

Original Article

Orientia tsutsugamushi — A Leading Cause of AES in West Bengal, India

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Introduction : Acute Encephalitis Syndrome (AES) is a major public health problem in West Bengal, India including West Bengal. Japanese encephalitis virus accounts for < 10% of AES cases, while the etiology of remaining cases is still largely unknown. Scrub typhus is known to cause AES but no data exists regarding the proportion of AES cases due to scrub typhus in the state of West Bengal.

Aims : The study was aimed at identifying the proportion of *Orientia tsutsugamushi* infection among the patients presenting with AES and to analyze the associated demographic characteristics, clinical profile and laboratory parameters.

Methods and Material : Serum samples of 430 suspected AES cases were collected from different hospitals of Kolkata and MAC ELISA was performed at referral virology laboratory of School of Tropical Medicine, Kolkata over the period, April 2018 to March 2019.

Results : 133 (30.93%) out of 430 suspected AES cases were found reactive for scrub typhus IgM. Most of the cases were reported during the monsoon and post-monsoon period and under-15 children were commonly affected.

Conclusions : In this study 30.93% of AES cases were positive for scrub typhus. So it needs to be included in the differential diagnosis of AES in West Bengal.

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Key words : Acute Encephalitis Syndrome, *Orientia tsutsugamushi*, MAC ELISA, West Bengal.

Acute Encephalitis Syndrome (AES) is a major public health problem in West Bengal, India.

Traditionally Japanese encephalitis (JE) has been considered to be the most important cause of AES in our country¹. The first major outbreak of JE occurred in 1973 in Bankura and Burdwan Districts of West Bengal with subsequent outbreak occurred in 1976².

The State Health Department of Government of West Bengal undertook mass vaccination program against JE in several endemic districts using live attenuated JE vaccine SA-14-14-2³. As a result incidence of JE was grossly reduced in the Southern Districts of West Bengal from 22.76% in 2011 to 5% in 2012³. Although JE cases have declined AES cases are on the rise³. Hence focus has been shifted to identification of treatable, Non- JE etiologies of AES

Editor's Comment :

- Unlike Japanese Encephalitis, Scrub typhus Acute Encephalitis Syndrome is curable if diagnosed and treated early. So, Scrub typhus IgM ELISA should be considered mandatory in every patient presenting with AES to avoid undue complications and mortality.

cases. Scrub typhus caused by *O tsutsugamushi* is a re-emerging disease in India and is known to cause Acute Encephalitis Syndrome. Several studies on AES from Assam, Uttarpradesh and Bihar revealed that scrub typhus is a major cause of AES in those states⁴⁻⁶. No data exists regarding the proportion of scrub typhus AES cases in West Bengal. Hence, this study was undertaken to investigate the etiology of *O tsutsugamushi* in AES cases and to determine its associated epidemiological, clinical and laboratory parameters.

MATERIALS AND METHODS

430 suspected AES cases of all age groups, admitted in different hospitals of West Bengal, whose serum samples were referred to the Virology Unit of School of Tropical Medicine, Kolkata during the period April, 2018 to March, 2019 were included in the study.

Hemolysed serum samples, inadequate samples, improperly labelled samples and samples where proper clinical information was lacking were excluded from the study.

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Serum samples were stored at 4°C in the refrigerator and tested within 24-48 hours. The study protocol was reviewed and approved by the Institutional Clinical Research and Ethics Committee.

IgM antibody capture (MAC) ELISA was performed by In Bios international Inc Scrub Typhus Detect™ IgM ELISA system. The samples were tested strictly following the manufacturer's protocol. The cut-off OD value in India is 0.5⁷.

OBSERVATIONS

During the one year study period (April 2018 to March, 2019) total 430 serum samples were selected as per the inclusion criteria among which 133 (30.93%) samples tested positive for scrub typhus IgM with slight female preponderance (Female- 68 ie, 51.12%).

Though all age groups were found to be affected, highest no of cases [90 cases out of 133 seropositive ie, 67.67%] were reported from under-15 age group.

Month wise distribution showed that the maximum number of cases of scrub typhus AES were found during monsoon and post monsoon period (August, September, October, November) while least or no cases were detected during the month of January, February and March (Fig 1).

As the study was conducted in Kolkata, most of the positive cases were from the adjoining rural Districts like South 24 Parganas, North 24 Parganas and Howrah. Few cases were reported from the metropolitan City of Kolkata.

Most common symptoms were fever (100%), headache (82.70%), bodyache/myalgia (78.19%) followed by convulsion (77.44%), altered sensorium (74.44%), nausea and vomiting (50.38%), lymphadenopathy (48.12%), skin rash (36.09%) and cough with/without shortness of breathing (32.33%). Both convulsion and altered sensorium was noticed among 70 (52.63%) patients (Table 1).

92(69.17%) out of 133 scrub typhus IgM seropositive AES cases had H/O fever for more than 7 days

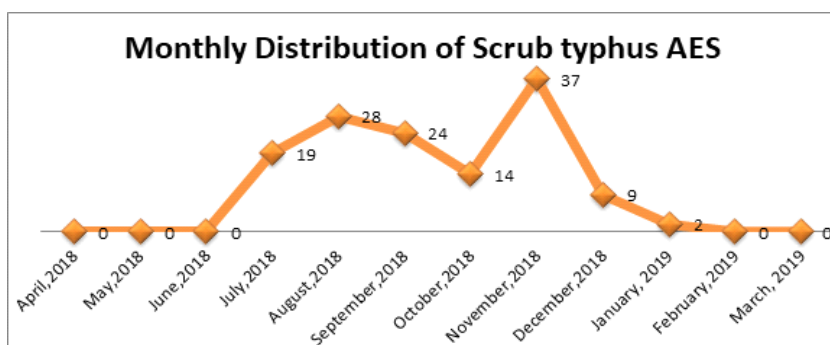


Fig 1 — Monthly distribution of scrub typhus AES cases

Table 1 — Age distribution of scrub typhus AES cases (n=133)

Age- group	Reactive cases (n=133)	Percentage (%)
0 - 15	90	67.67
16-30	22	16.54
31 - 45	9	6.77
46 - 60	4	3.00
>60	8	6.02

duration which indicates that AES develops more in the later course of the disease when fever remains undiagnosed for prolonged periods. The longest duration of fever recorded was 2 months.

Characteristic eschar was detected only in 27.07% cases while 25.56% patients presented with positive meningeal signs. Hemiparesis was noticed in two patients (Table 2).

Table 2 — Signs and symptoms of scrub typhus AES cases

Signs and symptoms	No of cases	Percentage
Fever	133	100.00
Headache	110	82.70
Bodyache / Myalgia	104	78.19
Convulsion	103	77.44
Altered Sensorium	99	74.44
Both Convulsion & Altered Sensorium	70	52.63
Nausea & vomiting	67	50.38
Lymphadenopathy	64	48.12
Skin rash	48	36.09
Cough & respiratory distress	43	32.33
Eschar	36	27.07
Abdominal pain	23	17.29
Meningeal signs	34	25.56
Hemiparesis	2	1.50
Pedal edema	1	0.75

Out of the 133 scrub typhus IgM reactive cases 68 (51.12%) had haemoglobin levels (9-12) gm/dl whereas 57(42.86%) cases had hemoglobin levels less than 9gm/dl. Leucocyte count was found to be in the normal range (4000-11000/cmm) in 56 (42.11%) cases. About 57.14% cases presented with leucocytosis (>11000/cmm) and most of them had a history of fever of >7 days duration. Thrombocytopenia (50,000—100000/cmm) was quite a common feature and detected in 31.58% but levels below 50,000 was rarely observed. Seum

bilirubin level was elevated in 65 (48.86%) cases but rarely exceeded 3 mg%. Raised serum creatinine level (>1.5mg%) was noticed among 20 (15.04%) cases (Table 3).

Laboratory parameters	No of cases	Percentage
Hemoglobin levels :		
<9 gm%	57	42.86
9-12 gm%	68	51.12
12-14gm%	8	6.02
Leukocyte count :		
< 4000	1	0.75
4000-11000	56	42.11
>11000	76	57.14
Thrombocyte count :		
Less than 50000/cmm	3	2.26
50001-100000/cmm	42	31.58
100001-150000/cmm	25	18.80
>150000/cmm	63	47.36
Serum bilirubin :		
1-3mg%	59	44.36
>3mg%	6	4.50
Liver enzymes :		
SGPT> 80 IU/L	56	42.11
SGOT> 80 IU/L	53	39.85
Serum Creatinine :		
> 1.5 mg%	20	15.04

Elevated INR (> 2) was found in 14(10.53%) cases.

Majority of patients (72.2%) had CSF cell counts >5 cells/cmm. Among them 56.4% patients had counts in the range of (5 – 100) /cmm, while 15.8% had counts more than 100/cmm. The highest count observed was 560cells/cmm. 27.8 % patients had CSF cell counts in the normal range (Table 4).

The biochemical parameters of Cerebrospinal Fluid (CSF) showed that majority of the cases (42.86%) had glucose levels in the normal range (50-80 mg%), 32.33% had CSF glucose level less than 50mg% and 24.81% had more than 80mg%. Micro Protein level is generally raised in scrub typhus encephalitis and in our study, 72.18% of the cases had more than 60mg%. 23.31% of the cases were in the range of 15-60mg%. 4.51% of the cases had levels below 15mg% (Table 4).

25 out of the 133 scrub typhus AES cases had pathological brain imaging (MRI) findings. Diffuse cerebral edema was the most common finding and was noticed among 11 ie, 44% cases. Less common

CSF cell count	No of cases (n=133)	Percentage (%)
< 5 cells per cmm	37	27.8
5-100 cells per cmm	75	56.4
>100 cells per cmm	21	15.8
CSF Glucose levels		
<50 mg/dl	43	32.33
50-80mg/dl	57	42.86
>80mg/dl	33	24.81
CSF Micro Protein		
<15mg/dl	6	4.51
15 - 60 mg/dl	31	23.31
> 60mg/dl	96	72.18

pathological findings were progressive multifocal leucoencephalopathy, bilateral increased signal intensities in lateral ventricles and mild cerebral atrophy (2 patients each ie, 8%) Other important findings were hyper-intense signals in both parietal regions, ventricles, fronto-parietal region and on flair sequences in thalami.

DISCUSSION

Acute encephalitis syndrome is characterized by rapid onset of febrile illness associated with convulsion, altered sensorium and focal neurological deficits such as aphasia, hemiparesis, involuntary movements, ataxia or cranial nerve palsies⁸.

It is a major seasonal public health problem in many states of India including Bihar (mainly in Muzaffarpur and its adjacent districts)⁹. AES is generally caused by different neurotropic viruses. But at present CNS involvement is being reported among a substantial number of scrub typhus patients from Dehradun (Uttarakhand), Vellore (Tamil Nadu), Puducherry and Lucknow (Uttar Pradesh)^{10,11}.

In our present study many AES cases which were positive for scrub typhus IgM were detected from various districts of West Bengal during the period April 2018 to March 2019. In our study, 30.93% AES cases had seropositivity for scrub typhus IgM ELISA, which almost matched with the study conducted at Chennai, Tamil Nadu by Kar *et al* in 2014¹² where seropositivity was 30%. Both the sexes were almost equally affected (Male-65, Female-68) and majority of cases were reported from the rural adjoining districts of Kolkata, namely South and North 24 Parganas, Howrah, Nadia and Murshidabad.

Scrub typhus is quite common among children and

most of them belong to under-fifteen age group. In our study 90 out of 133 ie, 67.67% of the seropositive cases were below 15 years of age.

Most of the cases were reported during the months of July to December. Such a seasonal upsurge of cases has been reported earlier in other studies also¹³. This is because of two factors. Firstly the higher incidence of scrub typhus in autumn and winter may be due to increased human activities in the agricultural fields and bushes during these periods. Secondly, in the immediate post-monsoon period (September to early January), there is growth of secondary scrub vegetation, which is the habitat for trombiculid mites (mite islands)¹⁴.

Fever is the hallmark of scrub typhus infection with various non-specific signs and symptoms. In our present study 100% patients presented with fever and it lasted for more than 7 days in most (69.17%) cases. Whereas longest duration of fever in this study was found to be two months, one patient presented with H/O only one day febrile illness before the onset of AES. Kar et al reported the onset of AES which was preceded by fever of 3 days only¹².

The other clinical features were headache (82.7%), bodyache/myalgia (78.19%), convulsions (77.44%), altered sensorium (74.44%), nausea and vomiting (50.38%), lymphadenopathy (48.12%), skin rash (36.09%), cough with/without respiratory distress (32.33%), eschar (27.07%), meningeal signs (25.56%), abdominal pain (17.29%), hemiparesis (1.50%) and pedal edema (0.75%).

In our study, 74.44% patients presented with altered sensorium and 50.38% had history of nausea and vomiting. Meningeal signs like nuchal (neck) rigidity with or without Kernig's sign was present in 34(25.56%) cases which was much less than the findings of Jamil et al (76.92%)¹⁵.

Eschar, the pathognomonic feature of scrub typhus, was detected in 27.07% of patients that closely correlates with the study conducted in North East India by M D Jamil et al at Neigrihms, Shillong where the detection rate was 30.76%¹⁵. On the other hand, UK Mishra et al¹⁶ found eschar among 46% scrub typhus cases. Lymphadenopathy, another important sign of scrub typhus, was noted in 64(48.12%) patients that matched with the study of Jamil et al ie, 46.15%¹⁵.

Respiratory symptoms were common non-neurological findings in complicated scrub typhus infection. In our study 43 (32.33%) patients presented with cough with/without respiratory distress which is almost thrice the findings of Stalin Viswanathan et al¹⁷.

Though both leucocytosis (>11000 cells/mm³) and

leucopenia (<4000 cells/mm³) could be seen in scrub typhus, leucocytosis (57.14%) was the predominant finding in our study. Similar finding was noticed in the study of Chakraborti et al¹³ where 48.31% had elevated leucocyte count. Normal leucocyte count was noted in 56 (42.11%) patients while only one patient presented with leucopenia (0.75%). The thrombocyte count < 150000/cmm was found in 52.64% of cases which nearly matched with the study conducted by Dr Murali Krishnan et al¹⁸. Only 3(2.26%) patients had thrombocyte count less than 50000/cmm.

Azotemia in the form of raised serum creatinine level (>1.5mg%) was found in 20 (15.04%) cases. Kidney involvement in the background of scrub typhus AES had been reported in earlier studies.

42.11% and 39.85% patients were reported to have high serum Serum Glutamic Pyruvic Transaminase (SGPT) and Serum Glutamic Oxaloacetic Transaminase (SGOT) level respectively. The highest elevation for SGPT was 1250 IU/ml and that of SGOT was 840 IU/ml.

Majority (72.2%) of scrub typhus AES patients had CSF cell count >5 cells/cmm. Among them 56.4% patients had count in the range of (5-100) /cmm, while 21 patients (15.8%) had count more than 100/cmm. Mittal et al¹⁹ conducted a study at Gorakhpur, Uttar Pradesh which detected 95.3% patients had cell count ranged from (5 - 100)/cmm and only 2 patients had CSF cell count >100/cmm. The aforesaid study differed from our study in terms of the nature of the study as well as the age groups of the patients included. While the study conducted by Mittal et al¹⁹ was a case control study exclusively devoted to paediatric patients, ours was an observational cross-sectional study involving different age groups.

The biochemical parameters of CSF showed that majority of the cases (42.86%) had glucose levels in the normal range, ie, 50-80 mg/dl, while 32.33% of the cases had CSF glucose level less than 50 mg/dl and 24.81% cases had more than 80mg/dl. High CSF glucose level might be due to intravenous fluid administration.

Microprotein levels are found to be raised in scrub typhus encephalitis. In our study, 72.18% cases had more than 60mg/dl and the highest level noted was 680 mg/dl. 23.31% had CSF microprotein level in the range of 15-60mg/dl while 4.51% had level <15mg/dl²⁰.

25 out of 133 scrub seropositive cases were advised for MRI Brain and 11 of them had diffuse cerebral edema, a common finding in scrub encephalopathy²⁰.

Two cases each showed progressive multifocal

leucoencealopathy, bilateral increased signal intensities in lateral ventricles and mild cerebral atrophy. Hyperintensity signals were also found in both parietal regions, in both ventricles, in fronto-parietal region and on flair sequences in thalami. Hypodense lesions were seen in the PCA territory and in left parietal region which were consistent with the findings of previous studies.

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Conflict of Interest : None

REFERENCES

- Jain A, Jain P, Jain B — Unveiling the Undiscovered: Etiology of Acute Encephalitis Syndrome in North India. *J Neuroinfect Dis* 2015; **6**: e101. doi:10.4172/2314-7326.1000e101
- Saxena V, Dhole TN — Preventive strategies for frequent outbreaks of Japanese encephalitis in Northern India. *J Biosci* 2008; **33(4)**: 505-14.
- Bandyopadhyay B, Bhattacharya I, Adhikary S, Mondal S, Konar J, Dawar N, *et al* — Incidence of Japanese Encephalitis among Acute Encephalitis Cases in West Bengal, India. *Biomed Research International*, vol.2013, Article ID 896749, 5 pages, 2013. <http://doi.org/10.1155/2013/896749>
- Mittal M, Thangaraj J, Rose W, Verghese VP, Kumar C, Mittal M, *et al* — Scrub Typhus as a Cause of Acute Encephalitis Syndrome, Gorakhpur, Uttar Pradesh, India. *Emerging infectious diseases* 2017; **23(8)**: 1414-6. <https://doi.org/10.3201/eid2308.170025>
- Jain P, Prakash S, Tripathi PK, Chauhan A, Gupta S, Sharma U, *et al* — Emergence of Orientia tsutsugamushi as an important cause of Acute Encephalitis Syndrome in India. *PLoS Negl Trop Dis* 2018; **12(3)**: e0006346. <https://doi.org/10.1371/journal.pntd>.
- Khan SA, Bora T, Laskar B, Khan AM, Dutta P — Scrub Typhus Leading to Acute Encephalitis Syndrome, Assam, India. *Emerg Infect Dis* 2017; **23(1)**: 148-50. doi: 10.3201/eid2301.161038. Epub 2017 Jan 15. PMID: 27875108; PMCID: PMC5176214.
- Sengupta M, Anandan S, Daniel D, Prakash JA — Scrub Typhus Seroprevalence in Healthy Indian Population. *J Clin Diagn Res* 2015; **9(10)**: DM01-2. doi: 10.7860/JCDR/2015/14708.6623. Epub 2015 Oct 1. PMID: 26557523; PMCID: PMC4625242.
- Hooper HA, Samuels MA — Viral infections of the nervous system, chronic meningitis, and prion diseases. In: Adam and Victor's Principles of Neurology. 9th ed. New Delhi: McGraw Hill Medical; 2009. p. 717
- Dinesh DS, Pandey K, Das VNR, Topno RK, Kesari S, V Kumar, *et al* — Possible factors causing Acute Encephalitis Syndrome outbreak in Bihar, India. *International Journal of Current Microbiology and Applied Sciences* ISSN: 2319-7706 Vol 2 No 12 (2013) pp. 531-538. <http://www.ijcmas.com>
- Peter JV, Sudarsan TI, Prakash JA, Varghese GM — Severe scrub typhus infection: Clinical features, diagnostic challenges and management. *World J Crit Care Med* 2015; **4(3)**: 244-50. doi: 10.5492/wjccm.v4.i3.244. PMID: 26261776; PMCID: PMC4524821.
- Kumar Bhat N, Dhar M, Mittal G, Shirazi N, Rawat A, Prakash Kalra B, *et al* — Scrub typhus in children at a tertiary hospital in north India: clinical profile and complications. *Iran J Pediatr* 2014; **24(4)**: 387-92. Epub 2014 Jul 19. PMID: 25755859; PMCID: PMC4339561.
- Kar A, Dhanaraj M, Dedeepiya D, Harikrishna K — Acute encephalitis syndrome following scrub typhus infection. *Indian J Crit Care Med* 2014; **18(7)**: 453-5. doi: 10.4103/0972-5229.136074. PMID: 25097358; PMCID: PMC4118511.
- Chakraborti R, Bandyopadhyay B, Goswami RP, Paul DK, Adhikari S, Sardar S, *et al* — Epidemiology, clinical profile and laboratory parameters of scrub typhus cases in West Bengal. *Int J Med Microbiol Trop Dis* 2019; **5(3)**:
- Tilak R — Ticks and Mites. In: Bhalwar RV, editor. Textbook on public health and community medicine, 1st ed. Pune; Department of Community Medicine, AFMC, Pune; 2009, P955-9
- Jamil MD, Hussain M, Lyngdoh M, Sharma S, Barman B, Bhattacharya PK — Scrub typhus meningoencephalitis, a diagnostic challenge for clinicians: A hospital based study from North-East India. *J Neurosci Rural Pract* 2015; **6(4)**: 488-93. doi: 10.4103/0976-3147.169769. PMID: 26752890; PMCID: PMC4692003.
- Misra UK, Kalita J, Mishra VN, Kesari A, Mittal B. A Clinical — Magnetic Resonance Imaging, and Survival Motor Neuron Gene Deletion Study of Hirayama Disease. *Arch Neurol* 2005; **62(1)**: 120-3. doi:10.1001/archneur.62.1.120
- Viswanathan S, Muthu V, Iqbal N, Remalayam B, George T — Scrub Typhus Meningitis in South India — A Retrospective Study. *PLoS ONE* 2013; **8(6)**: e66595. doi:10.1371/journal.pone.0066595
- Krishnan MP, Padarathi SC — Clinical, Laboratory Profile and outcome of Scrub typhus in children. *IOSR Journal OF Dental and Medical Sciences (IOSR-JDMS)*. e-ISSN:2279-0853, p-ISSN:2279-0861. Volume 15, Issue 3 Ver. X (February 2016), PP 30-32 www.iosrjournals.org
- Mittal M, Thangaraj JWV, Rose W — Scrub Typhus as a Cause of Acute Encephalitis Syndrome, Gorakhpur, Uttar Pradesh, India. *Emerging Infectious Diseases* 2017; **23(8)**: 1414-6. DOI: 10.3201/eid2308.170025.
- Vargese GM, Mathew A, Kumar S, Abraham OC, Trowbridge P, Mathai E — Differential diagnosis of scrub typhus meningitis from bacterial meningitis using clinical and laboratory features. *Neurol India* 2013; **61**: 17-20.