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LIVER FUNCTION TEST ABNORMALITIES IN SCRUB TYPHUS

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ABSTRACT

Introduction: Scrub typhus is a rickettsial disease caused by Orientia tsutsugamushi. It is an important re-emerging infection in most parts of India. It had wide spectrum of presentation involving various systems of the body. The most common laboratory abnormality is alteration in the liver function tests. Presence of rural background and varied manifestations and abnormalities in LFT can support suspicion towards the diagnosis of scrub typhus.

Methods: Diagnosis of scrub typhus was confirmed by weil felix test, immunochromatographic test and/or IgM ELISA. Clinical features and liver function tests were analysed.

Results: Total of 71 patients were diagnosed in 1 year duration and their liver function tests (LFT) were analysed. Hepatic enzyme derangement is the most common laboratory abnormality in this study. Fifty nine of 71(83.1%) had some degree of hepatic enzyme derangement. Mild aspartate aminotransferase (AST) elevation was seen in 22 patients (40-80 u), moderate elevation (81-120) in 18 patients and >3 times elevation was seen in 20 patients. Alanine aminotransferase (ALT) elevation was seen in 59 patients, < 2 times in 26 patients, < 3 times in 20 patients, and >3 times in 13 patients. Serum alkaline phosphatase (ALP) elevation was seen in 45 patients,< 2 times in 32 patients, < 3 times in 4 patients, and >3 times in 9 patients. ALP elevation is one of the characteristic findings of scrub typhus due to cholestatic hepatopathy like in other sepsis. Bilirubin elevation was seen in 41 patients, >3 times seen in 12 patients. Most of patients had conjugate hyperbilirubinemia. Hypoalbuminemia was seen in (90.1%) patients, among them severe hypoalbuminemia (<2.5) was seen in (47.9%) patients. One observation in our study was 90% patients had hypoalbuminemia and 50% had severe hypoalbuminemia. None had received albumin transfusion.

Conclusion: Liver function abnormalities are most common among various laboratory abnormalities. Elevation of transaminases and alkaline phosphatase are in favour of scrub typhus in suspicious cases.

KEYWORDS

scrub typhus, hepatitis, liver function tests, hepatic enzyme derangement, alkaline phosphatase.

INTRODUCTION:

Scrub typhus also known as tsutsugamuchi disease[1] is caused by *Orientia tsutsugamushi* an obligatory intra-cellular gram-negative bacterium, a major cause of febrile illness in Asia pacific region[2]. It is transmitted to humans by the bite of larval mites (chiggers) of *Leptotrombidium deliense*.[2] The clinical picture ranges from asymptomatic to fatal, but it is unclear whether severity is contributed by traits of the infecting strain, the bacterial dose, the patient's immune response or other host properties.[3] Scrub typhus, if diagnosed late, or untreated, may prove fatal. The clinical manifestations of this disease range from sub-clinical disease to organ failure.[3,4] The disease produces a disseminated vasculitis and perivascular inflammatory lesions resulting in significant vascular leakage and end organ injury.[5,6,7] Fever is the most common feature of scrub typhus and due to lack of awareness among clinicians, the condition is labelled as "fever of unknown origin".[8] Especially in the Indian scenario, scrub typhus is grossly under-diagnosed due to its non-specific clinical presentation, limited awareness and low index of suspicion among clinicians.[9] Scrub typhus has wide spectrum of manifestations which can mimic conditions like pneumonia, meningoencephalitis, acute hepatitis, acute renal failure, loose motions and occasionally joint pains.[8] Lack of access to specific laboratory tests is another problem in developing countries like India for the under-diagnosis of several infectious diseases including scrub typhus. Abnormalities in liver function tests gives a clue to scrub typhus infection. We are presenting our experience with the abnormalities in liver function tests in patients with scrub typhus.

MATERIALAND METHODS:

This is a prospective observational study of patients with scrub typhus who were admitted between August 2014 and August 2015. Data of clinical and laboratory features of patients aged more than 18 years, with fever, and confirmed diagnosis of scrub typhus was analysed. Scrub typhus cases confirmed by the Weil Felix test with a titre of 1 in 320 or IgM ELISA positive and a positive immunochromatography test were included in the study.

The Weil Felix reagents used are Progen OX K Weil Felix reagent (Tulip Diagnostics, India). The other reagents are Progen OX 2 and Progen OX 19. The test was performed on an agglutination slide with the Weil Felix reagents by adding one drop (50 ul) of serum and one drop each of OX K, OX 2 and OX 19 reagents in separate circles of the card. It was mixed well with a mixing stick and observed for a visual agglutination after 1 minute. If it was positive, doubling dilutions of the serum was prepared and the test repeated. The highest dilution in which the agglutination is visible was taken as the titre of the test. The dilutions included were:1: 80, 1: 160, 1: 320, and 1: 640. Any sera sample tested positive for agglutination positive with OX K reagent, was retested by the scrub typhus immunochromatography test (ICT) (Standard Diagnostics, Seoul, South Korea) card test. The ICT consists of a filter paper strip coated with the cultured somatic antigens of *O. tsutsugamushi* (Gilliam, Karpand Kato strains). Ten microlitres of serum was added into the test well of the ICT device followed by 4 drops of buffer solution. A positive test was indicated by the development of a coloured band near the well of the device. An internal positive control was added for confirming the test result which was kept away from the test well. If found positive by the ICT as well, the test serum sample was diluted in doubling dilutions and ICT was repeated. The highest dilution showing a colour band in the test well was taken as the titre. Scrub IgM ELISA: Detect IgM ELISA system from InBios international Inc. It is a qualitative ELISA for the detection of IgM antibodies to O.tsutsugamuchi in serum. Wells of each plate have been coated with unique recombinant antigen mix. During testing, the serum samples are diluted in InBios sample diluents and applied to each well. After incubation and washing, the wells are treated with polyclonal Goat anti-human IgM antibodies labelled with enzyme horse radish peroxidise(HRP). After a second incubation and washing step, the degree of enzymatic turnover of the substrate is determined by an absorbance measurement at 450nm. The absorbance measured indirectly proportional to the concentration of

antibodies to O.tsutsugamuchi present. A set of positive and negative controls are provided as internal controls. These are provided to inform the integrity of the kit components.

RESULTS:

A total 71 patients were enrolled in the study out of which 47 were males and 24 females patients. Out of the 71 patients, farmers were 28(39.4%). 62% are from the rural background (Table 1). Most of the cases are in the rainy season.

Table 1: Baseline Characteristics of the patients

Characteristics of the patient	Number of patients (%)
Males	47(66%)
Females	24(34%)
Rural background	62%
Occupation	
Farmers	28(39.4%)
Housewives	14(19.7%)
Others	29(40.8%)

In our study fever was present in all patients. Among the other symptoms, cough was present in 24 (33.8%) breathlessness in 22(31%), vomiting in 21(29.65%), headache in 20(28.2%), pain abdomen in 13(18.3%), altered sensorium in 6(8.5%) patients, jaundice in 6(8.5%) patients, diarrhoea in 5(7%), abdominal distension in 3(4.2%), decreased urine output in 3(4.2%), seizures in 1(1.40%), and hematemesis in 1(1.4%) patient. On examination, pallor was noted in 12(16.9%) patients, pedal oedema in 6(8.5%) patients, icterus in 6(8.5%), lymphadenopathy in 7(9.9%) patients, rash in 6(8.5%) patients, eschar in 5(7%) patients (Figure 1 & 2). Clinically signs of consolidation seen in 5(7%) patients, ARDS noted in 6(8.5%) patients (Figure 3 & 4), pleural effusion in 3(4.2%) patients. Examination of abdomen showed hepatomegaly in 4(5.6%) patients, splenomegaly in 7(9.9%) patients. Signs of meningeal irritation are seen in 5(7%) patients (Table 2).

Figure 1: Eschar in the loin area

Figure 2: Eschar in the left axilla

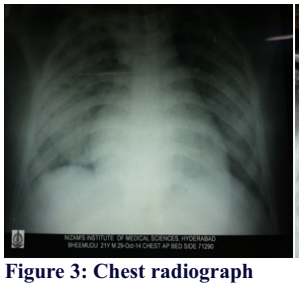

Figure 3: Chest radiograph showing features suggestive of ARDS

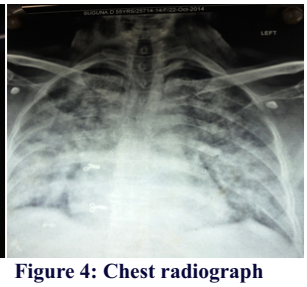

Figure 4: Chest radiograph showing bilateral pneumonia

Table 2: Clinical presentations in patients with Scrub Typhus

Signs & Symptoms	Total (n=71)	Signs & Symptoms	Total (n=71)
Headache	20(28.2%)	Pallor	12(16.9%)
Altered Sensorium	6(8.5%)	Edema	6(8.5%)
Seizures	1(1.4%)	Icterus	6(8.5%)
Cough	24(33.8%)	Lymphadenopathy	7(9.9%)
Breathlessness	22(31%)	Rash	6(8.5%)
Abdominal distension	3(4.2%)	Eschar	5(7%)
Vomitings	21(29.6%)	Consolidation on radiograph	5(7%)
Diarrhea	5(7%)	ARDS on radiograph	6(8.5%)
Jaundice	6(8.5%)	Pleural effusion on radiograph	3(4.2%)
Oliguria	3(4.2%)	Signs of ascites	1(1.4%)
Pain abdomen	13(18.3%)	Hepatomegaly	4(5.6%)
Hematemesis	1(1.4%)	Splenomegaly	7(9.9%)
		Meningeal signs	5(7%)

In our study, 59 of 71(83.1%) had some degree of hepatic enzymes derangement. Mild SGOT elevation seen in 22 patients (40-80 u), moderate elevation (81-120) in 18 patients and >3 times elevation seen in 20 patients. SGPT elevation seen in 58 patients, < 2 time in 26 patients, < 3 times in 20 patients and >3 times in 13 patients. ALP elevation in 45 patients ,< 2 times in 32 patients, < 3 times in 4 patients and >3 times in 9 patients. Bilirubin elevation seen in 41 patients, >3 times seen in 12 patients most of the patients had conjugate hyperbilirubinemia. Hypoalbuminemia was seen in 64 patients among them severe hypoalbuminemia (<2.5) was seen in 34 patients (Table 3).

Table 3: Liver Function test abnormalities

Liver Function test	n (%)
SGOT (U/L)	
• 0-40	11(15.5%)
• 41-80	22(31%)
• 81-120	18(25.4%)
• >120	20(28.2%)
SGPT (U/L)	
• 0-45	12(16.9%)
• 46-90	26(36.6%)
• 91-135	20(28.2%)
• >135	13(18.3%)
Alkaline Phosphate (U/L)	
• <130	26(36.6%)
• 131-260	32(45.1%)
• 261-390	4(5.6%)
• >390	9(12.7%)
Total Bilirubin (mg/dl)	
• <0.8	30(42.3%)
• 0.9-1.4	22(31%)
• 1.5-2.4	6(8.5%)
• 2.5-3.2	1(1.4%)
• >3.2	12(17%)
Albumin(gm/dl)	
• <2.5	34(47.9%)
• 2.6-3.5	30(42.3%)
• >3.5	7(9.9%)

DISCUSSION:

Hepatic enzyme derangement is the most common laboratory abnormality in our study. we observed that 59(83.1%) patients had some degree of hepatic enzyme derangement. Ming Leun Hu et al reported 89.3% patients having abnormal liver function tests. Unlike the infection with hepatotropic viruses, the elevation of liver enzymes is usually mild. 1-2 times in 26 patients, 2-3 times in 20 patients and >3 times in 13 patients. Serum (ALP) elevation was seen in 45 patients, 1-2 times in 32 patients, 2-3 times in 4 patients and >3 times in 9 patients. ALP elevation is one of characteristic findings of scrub typhus due to cholestatic hepatopathy as like in other sepsis. Bilirubin elevation seen in 41 patients, >3 times seen in 12 patients. Most of patients had conjugate hyperbilirubinemia. Hypoalbuminemia was seen in 64 patients, among them severe hypoalbuminemia (<2.5) was seen in 34 patients. One observation in our study was 90% patients had hypoalbuminemia and 50% had severe hypoalbuminemia. None had received albumin transfusion. We did not note the follow up albumin levels whether they were improved with cure of disease, as we included only the values at the time of presentation. From the values we can infer that mild enzyme elevation and mild unconjugated hyperbilirubinemia are thrice than normal limits. Mild enzyme elevation was seen in 59 patients, whereas >3 times enzyme elevation (SGOT, SGPT, ALP, all three) was seen in 9 (12.6%) patients.

Most of the studies considered hepatitis as thrice the normal values, but we observed in our population that mild enzyme elevation was seen in most of the patients. This finding is supported by Varghese et al,[10] as their case series also showed similar findings. In our study we took only one value at admission that might be the reason for mild enzyme elevation and during course of the disease, they might have developed more enzyme elevation.

Thrice normal elevation of AST was seen in 20 patients, ALT in 13 patients, ALP in 9 patients and bilirubin in 12 patients. Severe hepatitis (>3times SGOT, SGPT, ALP, Bilirubin) was seen in 9 patients.

Jamil et.al[12] observed 83.05% patients having deranged liver enzymes which was similar to our study. A case series[13] from our own institute previously done also had similar observation in liver enzyme derangement. Study done by Varghese et[10] al from CMC Vellore revealed mild transaminitis (elevation to 2–3 times normal) in 72.5%, and an elevated bilirubin in 26.6%. Case series done by Mahajan et al[14] in (66.7%), Kin Ming Wu et al[15] in (85.8%), Vivekanandan et al[9] in (95.9%), and other studies also observed LFT derangements in 70% to 95% patients.

CONCLUSION:

Scrub typhus re-emerged in many parts of India, especially in areas where agriculture is one of the major occupations. In Andhra Pradesh also recent outbreaks were reported. Many infections like dengue fever, leptospirosis, malaria and viral fevers have a similar picture. All have fever and associated symptoms, liver function abnormalities commonly. High index of suspicion has to be there in patients who hails from rural background with multiorgan involvement.

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