Scrub Typhus

SK Mahajan

Abstract

Scrub typhus, a dreaded disease in pre-antibiotic era, is an important military disease which caused thousands of cases in the Far East during Second World War. It is a zoonosis and is a widespread disease in Asia and Pacific Islands. Scrub typhus is an acute febrile illness which generally causes non-specific symptoms and signs. The clinical manifestations of this disease range from sub-clinical disease to organ failure to fatal disease. Deaths are attributable to late presentation, delayed diagnosis, and drug resistance. The public health importance of this disease is underestimated because of difficulties with clinical diagnosis and lack of laboratory methods in many geographical areas. Scrub typhus is known to occur all over India and physicians should be aware of this potentially serious but easily treatable disease. ©

INTRODUCTION

Scrub typhus was a dreaded disease in pre-antibiotic era with case fatality rates reaching 50%. It is an important military disease which caused thousands of cases in the Far East during Second World War. The public health importance of this disease is underestimated because of difficulties with clinical diagnosis and lack of laboratory methods in many geographical areas.

The typhus and ‘spotted’ fever are caused by bacteria of the family Rickettsiaceae, which are obligate intracellular, Gram negative, non-flagellate small pleomorphic coccobacilli.

The species of the genus Rickettsia are divided in to Typhus group : causing classical epidemic typhus. Spotted fever group : causing Rocky Mountain spotted fever.

Scrub typhus : Caused by Orientia tsutsugamushi.

The genus previously named Rochalimaea has been classified in the family Bartonellaceae which causes trench fever. Coxiella burnetti causes Q fever and tribe Ehrlichia can cause fever in human and several equine and canine species.

‘Typhus’ has been derived from Greek word ‘Typos’ for ‘fever with stupor’ or smoke cognate with the Sanskrit word for ‘smoke’, dhupa. The earliest medical accounts of typhus were written by Cardano in 1536 and Fracastrop in 1546. Coyttarus in 1578 first suggested that typhoid and typhus were different diseases, a distinction that took three centuries to resolve. Scrub typhus, a zoonosis, was known in Japanese folklore to be associated with the jungle mite or chigger which was named “dangerous bug” (tsutsugamushi). The illness was described by Hashimoto in 1810. In 1916, Weil and Felix, described heterophile antibody agglutination of OX-2 and OX-19 strains of Proteus mirabilis by typhus sera. This was extended to scrub typhus by Fletcher and Lesslar in 1926. They named another agglutinated variant strain OX-K in honour of their friend Kingbury. Ogata in 1931 isolated the organism and named it Rickettsia tsutsugamushi. Now it has been reclassified as Orientia tsutsugamushi. The organism lacks cell wall and at least six distinct serological strains (Gilliam, Karp, Kato, Shimokoshi, Kawasaki, and Kuroki) have been detected by immunoperoxidase reaction. In a case of scrub typhus in Australia, the gene sequence showed a strain of O. tsutsugamushi that was quite different from the classic strains and new strain has been designated Litchfield.

PATHOGENESIS

The vector is the larva of a number of trombiculid mites; in which trans-ovarian transmission maintains the infection in nature. The mites have a four-stage lifecycle: egg, larva, nymph and adult. The chigger phase is the only stage that is parasitic on animals or humans, and hence infected mites are only dangerous at this point.

These larvae feed on small rodents particularly wild rats of subgenus Rattus. Man gets infected accidentally, usually during rainy season, on encroaching a zone of infected mites. These zones are often made up of secondary ‘scrub’ growth, which grows after clearance of primary forest; hence term ‘scrub typhus’ However
mite habitats are as diverse as seashore, rice fields and semi-deserts. This disease often presents with outbreaks.1-3,7 Once the chiggers have grasped a passing host, they prefer to feed where the skin is thin, tender or wrinkled and clothing is tight. Chiggers do not usually pierce the skin when feeding, preferring to insert their mouthparts down hair follicles or pores. Once attached, they inject a liquid that dissolves the tissue around the feeding site. This liquefied tissue is then sucked up as sustenance for the chigger. As large numbers of the R. tsutsugamushi organisms are found in the salivary glands of the chigger, they are injected into its host when it feeds. After feeding, the engorged chigger will drop off its host, burrow into the ground and transform into the more mature nymphal version of the mite.6

The bacterium is an intracellular organism living and breeding within the cells of its host. Although it is difficult to isolate R. tsutsugamushi from the host cell, achieving this will allow a microscopic view of a long rod-shaped organism. The bacterium can bypass white blood cells. It actually divides and breeds within the phagocytes and escape from the cell back into the circulation to continue.1, 3, 6

The organisms proliferate on the endothelium of small blood vessels releasing cytokines which damage endothelial integrity, causing fluid leakage, platelet aggregation, polymorphs and monocyte proliferation, leading to focal occlusive end-angiitis causing micro-infarcts. This process especially affects skeletal muscles, skin, lungs, kidneys, brain and cardiac muscles. This can also cause venous thrombosis and peripheral gangrene.8, 9

Epidemiology

An estimated one billion people are at risk for scrub typhus and one million cases occur annually.10 Man’s behavior and climatic changes combine greatly to influence the occurrence of the disease. Increasing prevalence of the scrub typhus has been reported from some Asian countries and may coincide with the widespread use of beta-lactam antibiotics or to urbanization into rural areas.11 Scrub typhus is a zoonosis and is a widespread disease in Asia and Pacific Islands. It also occurs in Japan, South Korea, Nepal, Northern Pakistan, South China, Papua New Guinea, and the Australian states of Queensland and Northern New South Wales. Many cases surface in Europe and other parts of World, where this disease is not endemic, causing a serious problem in diagnosis and treatment. Rickettsiosis is generally believed to have disappeared from many parts of India. However, the serological testing of 37 residents of southern India who presented with fever of unknown etiology in 1996–1998 confirmed that spotted fever, epidemic/endemic typhus and scrub typhus continue to occur in southern India.12 Scrub typhus is known to occur all over India including the hills of North India.1, 3, 4 It is particularly important to consider scrub typhus in developing countries and in travelers returning from areas endemic for this disease.

CLINICAL FEATURES

The organisms infect previously healthy, active persons, and if undiagnosed or diagnosed late, or untreated, may prove life threatening. Scrub typhus is an acute febrile illness which generally causes non-specific symptoms and signs. Fever is most common feature of scrub typhus and in endemic areas it is one of the causes of “fever of unknown origin”.13 The clinical manifestations of this disease range from sub-clinical disease to organ failure to fatal disease.1-3 Deaths are attributable to late presentation, delayed diagnosis, and drug resistance.1-3

Clinical picture of scrub typhus is typically associated with fever, rash, myalgia and diffuses lymphadenopathy. A necrotic eschar at the inoculating site of the mite is pathognomonic of scrub typhus.1, 15 The eschar resembles the skin burn of a cigarette butt. Tsay et al16 in a hospital based study in Taiwan, noted fever (100%), chills (39%), cough (24%), headache (21%), diarrhea (18%), eschar (60%), adenopathy (33%) and rash (21%) in 33 patients of scrub typhus. However, occurrence of eschar is rare in South-East Asian patients. Moreover, indigenous peoples of endemic areas commonly have a less severe illness, often without any rash or eschar.1, 3, 11 The complications of scrub typhus usually develop after the first week of illness. Jaundice, renal failure, pneumonitis, ARDS, septic shock, myocarditis and meningo-encephalitis are various complications known with this
Disease. Patients coming from hyperendemic areas.22 Patients with scrub typhus may present with meningitis and/or encephalitis. Patients become delirious, agitated and may develop seizure. Focal neurological signs are rare but are known to occur. Cerebrospinal fluid profile may show changes similar to viral or tuberculous meningitis. It should be included in differential diagnosis of aseptic meningitis and encephalitis in patients exposed to endemic areas especially when accompanied by renal insufficiency and/or jaundice.16-20 In scrub typhus, gastro-intestinal tract involvement may lead to hemorrhage and patients can develop superficial mucosal hemorrhage, multiple erosions, and ulcers without any predilection sites. The endoscopic features are related to cutaneous lesions and severity of the disease.21 The unusual presentation with acute abdomen is also known to occur, especially in patients coming from hyperendemic areas.22 Hypoalbuminemia and albuminuria are also seen in large number of cases. Scratch typhus with septic shock may result in multiple organ failure, respiratory failure, DIC followed by renal and hepatic failure.15,16,23,24 Mortality from this disease is 7-30%.4,9

**Differential Diagnosis**

Scratch typhus should be differentiated from malaria, arbovirus infections e.g. dengue, leptospirosis, meningococcal disease, typhoid, infectious mononucleosis and HIV. The macular rash of dengue is much finer. Malaria can be ruled out by obtaining peripheral smear. Leptospirosis, typhoid and meningococcal disease can be diagnosed by culturing blood, CSF or bone marrow. Serology can diagnose leptospirosis, infectious mononucleosis and HIV.1

Dengue fever and scratch typhus are common infections in Asia that often present as acute febrile illness of unclear etiology. According to Watt G et al, Dengue virus infection is associated with hemorrhagic manifestations, particularly bleeding from the gums. A low platelet count (< 140,000/mm³) and low white blood cell count (< 5,000/mm³) are also strongly associated with dengue infections.25

In another study of 22 adults with leptospirosis, Watt G et al found 9 had serologic evidence of scratch typhus also. Of 9 individuals with possible co-infections, 5 had signs or symptoms typical of scratch typhus and atypical of leptospirosis. Patients who appeared to have mixed infections had significantly higher median platelet counts and significantly lower median serum bilirubin and creatinine concentrations than did individuals with leptospirosis alone. The possibility of scratch typhus infection should be considered in leptospirosis patients who respond poorly to treatment or who have atypical disease manifestations.26

**Diagnosis**

Although rickettsiae can be isolated from or detected in clinical specimens, serological tests still remain an indispensable tool in the diagnosis. Microimmunofluorescence is considered the best test of choice. Latex agglutination, indirect haemagglutination, immunoperoxidase assay, ELISA and polymerase chain reaction (PCR) are other tests available. The nested PCR may be more sensitive than the serological test for diagnosis of scratch typhus and prolonged persistence of O. tsutsugamushi DNA in blood can be demonstrated despite clinical recovery of the patients.27 No current diagnostic test is sufficiently practical for use by physicians working in rural areas. A new dipstick test using a dot blot immunoassay format has been developed for the serodiagnosis of scratch typhus. The dot blot immunoassay dipstick is accurate, rapid, easy to use, and relatively inexpensive. It appears to be the best currently available test for diagnosing scratch typhus in rural areas where this disease predominates.28

But these tests are not available commercially and their complexity limits their use to a small number of centers. Weil-Felix test (W-F) using Proteus OXK strain is commercially available sero-diagnostic test and is in use for many years. Only 50% of patients will have positive test during second week of illness. A minimum positive titer is 1:80 or a four fold rise over previous levels is significant. Others have proposed a titer of 1: 40-320 as minimum positive titers but low titers in endemic areas are likely to be non-specific.9,29 The most important consideration is an awareness of the antigenic diversity of R. tsutsugamushi strains in a given area. Unless an appropriate combination of strains of R. tsutsugamushi is included in the battery of test antigens, the titers of some serum specimens could appear falsely low, and a few infections could go even undetected.29

The use of W-F test should be limited for situations where other tests are not available.3,30 Amano et al31 noted a parallelism of increment between the titers in W-F test and titers of IgM antibodies in ELISA against Proteus mirabilis strain OXK. He again observed that 80% of sera, which were positive to R. tsutsugamushi by indirect immunoperoxidase test, were also positive to a Proteus OXK antigen by W-F test at 10 or more days from the onset of fever. Almost all the paired sera of these patients showed an increase in IgM titers with the rise of titers on W-F test.32 Weil-Felix agglutination test is a screening test, but detects more cases than misdiagnosed ones and when positive is reasonably specific. The use of this test is accepted in conditions where definitive investigations are not available.3,30 Chemically however the diagnosis of scratch typhus is based upon the geographical history, physical signs and is confirmed by the rapid response to specific chemotherapy.2
Chiggers. Control of the rodent and marsupial reservoirs
will remove both attached and unattached chiggers. Lathering with soap in a hot bath or
sitting around or working in infested areas should consider impregnating clothing with permethrin. When
exposed areas of skin and clothing itself should be treated with mite repellents. Repellents containing DEET,
doxycyclin 200 mgs, OD for seven days is treatment of choice. Chloramphenicol, 500 mgs, QID is an alternative. Rifampicin, 900 mgs per
day for a week, has been found effective in patients who respond poorly to conventional therapy. Favorable
outcome has been associated with fluoroquinolones therapy also. Azithromycin has been proved more
effective than doxycyclin in doxycyclin-susceptible and doxycyclin-resistant strains causing scrub typhus. Rapid
defervescence after antibiotic is so characteristic that it is used as a diagnostic test for R. tsutsugamushi. Treatment with oral antibiotics can be undertaken in mild cases however injectable treatment is recommended for seriously ill. Resistance to tetracycline has been noted in few areas.

Control and Prevention
Control of scrub typhus can be considered in three phases: prevention, prophylactic treatment, and curative treatment once the disease is present. Prevention generally works best when threat is perceived as real. The presence of potentially infected chiggers can easily be determined by placing a small piece of black cardboard edgewise on the ground. The chiggers will climb to the top of the card and congregate there. Tiny yellow or pink dots moving across the card will confirm the presence of the chiggers. The disease is best prevented by the use of personal protective measures including repellents, people entering an exposed area wear closed in footwear such as boots with socks, and long trousers. Exposed areas of skin and clothing itself should be treated with mite repellents. Repellents containing DEET, dusting sulphur, dimethyl phthalate or benzyl benzoate have been suggested as suitable agents. Those people working in infested areas should consider impregnating clothing with permethrin. When sitting around or camping, groundcovers and tents with closed floors should be used. Lathering with soap in a hot bath or shower will remove both attached and unattached chiggers. Control of the rodent and marsupial reservoirs may also assist to prevent chiggers coming into areas where humans are living and working. Simple options such as sealing food containers and burying waste will help with this.

Prophylaxis
Prophylactic treatment usually consists of broad-spectrum antibiotics. Several regimes have been recommended. Oral chloramphenicol or tetracycline given once every 5 days for thirty-five days or weekly doses of doxycycline during and for 6 weeks after exposure have both been shown to be effective regimes. Resistance to antibiotics has been noted in several areas, therefore prophylaxis with antibiotics cannot be guaranteed. No effective vaccine has been developed for scrub typhus.

References


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**Announcement**

International Symposium on Current Issues in Diabetes On January 6,7 and 8 2006 at Ahmedabad. Approved for 10 MSD Credits

Dr. Mayur Patel
Organising Chairman

Dr. Banshi Saboo
Organising Secretary

SWASTHYA
2 Jay Mangal Society
132ft Ring Road
Naranpura Ahmedabad 380 013
Phone +91 79 2743 9977 / 9922
Website : www.swasthyaиндia.com
Email : diabetes@swasthyaиндивидia.com