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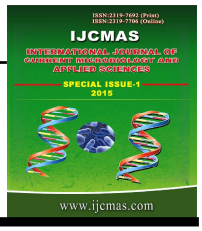

Original Research Article

Prevalence of Scrub Typhus – A Cause of concern in Uttarakhand Region, India

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A B S T R A C T

Acute febrile illness (AFI) is a very common problem in Medicine and Paediatric OPD. The common causes of AFI are enteric fever, malaria, UTI etc. And uncommon ones that may be common in a particular region is scrub typhus in Uttarakhand. The present study was undertaken to see the prevalence of scrub typhus in patients of AFI in Dehradun and to assess the efficacy of two common diagnostic modalities immunochromatography (ICT) and IgM ELISA for its diagnosis. Patients presenting as AFI attending Himalayan Hospital Dehradun from August 2012 to July 2014 were screened for scrub typhus by ICT besides being subjected to other tests for ascertaining the cause of AFI. Positive ICT samples were further confirmed by indirect IgM ELISA. Out of total 3540 patients of AFI, 692 (19.4%) were positive for scrub typhus by ICT and 412(59.5%) of them were also positive by IgM ELISA. Characteristic eschar was seen in 14.5% cases only. The maximum number of scrub typhus cases was from August to October each year. Majority of these patients were in the age group of 30-39 years, 78 %, had vegetation around their houses, 65 % had rat infestation .Approximately half of the patients were farmers and in habit of open field defecation. Many of them had visited forest also. Scrub typhus is an important cause of AFI in this region especially in rainy season.

Keywords

Orientia tsutsugamushi, Acute febrile illness, Scrub typhus, Uttarakhand

Introduction

Scrub typhus is endemic in regions of eastern Asia and the south- western Pacific (Korea to Australia) and from Japan to India and Pakistan. It is estimated that there are about one million cases of this disease each year (Vas and Gupta, 2006). This illness is caused by *Orientia* (formerly *Rickettsia*).

Orientia tsutsugamushi, an obligate intracellular Gram negative bacterium, which was first isolated in 1930. The causative organism is transmitted to human beings by the bite of a larval *Leptotrombidium* mite (chigger).

Uttarakhand is a mountainous state in northern India, situated in the outer Himalayas, with an altitude of 350-7,000 m above sea level. It is one of the least urbanized states in India. During the rainy season, areas at lower altitudes have an average temperature of 20°C to 35°C, which is conductive to the spread of arthropod vectors. An outbreak of scrub typhus in this area has also been reported (Sharma *et al.*, 2005).

Four factors are essential for the establishment of a microfocus of infection, namely, coexistence and intimate relationship among *O. tsutsugamushi*. Chiggers, rats and secondary or transitional forms of vegetation and are known as *zoonotic tetrad* (Hase *et al.*, 1978).

Human beings usually become infected when they accidentally encroach upon an area of infected chiggers mainly in rural and sub-urban areas. If the diagnosis is delayed, or the patient is not treated with the appropriate antibiotic, there can be serious complications such as renal failure, myocarditis, septic shock, meningoencephalitis and rarely, acute respiratory distress syndrome. The mortality rate is 7–30% (Mahajan, 2005).

The clinical symptoms vary depending on the duration of illness, strain of *O. tsutsugamushi*, immune status and the other host factors of the patient. In the early stage of the disease, the clinical symptoms are fever, rash, eschar, myalgia and lymphadenopathy, and it is difficult to distinguish scrub typhus clinically from many other febrile diseases especially in the absence of characteristic eschar (Lee *et al.*, 2008).

Almost all scrub typhus patients develop fever and headache. The maculopapular rash appears on the trunk 3–4 days after the onset of fever and spreads to the arms and legs. Regional lymphadenopathy develops in the drainage of the eschar and is usually present when the eschar appears. Generalized lymphadenopathy develops 2–3 days later. Bacteremia is detectable 1–3 days before the onset of fever (Scheie, 1947).

Respiratory symptoms are frequent. Interstitial pneumonia, pulmonary edema, pleural effusion, cardiomegaly and focal atelectasis are observed by chest radiography in patients (Song *et al.*, 2004). Gastrointestinal symptoms including nausea, vomiting, abdominal pain, diarrhea, hemetemesis and malena also occur. Myocarditis, pericarditis and relative bradycardia may develop, but congestive heart failure is rare. Clinical suspicion is based on the presence of fever, rash, conjunctival effusions, lymphadenopathy and epidemiological clues in endemic areas but scrub typhus is often difficult to differentiate from other febrile diseases or drug eruptions and is often overlooked cause of both pyrexia and pneumonitis of undetermined origin (Watt *et al.*, 2003).

The diagnosis is based on the patient's history of exposure, the clinical features, and an increase in antibody titre, antigen detection in blood or genetic material being detected by polymerase chain reaction (Yeon *et al.*, 2007). The disease is usually self limited and responds well to antibiotics with spontaneous recovery occurring in a few days.

Weil-Felix was the first test for detection of scrub typhus cases, it is easy to perform and cheap also, its specificity is low as the test employs Ag obtained from Proteus strains. ELISA has got good specificity (87%) but is relatively costly, time consuming & cannot be performed on single serum. On the other

hand, ICT has got almost equal sensitivity & specificity, easy to perform & single sera can be tested.

There are cluster of patients who present with acute febrile illness but are negative for common causes of fever such as typhoid, dengue, malaria and UTI. Some of them tests positive for scrub typhus. The present study was therefore undertaken to estimate the prevalence of the disease in this region.

Material and Methods

The study was conducted in the Department of Microbiology, Medicine and Pediatrics, Himalayan institute of Medical sciences, SRH University, a tertiary care teaching hospital at Dehradun, India over a period of 2 years from August 2012 to July 2014. The hospital caters to patients from Uttarakhand, western Uttar Pradesh and other adjoining areas of sub Himalayan north India. Scrub typhus was suspected in all patients who had fever for more than 5 days without an identifiable infection and one or more of the following clinical features: rash, hepatosplenomegaly, lymphadenopathy and an eschar. Serological diagnosis was made by a rapid immunochromatographic assay (SD Bioline Tsutsugamushi test from Standard Diagnostics, Inc. Hagal – dong, Kyonggi-do, Korea) containing a major surface protein 56-kDa antigen representstive of *O. tsutsugamushi* (Karp, Kato, Gilliam). The ICT test detected IgA, IgM and IgG. Positive samples were further confirmed by indirect IgM ELISA test (Scrub typhus detect ^{TM} IgM ELISA system from In BIOS International, Inc. Seattle, WA, USA) that used recombinant antigens to detect antibodies. The above tests were performed as per manufacturer's directions.

Clinical data, including the duration of fever, associated symptoms, vital signs, and the general, and systemic examination findings, were recorded. A careful search for eschar was performed in all patients. Data regarding age, sex, residential area, exposure to animals, exposure to farming and proximity to bushy and forest areas were collected.

Complete blood counts, chest X- rays, tests for renal and liver function, urinalysis and serum electrolytes estimation were performed at the time of presentation for all cases and were repeated if necessary. Common infectious conditions that could clinically mimic scrub typhus were ruled out by performing the following test: peripheral smear and rapid antigen test for malaria, Widal test for Enteric fever, Dengue (NS1 antigen and IgM antibody) test, urine and blood cultures. Tuberculin test, *Leptospira* serology and an HIV testing (as per NACO guidelines) were performed when clinically indicated. Cardiac evaluation and cerebrospinal fluid analysis were performed for selected cases with suspected myocarditis or meninngoencephalitis respectively. Ultrasound abdomen and computerized tomography scan were also done whenever necessary.

Results and Discussion

Six hundred and ninety two patients (19.4%) were diagnosed with scrub typhus by ICT out of three thousand five hundred and forty patients during the study period between August 2012 and July 2014. Further, four hundred and twelve (59.5%) of them were confirmed by IgM ELISA. The prevalence was more or less equal in both sexes (Table 1). The most commonly affected age group was 30–39 years in which one hundred and forty two (22.7%) were ICT positive cases and (19.9%) were IgM ELISA positive (Table 2).

All patients had fever at the time of presentation (100%). Eschar was present in 14.5% of patients. Groin and axilla were the most common sites of eschar. 26% patients had abdominal pain and 45% had vomiting and headache. 12%, 30%, 20% had splenomegaly, hepatomegaly and lymphadenopathy respectively. Cough was present in 57% of patients. Chest examination revealed crepitations in 38% cases. Diarrhoea and rash was present in 22% of cases. Altered sensorium and shock was observed in 13% of the cases (Table 3). It was also seen that the number of cases starts rising with the onset of rains and declines as winter ensues. Three hundred and thirty two (47.9%) cases were observed between the months of August to October in both the year (Figure 1). Four hundred and twenty nine (62%) cases were from hilly Garhwal division of Uttarakhand whereas two hundred and sixty two (38%) cases belonged to adjoining non-hilly Saharanpur and Bijnor districts of Western Uttar Pradesh, overall six hundred and eight (88%) cases resided in rural areas. Various environmental risk factors which act as predisposing factors such as living close to forests were present in 262 (38%) patients. A history of exposure to domestic animals (rats, cattle, dogs) was found in 449 (65%) of cases. Proximity to scrub vegetation was observed in 539 (78%) of patients. Grass cutting and open field defecation was observed in 350 (50%) of the cases (Table 4). Blood cultures and urine cultures were done in all patients and showed no growth. Antibodies against Salmonella species (Widal test) and *Leptospira* species were all negative in all patients. Dengue test was also negative in all patients.

Scrub typhus is prevalent in many parts of India. It is known to occur all over India, including Southern and Northern India (Chogle, 2010). Outbreaks have been reported from the sub- Himalayan belt, from Jammu to Nagaland. Outbreaks of scrub typhus have been reported from Himachal Pradesh, Sikkim and Darjeeling (West Bengal) during 2003–2004 and 2007 (Rajendran, 2011). An outbreak of scrub typhus in Uttarakhand has been reported in 2005 (Sharma *et al.,* 2005). Recently outbreaks of scrub typhus were also reported in southern India during the cooler months of the year (Mathai et al., 2003). Scrub typhus in humans results after the introduction of *Orientia tsutsugamushi* through the skin by the bite of a larval- stage (chigger) of trombiculid mite. It occurs in persons who engage in occupational or recreational behaviour that brings them into contact with mite–infested habitats such as bush and grass (Yeon *et al.,* 2007). The disease usually presents as an acute febrile illness with non specific symptoms like fever, headache, myalgia, cough and gastrointestinal disturbances. In the present study, all patients had fever at the time of presentation. An eschar at the wound site is the most characteristic feature of scrub typhus, but may not be present in all patients. Eschar is a black necrotic lesion resembling a cigarette burn usually found in areas where skin is thin, moist or wrinkled and where clothing is tight (Chin-Chou *et al.,* 2007).

Fever is constant feature of scrub typhus, in our study it was present in all the cases. In the studies from Thailand (Chanta and Chanta, 2005) and Eastern Taiwan (Chang *et al.,* 2009), eschar was present in 75% and 50% cases respectively. In the current study only 14.5% cases had eschar. Hepatosplenomegaly was present in 42% of cases in our study. However a much higher rate has been reported from the study in Karnataka where 85% cases presented with hepatosplenomegaly (Patil *et al.,* 2006). Another study conducted in Jammu revealed hepatosplenomegaly in 75% of the cases (Digra *et al.,* 2010). Similar study from

Chennai showed hepatosplenomegaly in 94% cases (Rajendran, 2011). Other clinical features that were present in our cases were abdominal pain, vomiting, rash, diarrhoea which was present in 26%, 45%, 26% and 22% respectively.

Scrub typhus is still regarded as a life threatening disease. Serious complications of scrub typhus include acute respiratory distress, pneumonia, myocarditis, meningoencephalitis, acute renal failure and gastrointestinal bleeding. A retrospective study from Taiwan (Chang *et al.,* 2009) reported hepatic dysfunctioning in 77% of their cases. On the other hand Digra *et al.* (2010) demonstrated hepatic dysfunction in only 14.2% of cases.

Transmission of disease occurs throughout the year in the tropical areas, whereas in the temperate zones transmission is seasonal (Chang, 1995). A large number of cases in the present study were encountered during the period of August to October, which receives the rainfall of 429-666 mm. This seasonal phenomenon was also seen in a similar study done in Darjeeling district in the state of West Bengal (Sharma *et al.,* 2009). Occurrence of *Leptotrombidium deliense* is influenced by rainfall, with more chiggers attached to the rodents in the wetter months of the year (Frances *et al.,* 1999). Risk of exposure to *O. tsutsugamushi* is greatest during the monsoon season, which may be the reason for clustering of cases during the monsoon in our study. Similar observations have been recorded by other authors, whereas a study from Taiwan found the greatest number of cases between May and August (Chang *et al.,* 2009).

No sex difference was observed in our study as mostly patients were from rural areas and both men and women are equally involved in work. The commonest age group affected in the present study was 30–39 years which is the young and active population involved in the occupational activities where visit to forests and accidental exposure to rats are frequent.

The distribution of mites can be very patchy as, to support the larvae, they require an environment where the adults have an abundant prey population and through which mammals frequently pass. The local climate must also be one in which the mites do not have to dig too deep for protection as this prevents egg-laying. Scrub typhus is endemic in a large part of India but it had not previously been observed in the north Indian state of Uttarakhand, despite the fact that the climate is one which is suitable for the breeding of the vector. The Garhwal region is hilly with ongoing infrastructural and industrial development conductive to vector breeding. The fact that the rainfall in this season was almost twice the annual average, causing the soil to remain loose, probably led to an increase in number of eggs laid by the mites.

Routine laboratory investigations do not have much of a diagnostic value in the diagnosis of scrub typhus. However elevated liver enzymes are frequently observed among patients with scrub typhus (Berman and Kundin *et al.,* 1973). Serological methods available for diagnosis of rickettsial diseases include microimmunofluorescence test, immunoperoxidase assay, latex agglutination test, indirect hemagglutination test, enzyme linked immunosorbent assay, dot blot immunoassay (including dip stick test) and Weil –Felix test (Digra *et al.,* 2010). Weil Felix test has been used widely in our country for diagnosing scrub typhus. It is non specific and it lacks sensitivity. IFA (Indirect immunofluorescence assay) is highly sensitive and considered ‘gold standard’.

Table.1 Age and Sex-wise distribution of patients presenting with AFI

Age groups	Male	Female	Total
<10 years	229	212	441
10-19	305	306	611
20-29	309	337	646
30-39	310	428	738
40-49	291	332	623
>50	322	209	531
Total	1766	1824	3590

Table.2 Positivity of scrub typhus cases in different age groups

Age Groups	Male		Female		Total	
	ICT	IgM ELISA	ICT	IgM ELISA	ICT	IgM ELISA
<10 years	48	32	48	18	96	50
10-19	50	38	54	20	104	58
20-29	70	38	74	48	144	86
30-39	70	52	84	30	154	82
40-49	60	42	72	42	132	84
>50	32	22	30	30	62	52
Total	330	224	362	188	692	412

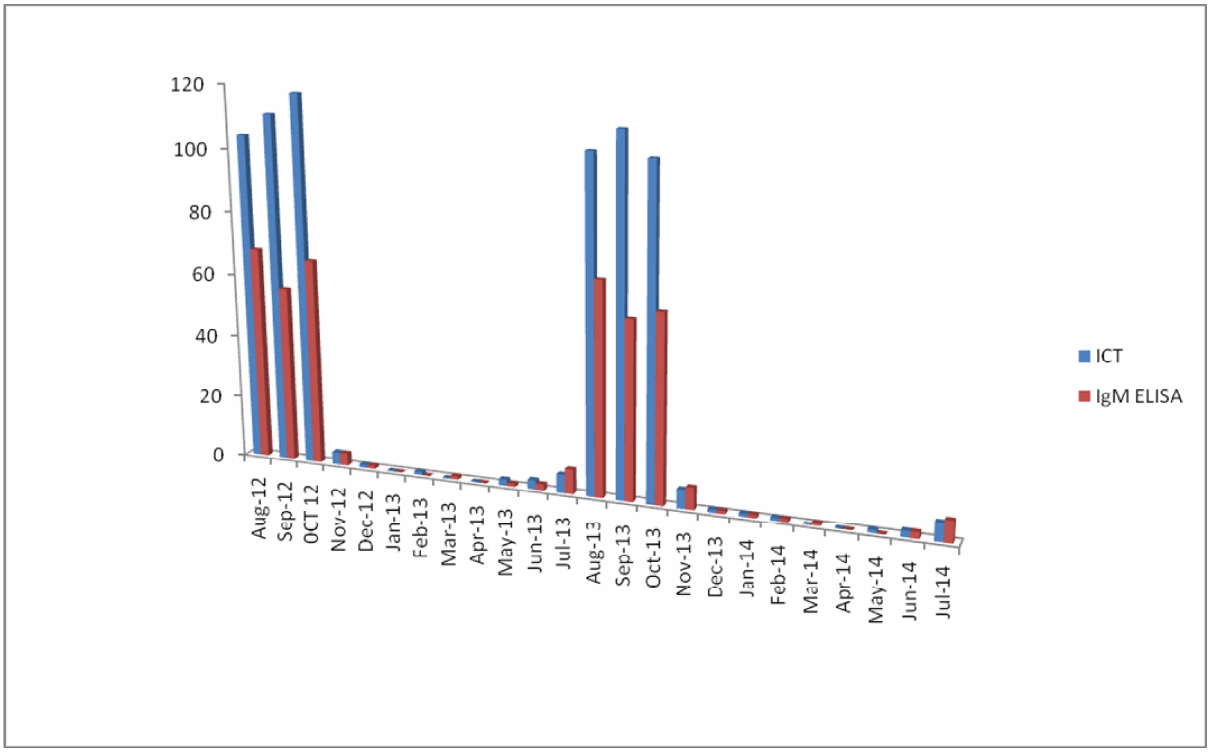
Table.3 Clinical features of scrub typhus cases at the time of presentation

Clincal features	Number of patients	Percentage
Fever	100	100
Cough	394	57
Vomiting	311	45
Headache	311	45
Dyspnoea	152	37
Abdominal pain	179	26
Altered sensorium	89	13
Diarrhoea	152	12
Crepitations	262	38
Hepatosplenomegaly	290	42
Lymphadenopathy	138	20
Eschar	100	12
Shock	89	13

Table.4 Presence of predisposing factors in scrub typhus positive cases

Predisposing factors	Number of patients	Percentage
Vegetation around houses	539	78
Infestation by rats	449	65
Open field defaecation	346	50
Grass cutting	332	48
Visit to forest	262	38

Figure.1 Month wise distribution of scrub typhus cases



However it is expensive and the test requires fluorescent microscope, trained personnel and cell culture procedures for preparing rickettsial antigen, hence not readily available in our country. Polymerase chain reaction has been used effectively to diagnose acute infection with *Orientia tsutsugamushi* (Yeon *et al.*, 2007). A rapid immunochromatographic assay which uses recombinant major outer membrane protein Antigen (r56) of *Orientia tsutsugamushi* to detect IgM, IgG and IgA antibodies has been shown to be reliable and suitable for use in developing countries but is expensive (Coleman, 2002).

The present study has some limitations. First the study was performed at a tertiary referral

hospital; therefore does not reflect the actual burden of the disease in the community, which may be higher. Second, rapid immunochromatographic assay and IgM ELISA were used for serological diagnosis because the indirect immunofluorescence assay, the gold standard confirmatory test is not yet widely available in our hospital.

In conclusion, scrub typhus is endemic in many parts of India and therefore surveillance should be continued in all these areas. Scrub typhus should be considered in patients presenting with fever, rash, myalgia and hepatic dysfunction and also if patient is from hilly area where scrub typhus is endemic especially during monsoon period.

References

Berman, S.J., Kundin, W.D. 1973. Scrub typhus in South Vietnam: a study of 87 cases. *Ann. Int. Med.*, 79: 26–30.

Chang, W.H. 1995. Current status of Tsutsugamushi disease in Korea. *J. Korean Med. Sci.*, 10: 227–38.

Chang-Ting, H, Hsin C, Hung-Chang L, Nan-Chang C and Fu-Yuan H, 2009; Scrub typhus in children in a teaching hospital in eastern Taiwan. *South East Asian J. Trop. Med. Public Health.*, 40(4): 789–794.

Chanta, C., Chanta, S. 2005. Clinical study of 20 children with Scrub Typhus at Chiang Rai regional hospital. *J. Med. Assoc. Thai.*, 88: 1867–72.

Chin-Chou, W., Shih-Feng, L., Jien-Wei, L., Yu-Hsiu, C., Mao-Chang, S., Meng-Chih, L. 2007. Acute respiratory distress syndrome in scrub typhus. *Am. J. Trop. Med. Hyg.*, 76: 1148–1152.

Chogle, A.R. 2010. Diagnosis and treatment of scrub typhus – the Indian scenario. *JAPI.*, 58: 11–12.

Coleman, 2002. Comparative evaluation of selected diagnostic assays for the detection of IgG and IgM antibody to *Orientia tsutsugamushi* in Thailand. *Am. J. Trop. Med. Hyg.*, 67: 497–503.

Digra, S.K., Ghan Shyam Saini, Virender Singh, Sunil Dutt Sharma, Rajesh Kaul. Scrub typhus in children: Jammu experience. *JK Sci.*, 12: 95–97.

Frances, S.P., Watcharapichat, P., Phulsoksombati, D., Tanskul, P., Linthicum, K.J. 1999. Seasonal occurrence of Leptotrombidium delience (Acari: Trombiculidae) attached to sentinel rodents in an orchard near Bangkok, Thailand. *J. Med. Entemol.*, 36: 869–74.

Hase, T., Roberts, L.W., Hildebrandt, P.K., *et al.* 1978. Stylostome formation by Leptotrombidium mites (Acari: Trombiculidae). *J. Parasitol*., 64(4): 712.

Lee, N., Ip, M., Wong, B. 2008. Risk factors associated with life threatening rickettsial infections. *Am. J. Trop. Med. Hyg*., 78(6): 973.

Mahajan, S.K. 2005. Scrub typhus. *J. Assoc. Phys. India*., 53: 954–8.

Mathai, E., Rolain, J.M., Verghese, G.M., Abraham, O.C., Mathai, D., Mathai, M., Raoult, D. 2003. Outbreak of scrub typhus in southern India during the cooler months. *Ann. N. York Acad. Sci.*, 990: 359–364.

Patil, D., Bidari, L.H., Tikare, N., Revankar, V.A. 2006. Profile of Rickettsial fever in children. Karnataka Pedicon–Conference Abstracts. *Pediatric Oncall* (Suppl. 11): 3.

Rajendran, 2011. Scrub typhus in pediatric age group: A report from a tertiary care hospital. *J. Pediatr. Sci.*, 3(2): e82.

Scheie, H.G. 1947. Ocular changes in scrub typhus. A study of 451 patients. *Trans. Am. Ophthalmol. Soc.*, 45: 637.

Sharma, A., Mahajan, S., Gupta, M.L., Kanga, A., Sharma, V. 2005. Investigation of an outbreak of scrub

typhus in Himalayan region of India. *Jpn. J. Infect. Dis.*, 58: 208–10.

Sharma, P.K., Ramakrishnan, R., Hutin, Y.J., Barui, A.K., Manickam, P., Kakkar, M., *et al.* 2009. Scrub typhus in Darjeeling India: Opportunities for simple, practical prevention measures. *Trans. R. Soc. Trop. Med. Hyg.*, 103: 1153–8.

Song, S.W., Kim, K.T., Ku, Y.M. 2004. Clinical role of interstitial pneumonia in patients with scrub typhus: a possible marker of disease severity. *J. Korean Med. Sci*., 19(5): 668.

Vas, L.S., Gupta, N.K. 2006. Outbreak of scrub typhus in Jammu – a report. *MJAFI.*, 62: 342–3.

Watt, G., Jongsakul, K., Chouriyagune, C. 2003. Differentiating dengue virus infection from scrub typhus in Thai adults with fever. *Am. J. Trop. Med. Hyg*., 68(5): 536.

Yeon, J.J., Suk, K., Yeh, D.W., Jun, W.L., Kun-11, K., Sun, H.L. 2007. Scrub typhus: Clinical, pathologic and imaging findings. *Radio Graphics.*, 27: 161–172.