

# Gastrointestinal Manifestations of Scrub Typhus in Children and Adults from Puducherry and Neighboring Tamil Nadu State, India

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## ABSTRACT

Scrub typhus (ST) is reported from almost every Indian state. In our tertiary care teaching hospital at Puducherry, we looked for gastrointestinal (GI) manifestations of ST in children as well as adults and correlated with laboratory findings. We examined 588 serum samples for immunoglobulin M (IgM) antibody against *Orientia tsutsugamushi* by enzyme-linked immunosorbent assay (ELISA) and observed that 335 (56.97%) of these clinically suspected ST patients were positive, comprising 134 children and 201 adults. Statistically significant ( $p \leq 0.05$ ) number of adults had nausea ( $p = 0.000$ ) and abdominal pain ( $p = 0.020$ ) than children. Similar trend was observed in adults with reference to increased liver enzymes (aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase;  $p = 0.000$ ), creatinine ( $>1.0$  mg/dL;  $p = 0.007$ ), and platelet count ( $\leq 1.5$  lakhs/mm<sup>3</sup>;  $p = 0.026$ ). Rash in children is the only statistically significant manifestation than adults ( $p = 0.03$ ). More number of children were positive than adults, but without any statistical significance, with reference to other parameters like cough/expectoration ( $p = 0.735$ ), hepatomegaly ( $p = 0.730$ ), and eschar ( $p = 0.721$ ).

**Keywords:** Gastrointestinal symptoms, *Orientia tsutsugamushi*, Scrub typhus, Scrub typhus immunoglobulin M enzyme-linked immunosorbent assay.

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**Conflict of interest:** None

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## INTRODUCTION

Scrub typhus once confined to a few geographical locations in “Tsutsugamushi triangle” has now become an emerging infection, with reports from almost every Indian state.<sup>1-7</sup> Availability of ST ELISA kits has facilitated reporting of ST cases from hitherto unknown areas. Presence of typical eschar is an important finding in febrile patients with ST, but the absence does not exclude it. Common as well as uncommon clinical presentation and complications involving different systems/organs have been observed by researchers. The aim of this study is to record and correlate the GI manifestations of ST cases confirmed by specific laboratory test (ST IgM ELISA). Emphasis is made on the GI manifestations in both the pediatric age group and the adults and to look for statistically significant differences, if any, regarding manifestations in other systems as well. Comparison is made regarding clinical findings and laboratory parameters between our study and other reports.

## MATERIALS AND METHODS

This prospective study was carried out in a tertiary care teaching hospital at Puducherry. The study was conducted from July 2015 to December 2016, after receiving approval from Institutional Human Ethical Clearance Committee. Patients were recruited based on the inclusion and exclusion criteria as described earlier.<sup>6</sup> This is a convenient sample size based on our time-bound study. All in- and outpatients who attended the hospital of Mahatma Gandhi Medical College & Research Institute from July 2012 to December 2016 with clinical suspicion of ST were included in this study.

We examined 588 febrile patients, comprising 178 children and 410 adults, with clinical suspicion of acute ST for the presence of IgM antibody against *O. tsutsugamushi* by Scrub Typhus Detect IgM ELISA kit (InBios International, California, USA). This kit has been sufficiently evaluated by Indian and overseas researchers, who found it to have sensitivity and specificity of 95% in comparison to the “gold standard” serological test of Indirect Immunofluorescence assay.<sup>3,4,6-8</sup> The procedure outlined in the technical brochure was strictly adhered to and the readings were interpreted as reported previously.<sup>6</sup> Briefly, ST IgM ELISA plates were

coated with ten recombinant antigens of *O. tsutsugamushi*. Patients' serum samples were initially diluted with 1:100 of the sample dilution buffer. About 100  $\mu$ L of diluted patients' sera and ready-to-use positive and negative controls were added to the plate, incubated at 37°C for 30 minutes followed by washing the plates with phosphate buffer solution. Enzyme horseradish peroxidase conjugate 100  $\mu$ L was added to each well and incubated at 37°C for 30 minutes, followed by washing. About 150  $\mu$ L EnWash was added to each well and plate was incubated at room temperature for 5 minutes followed by washing. Tetramethylbenzidine substrate (100  $\mu$ L) was added to each well, incubated at room temperature in dark for 10 minutes. Stop solution (50  $\mu$ L) was added to each well and after 1 minute, the optical density (OD) readings were taken at 450 nm in iMark Microplate Reader (Bio-Rad, Japan).

Twenty samples from healthy volunteers from ST endemic area (Kurinjipadi Taluk, Cuddalore district, Tamil Nadu) were tested by IgM InBios ELISA and average OD value was taken as cut-off value. Cut-off value considered by us was 0.560. This is considered as the normal endemic titer in this area. The GI symptoms like nausea, vomiting, diarrhea, and hematemesis were recorded. Similarly, GI signs like hepatomegaly/splenomegaly/jaundice and abdominal pain were also noted. Physical examination included a search for the typical

ST eschar. The GI manifestations of these patients are correlated with other laboratory parameters.

### Statistical Analysis

Patients' data were analyzed by chi-square test, using GraphPad QuickCalcs (GraphPad Software Inc, USA) and p-values of  $\leq 0.05$  were considered as statistically significant.

### RESULTS

Of the 588 patients, comprising of 343 men and 245 women with febrile illness and presenting symptoms of acute ST, 335 (56.97%) were positive in ST IgM ELISA (153 males and 182 females). Among 178 children with clinical suspicion of ST, 134 were positive in ST IgM ELISA (75.28%), whereas of 410 adults, 201 (51.21%) were confirmed as ST positive by IgM ELISA. Table 1 records GI manifestations of laboratory-confirmed ST cases with hematological and biochemical findings. Statistically significant number of adults had nausea ( $p=0.000$ ) and abdominal pain ( $p=0.020$ ) compared with children. Similar trend was observed in adults with reference to elevated liver enzymes (AST/ALT/AP;  $p=0.000$ ), creatinine ( $>1.0$  mg/dL;  $p=0.025$ ), and low platelet count ( $\leq 1.5$  lakhs/ $\text{mm}^3$ ;  $p=0.026$ ). Rash is the only clinical finding seen more in children than in

**Table 1:** Gastrointestinal manifestations and laboratory parameters of ST IgM ELISA-positive cases

Clinical/laboratory findings	Children (0–18 yr) n = 134	Adults (>18 yr) n = 201	Total n = 335 (%)	p-values
Headache	43	103	146 (43.58)	0.000*
Chills and rigor	59	127	186 (55.52)	0.000*
Cough/expectoration	43	61	104 (31.04)	0.735
Retro-orbital pain	0	2	2 (0.59)	0.518
Malaise	16	41	57 (17.01)	0.043*
Nausea	26	77	103 (30.74)	0.000*
Vomiting	56	104	160 (47.76)	0.074
Abdominal pain	43	90	133 (39.70)	0.020*
Myalgia	34	93	127 (37.91)	0.000*
Rash	13	7	20 (5.97)	0.034*
Bleeding episodes	0	3	3 (0.89)	0.277*
Hepatomegaly	26	36	62 (18.50)	0.730
Splenomegaly	14	26	40 (11.94)	0.491
Eschar	24	33	57 (17.01)	0.721
Pneumonitis	6	13	19 (5.67)	0.595
Lymphadenopathy	15	23	38 (11.34)	0.943
Pleural effusion	2	7	9 (2.68)	0.324
Endocarditis	0	2	2 (0.59)	0.518
Complications	7	24	31 (9.25)	0.052
Platelet count ( $\leq 1.5$ lakhs)	32	71	103 (30.74)	0.026*
Increased liver enzymes (AST/ALT/AP)	18 <sup>#†</sup>	71 <sup>###†</sup>	89 (26.56)	0.000*
Creatinine ( $>1.0$ )	8 <sup>§</sup>	33 <sup>§§</sup>	41 (12.23)	0.007*
Leukopenia ( $<4,000$ $\text{mm}^3$ )	7	13	20 (5.97)	0.813

\*p-values  $<0.05$  were considered significant; <sup>#†</sup>Out of 78 children; <sup>###†</sup>Out of 138 adults; <sup>§</sup>Out of 90 children; <sup>§§</sup>Out of 169 adults

adults, which is of statistical significance ( $p = 0.034$ ). With reference to other clinical findings, children had a slightly higher percentage positivity than adults but without any statistical significance (cough/expectoration,  $p = 0.735$ ; hepatomegaly,  $p = 0.730$ ; eschar,  $p = 0.721$ ). Males had statistically significant higher positivity than females with reference to splenomegaly ( $p = 0.008$ ) and increased liver enzymes ( $p = 0.020$ ). Female patients had a higher positivity percentage than male patients in two parameters, viz., lymphadenopathy ( $p = 0.010$ ) and chills/rigor ( $p = 0.015$ ). Regarding the complications, hepatic dysfunction was observed in one child. Four adults developed hepatic dysfunction and two acute renal failures. Meningeal involvement, myocarditis, congestive cardiac failure, and acute respiratory distress syndrome were observed in one adult patient each.

## DISCUSSION

Various clinical manifestations of ST have been reported in the Indian and world literature.<sup>1-13</sup> Presence of ST eschars vary from a very low 7%<sup>8</sup> to moderate 22 to 40%<sup>6,7,10</sup> and a very high 97%.<sup>8</sup> Typical ST eschar was observed in 24 children and 33 adults in our study (17.01%). Finding of ST eschar requires a thorough physical examination, especially in the covered areas of the body, which may not be accepted by local customs. Besides, in dark-skinned people, eschars may not be clearly visible.

We preferred to highlight GI manifestations of ST. Among GI symptoms, nausea and vomiting were observed respectively, in 30.74 and 47.76% of the ST positive patients, but in contrast, 100% patients with nausea was reported by Narvencar et al.<sup>3</sup> Moderately high level of nausea and vomiting (60%) and bleeding episodes of 25% were recorded by Aung-Thu et al.<sup>10</sup> Patients who had diarrhea/loose motion were in the range of 11.2 to 45%.<sup>3,4,7,10</sup> Ascitis to the tune of 34% in ST patients has been reported by Singh et al.<sup>4</sup>

Regarding GI signs, abdominal pain in 39.7% of ST patients has been observed in our study, whereas Narvencar et al,<sup>3</sup> Singh et al,<sup>4</sup> and Aung-Thu et al<sup>10</sup> had positive findings ranging from 46.7, 29.8, and 20% respectively. Few researchers have observed acute abdomen in some of their ST patients.<sup>2,5</sup> According to Kundavaram et al<sup>5</sup> "possibility of scrub typhus presenting with fever and acute abdomen should be kept in mind." Yang et al<sup>9</sup> have also reported two cases of ST with unusual presentation of acute abdomen—one case of acute appendicitis and another of acute cholecystitis. Rare manifestation of peritonitis in two ST patients was reported by Lee et al.<sup>13</sup> Pancreatic abscess following ST associated with multiorgan failure was reported by Yi and Tae.<sup>12</sup> None of our ST patients had GI signs like acute abdomen/appendicitis/peritonitis.

Aung-Thu et al<sup>10</sup> observed that 40% of their cases had hepatomegaly. Singh et al<sup>4</sup> reported that 27.7% of their patients had hepatomegaly and 25.5% splenomegaly. In the experience of Kumar et al,<sup>7</sup> splenomegaly was present in 22.7%, but only 0.9% had hepatomegaly. In the present study, 18.50 and 11.94% of our ST patients had hepatomegaly and splenomegaly respectively.

Among the laboratory parameters, thrombocytopenia in 90% of ST cases was reported by Varghese et al,<sup>1</sup> followed by 46.8%,<sup>4</sup> 26.7%,<sup>3</sup> and 25.7% by Anitharaj et al.<sup>6</sup> Liver enzyme levels are normally elevated in ST. Highest levels of 91.7% ALT and 89.3% AST were recorded by Hu et al.<sup>11</sup> Similar higher levels of liver enzymes, viz., AST/ALT/AP, have been reported by other researchers as well.<sup>3,4,10</sup> In our study, a moderate number of patients (26.6%) had elevated liver enzymes, with adults alone contributing for 51.45%. Increased serum creatinine levels were found in one-third of ST patients,<sup>3,4</sup> compared with a lower 12.23% positivity among our patients.

According to Kumar et al,<sup>7</sup> complications were seen in 71.2% of ST patients, whereas only 9.25% of our patients developed complications, probably because of early intervention with appropriate antibiotic therapy. We observed that in this study children responded very well to azithromycin/doxycycline, with defervescence of fever observed within 2 days and in some cases after the first dose itself. There was no mortality among both children and adult ST patients.

## CONCLUSION

Different parts of India have become endemic foci for ST. The clinicians therefore need to be sensitized regarding the common clinical manifestations of ST. Gastrointestinal signs and manifestations of patients are to be sought after since they provide additional points for clinical diagnosis of ST. Children and adults as well as male and female might exhibit differences in their clinical presentation and laboratory test results.

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## REFERENCES

1. Varghese GM, Abraham DC, Mathai D, Thomas K, Aaron R, Kavita ML, Mathai E. Scrub typhus among hospitalized patients with febrile illness in South India: magnitude and clinical predictors. *J Infect* 2006 Jan;52(1):56-60.

2. Mahajan SK, Babu SN, Sharma D, Singh D, Kanga A, Kaushal SS. Scrub typhus presenting as acute abdomen. *Trop Doct* 2011 Jul;41(3):185-186.
3. Narvencar KP, Rodrigues S, Nevrekar RP, Dias L, Dias A, Vaz M, Gomes E. Scrub typhus in patients reporting with acute febrile illness at a tertiary health care institution in Goa. *Indian J Med Res* 2012 Dec;136(6):1020-1024.
4. Singh SP, Singh R, Ahmad N. A study of complications of scrub typhus in a tertiary health care institute of Uttarakhand, India. *Int J Res Med Sci* 2014 Feb;2(1):246-249.
5. Kundavaram APP, Das S, George VM. Scrub typhus presenting as an acute abdomen. *J Glob Infect Dis* 2014 Jan;6(1):17-18.
6. Anitharaj V, Stephen S, Pradeep J, Park S, Kim SH, Kim YJ, Kim EY, Kim YW. Serological diagnosis of acute scrub typhus in south India: evaluation of InBios scrub typhus detect IgM rapid test, and comparison with other serological tests. *J Clin Diag Res* 2016 Nov;10(11):DC07-DC10.
7. Kumar R, Thakur S, Bhawani R, Kanga A, Ranjan A. Clinical profile and complications of scrub typhus: hospital-based study in sub-Himalayan region. *J Assoc Physicians India* 2016 Dec;64(12):30-34.
8. Paris DH, Shelite TR, Day NP, Walker DH. Unresolved problems related to scrub typhus: a seriously neglected life threatening disease. *Am J Trop Med Hyg* 2013 Aug;89(2):301-307.
9. Yang CH, Young TG, Peng MY, Hsu GJ. Unusual presentation of acute abdomen in scrub typhus: a report of two cases. *Zhonghua Yi Xue Za Zhi (Taipei)* 1995 May;55(5):401-404.
10. Aung-Thu, Supanaranond W, Phumiratanaprapin W, Phonrat B, Chinprasatsak S, Ratanajaratroj N. Gastrointestinal manifestations of septic patients with scrub typhus in Maharat Nakhon Ratchasima Hospital. *Southeast Asian J Trop Med Public Health* 2004 Dec;35(4):845-851.
11. Hu ML, Liu WJ, Wu KL, Lu SN, Chiou SS, Kuo CH, Chuah SK, Wang JH, Hu TH, Chiu KW, et al. Abnormal liver function in scrub typhus. *Am J Trop Med Hyg* 2005 Oct;73(4):667-668.
12. Yi SY, Tae JH. Pancreatic abscess following scrub typhus associated with multiorgan failure. *World J Gastroenterol* 2007 Jul;13(25):3523-3525.
13. Lee CH, Lee JH, Yoon KJ, Hwang JH, Lee CS. Peritonitis in patients with scrub typhus. *Am J Trop Med Hyg* 2012 Jun;86(6):1046-1048.