease outcome and found that patients with hypoalbuminemia, that is serum albumin < 3 gm/dl had higher incidence of confusion, pulmonary edema, pleural effusion, arrhythmias, non-oliguric acute renal failure and longer duration of hospital stay. This emphasizes on the importance of hypoalbuminemia being one of the important predictors of severity in scrub typhus (34).

Another study conducted in non-ICU patients by Premraj SS *et al* concluded that elderly patients, residence in rural area, absence of eschar and those with longer duration of symptoms prior to presentation were independent risk factors for development of severe illness (35).

A study done by Adhikari S *et al* in Nepal in scrub typhus patients requiring intensive care support found that there was a mortality rate of 20 % with risk factors being presence of tachycardia, hypotension, elevated serum creatinine, AKI requiring hemodialysis, shock requiring inotropic support and ARDS. Old age and elevated serum creatinine were found to be independent predictors of poor outcome in scrub typhus patients admitted in ICU (36).

Chrispal A *et al* found that metabolic acidosis, ARDS, altered sensorium and shock were independent predictors of mortality with a case fatality rate of 12.2 % (37). Scrub typhus patients with ARDS had a mortality rate of about 25%. Low serum albumin, elevated total bilirubin, prolonged prothrombin time and delayed use of antibiotics were independent predictors of ARDS (17).

Elevation of aspartate transaminase was used as a screening tool for diagnosing scrub typhus where commercial diagnostic kits were not readily available. Elevation of SGOT, SGPT and hypoalbuminemia were also related with severity of the disease (38).

In a study conducted at Rajasthan, the overall mortality from scrub typhus infection was reported to be 21.2 % (39).

Treatment

Antibiotic therapy should be initiated when rickettsial disease is suspected without waiting for laboratory confirmation of the infection.

On presentation, at a primary level, disease severity should be recognized by the health care provider. If the patient comes with complications and rickettsial infection is suspected, treatment with doxycycline should be started before referring the patient.

In case complications like ARDS, acute renal failure, multi-organ dysfunction, meningoencephalitis arise, patient should be referred to secondary or tertiary care center.

Doxycycline 200 mg in 2 divided doses for 7 days is the treatment of choice. Or Azithromycin 500 mg in a single dose for 5 days. Azithromycin is the preferred drug of choice in pregnant women as doxycycline is contraindicated.

At secondary and tertiary care level, oral antibiotics to be administered for uncomplicated cases. In complicated cases, intravenous doxycycline 100 mg twice daily in 100 ml normal saline to be administered as infusion over half an hour initially and then changed to oral therapy with complete duration of therapy for 7-15 days. Intravenous azithromycin 500 mg once daily for 1-2 days followed by oral therapy for a total duration of 5 days. Or alternatively, intravenous chloramphenicol 50-100 mg/kg/day 6-hourly doses can be administered followed by oral therapy for 7-15.

Management of individual complications should be handled as appropriate.

Doxycycline and chloramphenicol resistant strains have been seen in South-East Asia. These strains are sensitive to azithromycin(31).

Prevention

Individuals presenting with scrub typhus were more likely to work on farms, observe rodents at home or work, live close to bushes and wood piles and read domestic animals. It was also found to occur more frequently in cases who did not wash or change clothes after work. Thus a cleaner, rodent-controlled environment, use of personal protection measures and better hygiene may prevent exposure to the mite, and thus the pathogen and further reduce individual risk (40).

Conclusion

Acute undifferentiated fever with hepatic dysfunction had prompted a diagnosis of scrub typhus in most of the cases in endemic areas and early initiation of treatment had been imperative to prevent complications. Early identification of unfavorable prognostic indicators including dyspnoea, altered sensorium, tachypnoea,elevated liver and renal parameters, albuminuria, Chest X-ray and ABG suggestive of ARDS and CSF analysis suggestive of meningitis were crucial to anticipate severe illness and management of the same.

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