ORIGINAL RESEARCH PAPER

Volume - 12 | Issue - 05 | May - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

EFFECT OF SCRUB TYPHUS DISEASE ON LIVER FUNCTION – A HOSPITAL BASED OBSERVATIONAL STUDY AT A TERTIARY CARE CENTRE, ASSAM, INDIA

Biochemistry

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ABSTRACT

Background And Objectives : Scrub typhus is a chigger-borne zoonotic disease, caused by Orientia tsutsugamushi. Humans are accidental hosts. It occurs all along East Asia with many recent outbreaks in North-East India. It shows similar symptoms to other tropical infections and its disease spectrum ranges from mild febrile illness to severe life-threatening illness with multi organ dysfunctions. This study was done to observe relationship between scrub typhus and liver function. **Methods :** A hospital based observational study was conducted on randomly selected 40 scrub typhus patients (between 12 and 60 years) diagnosed by detecting IgM antibody using enzyme linked immunosorbent assay (ELISA) over a period of 1 year at a tertiary care centre, Assam. Liver function tests were performed on the diagnosed cases using reflectance spectrophotometry method on automated analyser. The values of LFT were estimated and p-values were calculated to establish statistical significance. **Results :** Total 40 number of cases of scrub typhus was taken for our study with a mean age of 29.28 years among which, males were 57.5% and females were 42.5%. Bilirubin elevation was seen in 25 patients (62.5%), AST was increased in 36 patients (90%), ALT was increased in 35 patients (87.5%), ALK was high in 25patients (62.5%), 32 pateints (80%) had hypoalbuminemia, with a p value of < 0.05, which is statistically significant. **Interpretation And Conclusion :** Our study concluded that scrub typhus could to be taken into consideration in patients with undifferentiated fever with abnormal liver function tests.

KEYWORDS

Assam, liver function test, orentia tsutsugamushi, scrub typhus

INTRODUCTION

Scrub typhus also known as 'tsutsugamushi disease' (tsutsuga, meaning something small and dangerous and mushi, meaning insect or mite), a resurging zoonotic disease that is caused by Orientia tsutsugamushi [3,5]. Orientia tsutsugamushi (formerly Rickettsia tsutsugamushi) is an obligatory intracellular gram negative bacterium, belongs to family rickettsiaceae[4,9]. This infection is usually transmitted to hosts by either saliva inoculation (tick- or mite-transmitted), by autoinoculation after scratching lesions contaminated by the bite of only larval mite stage (chiggers) of Leptotrombidium delense because other stages of mites (nymph, adult and eggs) do not feed on vertebrate animals[5]. Humans become accidental hosts when they visit into an area which can serve as a habitat for mites[5] .

This mite borne or chigger borne typhus is prevalent in a part of world known as 'tsutsugamushi triangle' extending from Japan and eastern Russia in north, northern Australia in South to Afganistan in west with many recent outbreaks in India[3]. In India, scrub typhus was first seen in Assam and West Bengal during world war II (1944-1945).It is found in whole of the Shivalik ranges from Kashmir to Assam, Eastern and Western Ghats and the Vindhyachal and Satpura ranges in the central part of India[9].

Scrub typhus is an acute febrile disease which is one of the causes of 'fever of unknown origin' in endemic areas[2]. After an incubation period (1-3 weeks), the infected persons often develop triad of classic presentation of scrub typhus consisting of eschar (at the site of bite), regional lymphadenopathy and maculopapular rash[5,7]. If it is not treated quickly, the bacteria can spread systemically and can cause hepatic lesions, myocardial lesions, interstitial pneumonia, meningoencephalitis, acute respiratory distress syndrome and multiorgan failure[4,6]. Hepatic infection is most common during scrub typhus. Our research work is to study effect of scrub typhus disease on liver function.

At the site of bite, chigger inoculates O. tsutsugamushi pathogens[5]. Now the bacterium multiply at the inoculation site and a papule is formed that ulcerates and becomes necrotic, forming an eschar[5]. After entry, the rickettsiae generally spreads through the lymphatics from the portal of entry[8]. Endothelial cells are the primary target cells[5]. Endothelial cell activation can be triggered by two ways- directly via pathogen replication and recognition of pathogen associated molecular patterns (PAMP) or indirectly via recognition of damage associated molecular patterns (DAMP) and inflammatory cytokines[6]. The bacteria adheres to host cells by rickettsial outer membrane proteins such as rOmp[8]. Rickettsiae enter host cells via phagocytosis[8]. Phagocytic vacuoles are lysed and bacteria escape the phagocytic vacuoles to multiply freely in the cytoplasm[8]. The infected endothelial cell is damaged via lipid peroxidation of host cell membrane by enzyme phospholipase A^{8}. Damage to the vasculature causes production of pro-inflammatory cytokines (i.e. CXCL8 and TNFβ) leading to recruitment of neutrophils, monocytes etc., which secrete their own chemokines and effector proteins, inducing a pro-inflammatory microenvironment in multiple organs like liver causing hepatic dysfunction[8].

MATERIAL AND METHODS

This retrospective observational study was conducted for 1 year at Gauhati medical college and hospital, Guwahati which is a tertiary care centre of Assam, India. Every individuals included in our study signed a written protocol consent. The study group contained 40 patients aged more than 12 years and less than 60 years diagnosed with scrub typhus which was randomly selected attending hospital. The diagnosis was done if any of the following criterias are fulfilled (a) history of travel to endemic area to scrub typhus, (b) acute fever, (c) pathognomonic eschar and (d) positive serologic tests for scrub typhus at the initial visit. The serologic test for scrub typhus was done using ELISA, particularly immunoglobulin M (IgM) capture assays. The exclusion criterion was patients with previously known hepatitis and abnormal liver function tests, chronic alcoholic patients, patients with some other associated infections like leptospirosis, dengue, malaria, enteric fever etc. The diagnosis was confirmed by detecting IgM antibodies against O. tsutsugamushi using enzyme-linked immunosorbent assay (ELISA) kit (InBios).

During testing, the serum samples were diluted in InBios sample diluent and applied to each well. After incubation and washing, the wells were treated with polyclonal Goat anti-human IgM antibodies labeled with the enzyme horseradish peroxidase (HRP). After a second incubation and washing step, the wells were incubated with

tetramethylbenzidine (TMB) substrate. An acidic stopping solution was then added and the degree of enzymatic turnover of the substrate was determined by absorbance measurement at 450nm. The absorbance measured is directly proportional to the concentration of IgM antibodies to Orientia tsutsugamushi present.

Liver function tests were done in the serum of diagnosed scrub typhus patients within the initial days of visiting the hospital. Under all aseptic and antiseptic conditions, 5ml of venous blood was drawn from the diagnosed scrub typhus patients and transferred into a vacutainer. The whole blood was allowed to clot and centrifuged for 10 min at 4000rpm. The supernatant part was separated from the vacutainer, followed by aliquoting and kept frozen at -20 until LFT analysis was done. Liver function tests were performed on the collected serum using reflectance spectrophotometry method on autoanalyser (ortho clinical diagnostics vitros 5600 autoanalyser).

Data of parameters of liver function tests such as total bilirubin, AST, ALT, ALKP and albumin of scrub typhus patients were entered into MS excel. One sample t-test was performed for each parameters and p-values were estimated by using MS excel which were found significant for each parameter.

RESULTS

Total 40 number of cases of scrub typhus was taken for our study with a mean age of 29.28 years among which males were 57.5% and females were 42.5%. Fever was present almost in all patients in our study. The results of this research are explained by the following tables:

Table I : Percentage Distribution Of Total Bilirubin Values In Cases

Liver function test				
Total Bilirubin (mg/dl)	Number (n=40)	Percentage (%)	t-test	p-value
≤1.3	15	37.5	2.88	0.03
>1.3	25	62.5		

Out of 40 cases, 15 patients (37.5%) showed total bilirubin within normal range and 25 patients (62.5%) patients showed increased bilirubin values with p-value 0.03.

Table II : Percentage Distribution Of AST Values Of Cases

AST (U/l)	Number (n=40)	Percentage (%)	t-test	p-value
≤59	4	10	2.37	0.01
>59	36	90		

4 patients (10%) showed AST values within normal range and 36 patients (90%) showed increased AST values with p-value 0.01

Table III : Percentage Distribution Of ALT Values In Cases

ALT (U/l)	Number (n=40)	Percentage (%)	t-test	p-value
≤50	5	12.5	1.92	0.03
>50	35	87.5		

Out of 40 patients, 5 patients (12.5%) showed ALT values within normal range and 35 patients (87.5%) showed increased ALT values with p-value 0.03

Table IV: Percentage Distribution Of ALKP In Cases

ALKP (U/l)	Number (n=40)	Percentage (%)	t-test	p-value
≤126	15	37.5	3.18	0.01
>126	25	62.5		

Out of 40 patients, 15 patients (37.5%) showed ALKP values within normal range and 25 patients (62.5%) showed increased ALKP values, with p-value 0.001 .

Table 5 : Percentage Distribution Of Albumin Values In Cases

Albumin (U/l)	Number (n=40)	Percentage (%)	t-test	p-value
≤3.5	8	20	-7.41	<0.001
>3.5	32	80		

Among 40 cases, 8 patients (20%) showed albumin values within normal range and 32 patients (80%) showed decreased albumin values, with p-value <0.001

DISCUSSION

The present study reported liver function tests were abnormal in patients diagnosed with scrub typhus which is consistent with the findings of other studies. In a study conducted by Saurabh Gaba et al.[3], out of 176 cases of scrub typhus, 93 cases (52.8%) were males and 83 cases (47.2%) were females. This percentage of gender distribution is consistent with our study. In our study, Hyperbilirubinemia was seen in 25 patients (62.5%). AST, ALT and ALKP were elevated in 36 cases (90%), 35 cases (87.5%) and 25 cases (62.5%) respectively. Hypoalbuminemia (serum albumin <3.5 gm/dl) was seen in 32 cases (80%). In a similar study by Subbalaxmi M et al.[10], hyperbilirubinemia was seen in 57.75% cases. AST, ALT and ALKP were increased in 84.5%, 81.7% and 63.4% respectively which were in accordance with our study. In the study conducted by Saurabh Gaba et al.[3], AST and ALT levels in scrub typhus cases were elevated in 88.6% and 90.3% respectively. Similarly, a study by Ming-Luen Hu et al.[4] showed that AST, ALT and ALKP were raised in 89.3% , 91.7% and 84.2% cases respectively. Hypoalbuminemia was seen in 83.3 % which is consistent with our study.

CONCLUSION

Scrub typhus is re-emerging zoonotic disease in many parts of India, specially in rural areas but remains undiagnosed due to its non-specific signs and symptoms, low index of suspicion amongst clinicians, less awareness and less diagnostic features. Our study showed that the most patients diagnosed with scrub typhus has liver dysfunction. Therefore, high index of suspicion for scrub typhus has to be there in patients with fever of unknown origin who hails from rural background with liver involvement.

Limitations And Further Scope Of Study: This study has been done in a single tertiary care centre with limited number of patients for a limited duration which may fail to generalise for the whole scrub typhus patients group. Therefore, including larger number of cases over longer duration might be required for further validation.

Acknowledgement : We would like to thank the Department of Microbiology and Department of Medicine, Gauhati medical college and hospital, Guwahati, Assam for their cooperation.
Finalcial support and sponsorship : Self-funded
Conflicts of interest : None

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