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Scrub Typhus, An Emerging Cause Of Acute Encephalitis Syndrome

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Abstract

Scrub typhus is a rickettsial infection caused by the bite of the chigger of a mite *Orientia tsutsugamushi*. It is a re-emerging zoonosis and one of the major causes of Acute encephalitis syndrome.

Objective: The present study was undertaken to study the contribution of scrub typhus to the etiology of AES.

Material and method: A total of 729 serum samples were tested for scrub typhus IgM ELISA (Enzyme Linked Immunosorbent Assay) using commercially available kits from clinically suspected cases of AES from the year 2019-2022.

Results: Out of the 729 AES serum sample processed, 133 (18.24%) cases were found to be positive for scrub typhus IgM ELISA. Seropositivity amongst the males was found to be 54.89% (73/133) and 45.11% (60/133) among the females with no gender difference. Predominant age group affected was the 20-50 years age group. Majority of cases were reported during the months from May to November. Demographically maximum cases of scrub typhus were reported from Sonitpur (79) and Biswanath (19) district and area wise most cases of scrub typhus reported from Semi-rural 68 (22.37%), rural 35(14.52%), Urban 24(16.22%) and Tea-estate 6(16.67%). The most common symptom observed among the patients were fever 110 (82.71%), headache 39 (29.32%), change in mental status 30 (22.56%), seizure 18 (13.53%), rigor 17 (12.78%), unconsciousness 17 (12.78%) etc. No eschar was reported in our study.

Conclusions: Scrub typhus is one of the major causes of acute encephalitis syndrome in this part of Assam after Japanese encephalitis, so it should be included in routine differential diagnosis of fever of unknown origin along with Dengue, leptospirosis, Japanese encephalitis, malaria. This will help in timely diagnosis and treatment of the cases and reduces the disease burden.

Keywords: Scrub typhus, Enzyme linked Immunosorbent assay, seroprevalence, re-emerging, zoonosis, seropositivity

Introduction

Acute Encephalitis Syndrome (AES) has been defined by WHO as an acute-onset of fever with change in mental status including symptoms such as confusion, disorientation, coma or inability to talk and/or often with new onset of seizures (excluding simple febrile convulsion) in a person of any age at any time of the year [1].

AES is a major public health concern in India. Large outbreaks of AES affecting particularly children

occur annually in India post monsoon from July to November leading to considerable morbidity and mortality [2].

Viral infections are the most common causes of AES however it also encompasses several other illnesses; like malaria, enteric encephalopathy, tubercular meningitis, scrub typhus, leptospirosis, bacterial meningitis, etc [3].

For the cases of AES not explained by JE, aetiology could be scrub typhus, a hidden entity. The name typhus was derived from a Greek word meaning stupor; this name is justified by its CNS involvement. Aseptic meningitis is very commonly seen but other complication like cerebritis, myelitis and cerebral haemorrhage has been reported [4]. Although available medical literature mentions many of these complications, central nervous system involvement, in the form of acute encephalitis syndrome (AES), has seldom been highlighted [5,6].

Scrub typhus is caused by a small (0.3 to 0.5 by 0.8 to 1.5μm) intracellular Gram-negative bacterium *Orientia tsutsugamushi* of the family *Rickettsiaceae*. 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* [7]. The genus Rickettsia is divided into three different groups such as spotted fever, typhus and scrub typhus. The major symptoms of scrub typhus are fever, mental status changes, headache, eschar and lymphadenopathy. Scrub typhus is still a life threatening disease despite the availability of efficient treatment [8].

The World Health Organization has described scrub typhus as "probably the most under- diagnosed and under- reported febrile illness which requires hospitalization in the South east Asian region" [9]. Low index of suspicion among clinicians and lack of access to reliable testing methods for hospitals functioning at a community level and the hazards of handling these microorganisms aggravate the difficulties of diagnosis and treatment [10]. For India, the reported numbers are an underestimate due to lack of community-based data and non-availability of laboratory tests [11]. Rickettsial disease in India has been documented from Jammu and Kashmir, Himachal Pradesh, Uttaranchal, Rajasthan, Assam, West Bengal, Maharashtra, Kerala and Tamil Nadu [12].

Since 2005, the overall incidence of acute encephalitis syndrome in India has not decreased, with 10867–13 672 cases reported each year to the NVBDCP between 2014 and 2017 [13]. Among reported cases of acute encephalitis syndrome, only 14–18% are associated with JEV infection and the aetiology of most cases in India remain unknown [14]. Three states of India with the highest burden of acute encephalitis syndrome are Uttar Pradesh, Assam, and West Bengal, together these states accounted for 63–73% of acute encephalitis syndrome cases which are reported to the NVBDCP [13].

Scrub typhus is easily treatable when diagnosed correctly, though untreated cases have a case fatality rate of 30–35% [15]. The differential diagnosis of scrub typhus is a long list, because of its nonspecific clinical and laboratory features, combined with limited diagnostic facilities in developing countries like India. Therefore, the clinicians need a high index of suspicion for detecting this neglected and treatable disease in cases with AES at least in endemic areas [16,17,18].

Assam, a northeastern state in India, is recognized as an endemic zone for acute encephalitis syndrome (AES), especially that caused by Japanese encephalitis virus (JEV). However, the etiology of >50% of the AES cases in Assam remains unrecognized [19]. With this aim the present study was undertaken to study the contribution of scrub typhus to the etiology of AES.

Materials And Methods:

This study was conducted in the Viral Research and Diagnostic Laboratory (VRDL) of Department of Microbiology, Tezpur Medical College and Hospital (TMCH), Assam, over a period of from January 2019- December 2022. It was a retrospective study done among patients with suspected Acute Encephalitis Syndrome (AES).

A total of 729 serum sample collected during the study period was tested for scrub typhus by using commercial IgM ELISA kit. Serum samples collected from suspected cases of AES were sent to VRDL, laboratory for testing. Serology was done by using In Bios ST Detect IgM ELISA kit (InBios International,

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Seattle, WA, USA). A cut off optical density (OD) >0.5 was considered positive in IgM ELISA.

Statistical analysis: The data were analyzed by using MS-XL STAT (version 2010) and Chi square calculator software were P value less than 0.05 was considered significant.

Ethical statement: Approval received from Institutional Ethics Committee. Serum samples were collected after obtaining consent from the patients.

Results and Observations:

Out of the 729 AES serum sample processed, 133 (18.24%) cases were found to be positive for scrub typhus. Seropositivity amongst the males was found to be 54.89% (73/133) and 45.11% (60/133) among the females with a male to female ratio of 1.2:1. Gender wise both the groups were equally affected and there was no significance difference seen (Table 1 and 2). Majority of cases were reported during the months of May to November i, e. the monsoon and post monsoon period (Fig 3). Seropositivity was highest in the age group from 20-50 years. When chi-square test was conducted among age groups it showed statistically no significant result (Table 2).

Year- wise distribution of Scrub typhus positive cases showed that seropositivity was more during the years 2019 and 2022. In the year 2020 and 2021 testing was less due to Covid-19 pandemic hence the lesser number of seropositive cases (Table 1). Statistically analysis of year wise positive cases of scrub typhus showed the chi-square statistic at 11.9466 where the p-value was 0.007568 and the result was statistically significant as $p < 0.05$.

Demographically the district which reported maximum positive cases of scrub typhus was Sonitpur (79) followed by Biswanath (19), Nagaon (12) and Udalguri (11) (Table 3; Fig 2). Area wise scrub typhus seropositivity was mostly reported from Semi-rural 68 (22.37%), rural 35 (14.52%), Urban 24 (16.22%) and Tea-Estate 6 (16.67%) (Fig 4). Most common symptoms seen in positive patients was fever 110 (82.71%), headache 39 (29.32%), change in mental status 30 (22.56%), seizure 18 (13.53%), rigor 17 (12.78%), unconsciousness 17 (12.78%), vomiting 11 (8.27%), body pain 8 (6.02%), chills 6 (4.51%), jaundice 5 (3.76%), skin rash 3 (2.26%) and pain in abdomen 3 (2.26%) No eschar was reported in our study (Table 4).

Table 1: Year-wise distribution of Scrub typhus positive cases:

Year	Total No. of AES cases	Negative (%)	Positive (%)
2019	198	154 (77.78)	44 (22.22)
2020	60	52 (86.67)	8 (13.33)
2021	134	122 (91.04)	12 (8.96)
2022	337	268 (79.53)	69 (20.47)
TOTAL	**729**	**596 (81.76)**	**133 (18.24)**

Table 2: Demographic data

		All patient (n=729)	Positive patient n=133		Chi square ($\chi 2$)	P-value
			Male (n=73)	Female (n=60)		
Age group	**< 10**	107 (14.68%)	9 (14.29%)	7 (15.91%)	0.0537	0.816771
	11-20	107 (14.68%)	11 (20.37%)	9 (16.98%)	0.2022	0.652978

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(yrs)	**21-30**	167 (22.91%)	17 (19.77%)	15 (18.52%)	0.042	0.837613
	31-40	116 (15.91%)	9 (13.24%)	8 (16.67%)	0.2649	0.606783
	41-50	100 (13.72%)	12 (21.82%)	9 (20 %)	0.0493	0.824255
	51-60	73 (10.01%)	10 (26.32%)	8 (22.86%)	0.1173	0.731966
	>61	59 (8.09%)	5 (14.71%)	4 (16%)	0.0187	0.891334
Note: P-value is not significant at p<0.05						
Gender	**Male**	398 (54.60%)	73 (54.89%)		0.0056	0.940395
	Female	331 (45.40%)	60 (45.11%)			
Note: P-value is not significant at p<0.05						
Location	Rural	241 (33.06%)	16 (11.85 %)	19(17.92%)	**1.7639**	**0.184135**
	Tea Estate	36 (4.94%)	5(26.31 %)	1(5.88 %)	**2.6972**	**0.100524**
	Semi-rural	304 (41.70%)	38(23.17%)	30 (21.43%)	**0.132**	**0.716359**
	Urban	148 (20.30%)	14(17.5%)	10(14.71%)	**0.2112**	**0.64582**
Note: P-value is not significant at p<0.05						

Fig 1: Age and Gender wise distribution of scrub typhus.

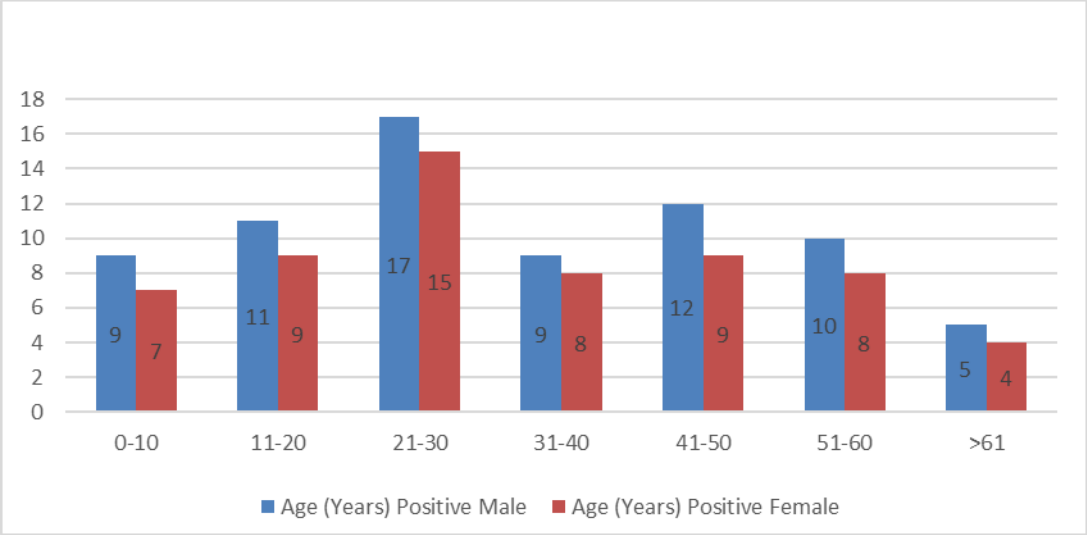

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Table 3: District wise distribution of the scrub typhus positive cases:

State (Assam)	Total case (n=729)	Total Positive cases (n= 133)
Districts		
Sonitpur	475	79
Biswanath	98	19
Jorhat	1	1
Karbi Anglong	2	0
Darrang	18	2
Lakhimpur	5	3
Udalguri	63	11
Nagaon	56	12
Baksha	1	0
Golaghat	1	0
Sate (Arunachal Pradesh)		
West Kameng	8	5
Bhalukpong	1	1

Fig 2: Map of Assam & Arunachal Pradesh with Scrub typhus positive cases (marked in red star).

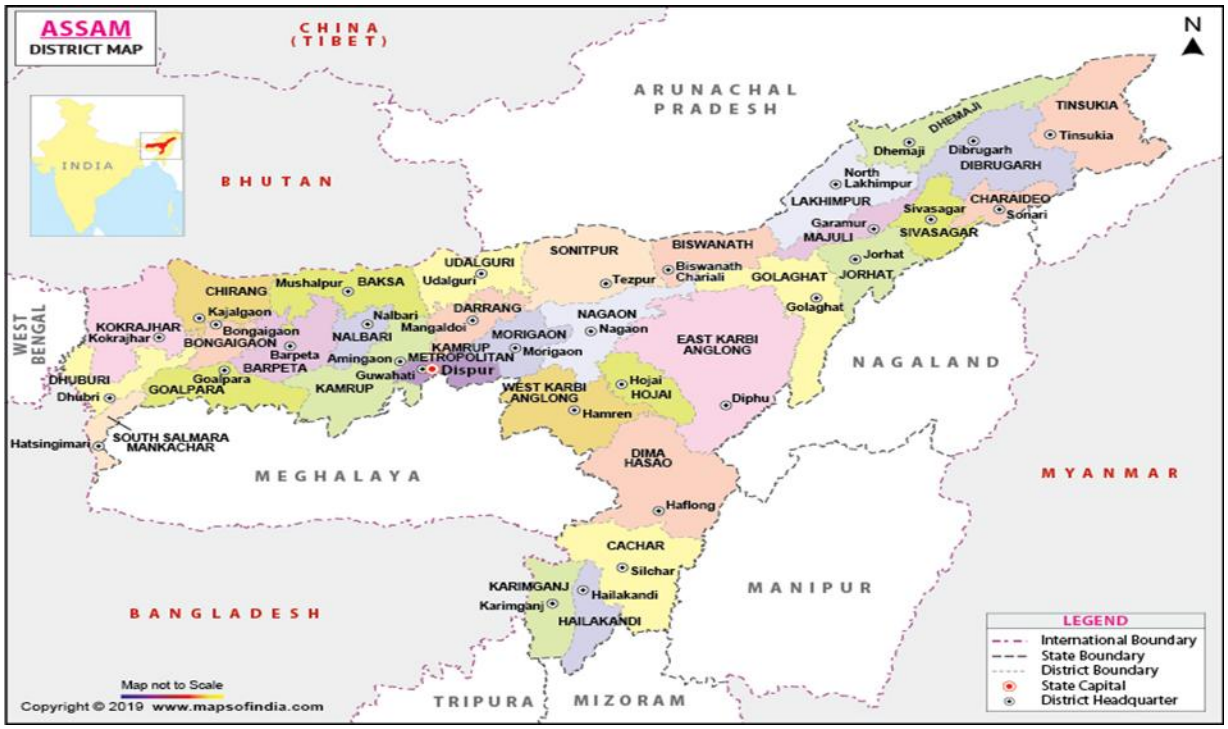

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Fig 3: Month wise distribution of Scrub Typhus positives.

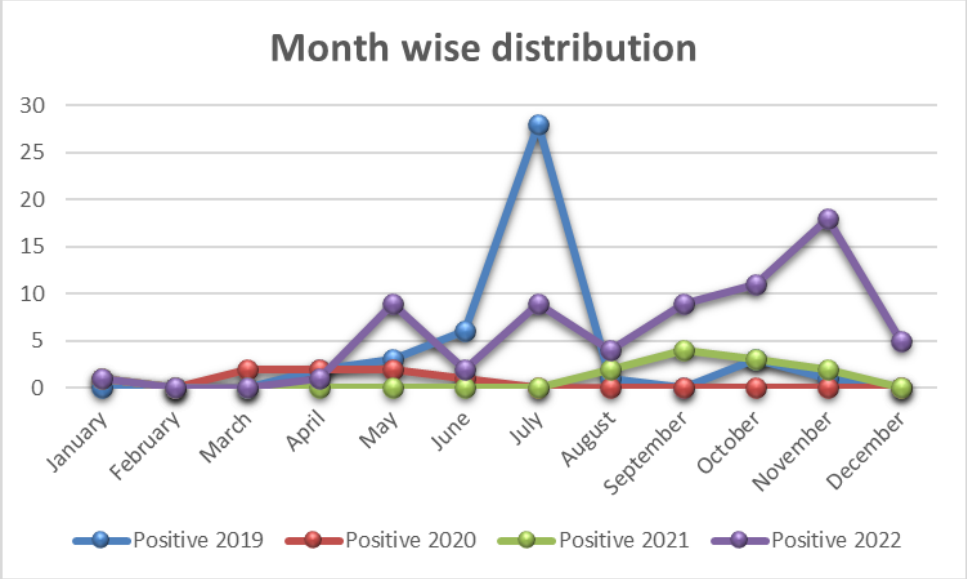

Table 4: Clinical symptoms of the scrub typhus positive cases:

Clinical symptoms	Total Positive (%) n=133
Fever	110 (82.71%)
Skin rash	3 (2.26%)
Seizures	18 (13.53%)
Vomiting	11 (8.27%)
Pain in abdomen	3 (2.26%)
Body pain	8 (6.02%)
Chills	6 (4.51%)
Headache	39 (29.32%)
Jaundice	5 (3.76%)
Change in mental status/ Neurological symptoms	30 (22.56%)
Rigor	17 (12.78%)
Diarrhoea	3 (2.26%)
Cough	3 (2.26%)
Retro-orbital pain	2 (1.50%)
Unconsciousness	17 (12.78%)

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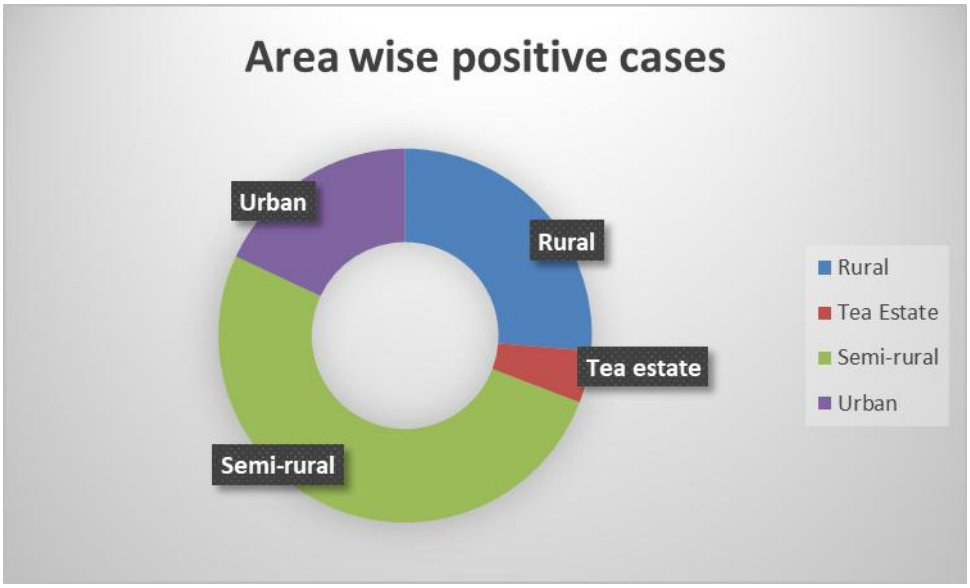
Fig 4: Area wise distribution of Scrub typhus positive cases.



Discussion:

Our study reported a seroprevalence of 18.24 % for scrub typhus which was found to be concordant with a study done by Khan *et al* in northeast India, where the sero-prevalence of scrub typhus was found to be 20.3% [16]. A sero-prevalence of 22.8% was reported in a study from Rajasthan by Takhar *et al*. in 2017 [20]. A seroprevalence of 19.75% of scrub typhus was reported from Uttar Pradesh by Tripathi *et al*. [21]. Mittal *et al*. also reported a seroprevalence rate of 20% in her study [22]. The male to female ratio in the present study was found to be 1.2:1; hence both the sexes were equally affected. Similar findings were reported by Khan *et al* where prevalence among the males and females was 55.7% and 44.2% respectively [16].

The most common age group to be affected in our study was the 20 to 50 years age group with no gender predominance which was quite similar to a study done by Lakshmi *et al* where they found that the cases were seen in 20 to 50 years age group with no gender predominance [23]. Bithu *et a*l. and Pathania *et al*. also reported that majority of the patients belonged to 21 to 40 years of age group affected by scrub typhus [24, 25]. The reason for this might be that the adults spent most of the time outdoors involved in various activities. Scrub typhus is a zoonotic as well as an occupational disease and can occur in all age groups, particularly adults involved in agriculture and forest occupations.

The predominant symptoms observed in our study were fever, headache, change in mental status, seizure, rigor, unconsciousness, vomiting, body pain etc with no record of eschar. These were concordant with Khan *et al.* where he reported common symptoms such as fever (100%), altered sensorium (100%), headache (67.3%), unconsciousness (55.7%), nausea (40.3%) and neck rigidity (0.9%), none had and record of eschar [16]. Mittal *et al*. also reported generalized symptoms of fever, headache and myalgia in all positive cases [22]. Paulraj *et al*. also reported common symptoms such as fever, myalgia, cough, headache [26].

Majority of the cases in our study were seen in the monsoon and post monsoon period i, e. from May to November. Mittal *et al*. also reported majority of the cases of scrub typhus (96%) in their study from monsoon and post monsoon months (July–October) [22]. Earlier studies have reported higher rates of scrub typhus in rainy season. Rainfall provides a favorable environment during monsoon and post-monsoon period for multiplication of mites, proliferation of shrubs and rodents population which is found to have statistically significant association with scrub typhus positivity. North eastern region has a subtropical climate which provides a conducive environment for its flourishment. Rainfall. Khan *et al* also reported highest number of scrub typhus cases during July-September [16]. This is because the mites are more active during or at the end of rainy

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season which coincides with the months of August to September in India [27, 28].

In the present study, seropositivity was more in the semi-rural and rural areas. Mittal *et al* also showed higher positivity in rural areas [22]. Most of the studies showed existence of mite habitats which are predominantly in rural and periphery of urban areas; as well as the existence of small mammals such as rodents in these areas. The rainy season is always favorable for the development of grassland where the proliferation of vectors takes place with an inevitable contact with the human host [29, 30].

Conclusion:

Active monitoring and surveillance along with timely diagnosis of scrub typhus cases can help in reducing the disease burden. Treatment of the disease is easy and affordable which depends on early diagnosis. Molecular tools and vector surveys can also be considered for further future study which will help in determining the disease dimension.

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