Original Article

Scrub typhus Meningoencephalitis in Children from a Tertiary Care Centre, Uttarakhand, India

Ritu Rakholia, Vinita Rawat*, Preeti Chaturvedi

Department of Microbiology, Government Medical College, Haldwani, Nainital, Uttarakhand, India

Corresponding author:
Vinita Rawat,
Department of Microbiology,
Government Medical College,
Haldwani, Nainital, Uttarakhand,
India,
Tel: 918954630885;
E-mail: drvinitarawat31@rediffmail.com

Abstract

Meningoencephalitis, a potentially fatal complication of scrub typhus is known to occur but has not been well documented in children. **Objectives:** To document the epidemiological, clinical and laboratory parameters of scrub typhus meningoencephalitis in children to help the clinician in clinching the diagnosis of scrub typhus infection from Kumaon region. **Materials and methods:** This is a prospective one year study (June 2015 to July 2016) in which epidemiological, clinical, laboratory profile and detail of cerebrospinal fluid (CSF) analysis and outcome of the scrub typhus meningoencephalitis cases were recorded. Diagnosis of scrub typhus was confirmed by positive IgM Enzyme Linked Immune Sorbent assay (ELISA), IgM Immuno Fluorescence Assay (IFA) and/ or by nested polymerase chain reaction (PCR) **Results:** A total of 13 children (<18years) presenting with fever, headache and neck rigidity were confirmed as scrub typhus meningoencephalitis during post monsoon season. Myalgia, facial suffusion, seizures, altered sensorium and eschar were found in 84%, 46%, 23%, 30.1% and 15.4% of patients, respectively. Renal, respiratory and gastrointestinal (GIT) involvements were observed in 46%, 61.54%, and 75% of patients respectively. Splenomegaly was seen in 7(53.8%) of patients. Thrombocytopenia (92.3%) and raised transaminase (100%) along with CSF lymphocytosis (100%) were consistent findings. Mean CSF protein, cells and sugar were 80 mg/dl, 27cells/cumm and 63.8 mg/dl respectively. All patients had received azithromycin or doxycyclineand outcome was favorable. **Conclusion:** In hilly areas scrub typhus should be considered as one of the differential diagnosis in children with suspected aseptic meningoencephalitis, especially when accompanied with raised transaminase level and thrombocytopenia.

Keywords: Scrub typhus; Meningoencephalitis; Azithromycin

Introduction

Scrub Typhus is a zoonotic disease caused by bacteria *Orientia tsutsugamushi*, an obligate intracellular gram negative bacterium, transmitted through bite of infected chigger phase of the trombuculid mite. This disease is seen classically in tsutsugamushi triangle. It is presently seen in increasing numbers in various South Indian states, North- East and of late from North Indian states, and Himalayan foothills –Himachal Pradesh and Uttarakhand. [1,2]

In endemic areas, scrub typhus is becoming an increasing cause of meningoencephalitis/ meningitis. However, in the absence of rash or eschar it can remain undetected and wrongly diagnosed. [3] Scrub typhus meningoencephalitis has not been reported earlier from Kumaon region of Uttarakhand, though studies from Garhwal and Himachal Pradesh do show increasing presence of scrub typhus. [4,5] Studies on Scrub meningoencephalitis in adults have been reported [6-9] but it has been poorly documented in children. [4] This study seeks to document the epidemiological, clinical, laboratory parameters and outcome of confirmed cases of Scrub meningitis/ meningoencephalitis in pediatric population from Kumaon region of Uttarakhand., thus helping to provide clinical and laboratory algorithm for this underreported and under suspected disease from this region.

Materials and Methods

This study was conducted in Dr. Sushila Tiwari Government Hospital affiliated to Government Medical College Haldwani which is a tertiary care hospital catering to hilly areas of Kumaon in Uttarakhand and adjoining areas of Uttar Pradesh and Nepal. We did a prospective study of all children (below 18 years) admitted in the hospital with scrub typhus meningoencephalitis between June 2015 to July 2016.

Diagnosis of scrub typhus was confirmed by IgM ELISA, IgM-IFA and or by nested PCR targeting 47 kDa antigen. IgM antibodies in serum were detected by IgM ELISA (Scrub Typhus Detect IgM ELISA, InBios USA), For IgM-IFA, slides (OTM-120) were procured from Fuller Laboratories (Fullerton, California, USA). These tests were performed as per manufacturer's instructions. Samples with optical density > 0.5 for ELISA and titer >256 for IFA were considered positive.

The Conventional PCR targeting the 47-kDa gene was performed using forward primer (5'TCCTTTCGGTTTAAGAGGAACA3') and reverse primer (5'GCATTCAACTGCTTCAAGTACA3'). Nested PCR for the 47-kDa gene was performed using the first PCR (Conventional PCR) product as the template DNA and primer (forward primer

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5'AACTGATTTTATTCAACTAATGCTGCT3') and reverse primer (5'TATGCCTGAGATAGATACCTGAATCGA3'). Amplified PCR products (118bp) were detected by 2% agarose gel electrophoresis. One PCR product was outsourced for sequencing from DNA Data Base Japan (DDBJ). Accession no assigned to our sequence was LC169590.

Data was collected regarding patient demographics, risk factors (exposure to rodent, bushes, agricultural fields) clinical features, laboratory investigations, complications, treatment and outcome in a predesigned data abstraction form. Meningitis or meningoencephalitis was defined by the presence of headache, neck rigidity, with either altered sensorium or focal neurological signs and CSF pleocytosis (Cells>5/cumm). Malaria, Dengue, Enteric fever and Leptospirosis were excluded by Malaria antigen test (Advantage Mal Card, J. Mitra and Co. PVT,), dengue NS-1 ELISA (Pan Bio) and IgM Mac ELISA, Widal test (Span diagnostics) and IgM Elisa for Leptospirosis (Scimedex) respectively as these illnesses share same clinical and epidemiological features.

Results

A total of 13 cases were confirmed as scrub typhus meningoencephalitis by IgM ELISA and IgM IFA both. Out of these 13 cases, 8 were also positive by nested PCR (61.54%). All patients were admitted in the post monsoon season in months of September 2015 to November 2015. Most patients were from cooler high altitude districts of Almora and Nainital as compared to warmer low altitude districts. Mean age of patients was 12.30 years and there was a female preponderance (69.2%). All patients belonged to rural and semi-urban areas with exposure to scrub vegetation (61.5%) or rodents (92.3%). Majority of the patients belonged to agricultural families. [Table 1].

Table 1: Socio-demographic characteristics and risk factors of children with scrub meningoencephalitis.

Age (years)	Male (n=4)	Female (n=9)	Total (n=13)
≤ 5 yrs	1	0	1
6 ≤ 10	0	0	0
11 ≤ 18	3	9	12
Districts			
Nainital	2	2	4
Almora	1	6	7
Udham Singh Nagar	1	1	2
Risk factors			
Rodent exposure	4	8	12
Bushes around house	2	6	8
Farming	3	8	11

Clinical trial of fever, headache and meningeal signs was present in all patients. Mean duration of fever before presentation was 7-9 days. Along with clinical trial, majority had a toxic look along with severe myalgia (84.2%) and facial suffusion (46.2%). Eschar earlier considered diagnostic was seen in only two patients (15.4%). Other common presenting complaints were nausea and vomiting (46%, and 76.9%), altered sensorium (30.8%), seizures (23%). Spleno-hepatomegaly was present in most of the patients. [Table 2].

Mean hemoglobin was 9.8 g/dl, mean TLC was 6500/cumm and mean platelet count was 85 000/cumm. A platelet count less than one lakh/cumm was seen in 92.3%. All children had abnormal CSF findings with mean CSF protein, sugar, cell count of 80 mg/dl, 63.88 mg/dl and 27 cells/mm^3 respectively and CSF lymphocytosis was seen in all cases. Hepatic involvement in the form of raised liver enzymes (SGPT, SGOT beyond the normal range SGPT >35 U/L and SGOT >40 U/L) was seen in 100% while elevated serum bilirubin levels (>2 mg/dl) was seen in 69.3%. Pulmonary involvement was predominantly in the form of cough (61.54%), pneumonia (46%) and ARDS needing ventilator support was seen only in 7.6% of cases. Renal dysfunction in the form of elevated blood urea, creatinine was seen in 15.3%. No child needed dialysis. Cardiovascular involvement in the form of shock needing inotropic support was seen only in one child with ARDS. One patient was found to have co-infection with dengue.

Table 2: Clinical signs and symptoms of children with scrub meningoencephalitis.

	Clinical signs/symptoms	Male	Female	Total no. (%)
	General			
	Fever	4	9	13 (100)
	Eschar	1	1	2 (15.38)
1	Myalgia	3	8	11 (84.16)
	Sore throat	2	6	8 (61.54)
	Conjunctivital suffusion	3	3	6 (46.15)
	Facial flushing	3	3	6 (46.15)
	CNS Features			
	Headache	4	9	13 (100)
	Neck rigidity	4	9	13 (100)
2	Seizures	2	1	3 (23.08)
	Altered sensorium	2	2	4 (30.77)
	Delirium	2	0	2 (15.38)
	Stupor	2	0	1 (7.69)
	Coma	1	0	1 (7.69)
	Renal symptoms-			
3	Oliguria	2	4	6 (46.15)
	Uremia	1	0	1 (7.67)
	Edema			
	Respiratory symptoms			
	Respiratory failure	1	0	1 (7.67)
4	Cough	2	6	8 (61.54)
	Pneumonia	3	3	6 (46.15)
	Chest pain	1	1	2 (15.38)
	Pharyngitis	1	3	4 (30.77)
	Cardiovascular symptoms			
5	**Shock**	1	0	1 (7.67)
	Shock			
	Gastro intestinal Symptoms			
	Nausea		4	6 (46.15)
	vomiting	2 4	6	10 (76.92)
6	Diarrhea	0 1	1	1 (7.67)
	Gastro intestinal bleeding	2	0	1 (7.67)
	Hepatosplenomegaly	2	0	2 (15.38)
	Hepatomegaly	3	2	4 (30.77)
	Splenomegaly		4	7 (53.84)

Out of 13 children, 8 were treated with oral or IV azithromycin (10 mg/kg of body weight) and doxycycline (2.2 mg/kg body weight) was used in 6 children for a total duration of seven days. Younger children less than 8 years or those with hepato-renal involvement were started on azithromycin and older children on doxycycline. All children were given supportive management and intravenous ceftriaxone 100 mg/kg initially to cover for septic meningitisas per protocol which was stopped after positive confirmation of scrub typhus.

All patients showed rapid response to azithromycin as well as

Table 3: Laboratory parameters in children with scrub meningoencephalitis.

Laboratory test and their normal range	Range in patients With scrub meningitis	Mean	% children with abnormal value n=13 (%)
Hemoglobin (>11 g/dl)	6.8-12.4	9.28	↓in 9 (69.23)
TLC (4000-110000/mm^3)	3200-25000	6500	↑in 2 (15.38)
Platelet count (1.5-4 lakhs/mm^3)	32000—2.2 lakhs	85,500	< 1 lac/mm^3 in 12 (92.3)
SGPT (<35 IU/L)	50-287	123.38	↑ in 13 (100)
SGOT (<400 IU/L)	49-152	116.7	↑in13 (100)
Serum bilirubin (<1.1 mg/dl)	1.5-2.6	2.5	↑in 9 (69.23)
Urea (<40 mg/dl)	19-74	35	↑in 2 (15.38)
Sodium 135-145 meq/l	128-145	138	↓in 2 (15.38)
Potassium (3.5-5.5 meq/l)	3-4.8	4.0	↓in 1 (7.69)
CSF (<5 cell/mm^3)	10-85 cells	27	↑13 (100)
CSF protein (20-45 mg/dl)	40-191	80.18	↑13 (100)
CSF cell differential (%)	P 8-30, L 70-92	P-15, L-85	↑13 (100) lymphocytosis
CSF sugar (>mg/dl or 75% of serum sugar)	40-78	63.88	↓in 2 (15.4)

doxycycline in the form of defervescence of fever by 48-72 hours, improvement in neurological status and normalization of liver function and kidney function tests and platelet counts. Complete recovery was seen by 5-7 days. No mortality or neurodeficit was documented in any child.

Discussion

Scrub typhus was a dreaded disease in the pre antibiotic era. Of late it has been increasingly reported from various parts of India from Himachal Pradesh [10] and Uttarakhand [5] in the north to Andhra, Vellore, Chennai, Salem and Kerala [7-9] in the South. Studies from children in Thailand [11] to Srilanka [12] have shown that CNS involvement in the form of meningoencephalitis may occur. Earlier such involvement was reported as a rarity as case reports, now however more case as series are being reported from adults [6-9] and few from children. [4] In the absence of high index of suspicion and absence of confirmatory tests, diagnosis may be missed as it closely mimics viral meningoencephalitis, leptospirosis, malaria, enteric fever and in some cases pyogenic or tubercular meningitis. First line antibiotics used for the treatment of these illnesses may not cover scrub typhus and the illness may thus be fatal or patient may wrongly be given Anti tubercular therapy (ATT) where he may improve due to rifampicin but will have to endure a long drug therapy and its side effects.

Most of the children were in the adolescent age group and predominantly females (M:F=1:2.25) unlike other studies [4] where a uniform distribution in all age group and both sexes was seen. Children get infected accidentally when they encroach on zones made of secondary 'scrub' growth which grows after clearance of primary forest especially following the rainy season for work or play. [2] The incidence in adolescent females is more probably because adolescent females in the hilly states help in procuring fodder, grass for livestock at home and help out in the fields hence have a greater chance of coming in contact with the vector. All children were admitted in post monsoon similar to studies in north India [13] and unlike others from South India where patients were seen in cooler months of Jan to march. [14] Being a zoonoses occupation and scrub vegetation surrounding the house of patients is known to have a strong association seen in nearly all children indicating the vulnerability of children in the hilly areas to scrub typhus.

Lymphadenopathy was not seen in this study unlike others where it is a significant finding. [2] Edema due to vascular leak was observed in only one child in whom there was co- infection with dengue contrary to earlier reports where it has been seen in half to three fourth of the population. [6]

Clinical diagnosis has classically been aided by the presence of eschar. [1-3] However it was seen in only 15.4% children in our study similar to other Indian studies. [6-9] Higher percentage of patients presenting with eschar has been documented in South Indian studies (49%). [15] This may be due to different geographic distribution of various strains.

Multiorgan involvement has been the hallmark of scrub typhus infection seen in other studies as well. Respiratory involvement was the most common dysfunction seen in a majority (61%) higher than other Indian studies. [4-9] In the present study, ARDS with respiratory failure requiring ventilator support and shock needing inotropic support was found only in one child. Renal impairment was seen only in 15.3% with no child needing dialysis, which is much milder and lower than 66% as reported by Mahajan et al. [2] Mild hepatitis seen as elevation of liver enzymes (SGPT) was seen in various North Indian studies where incidence ranges from 35-75%. [4-9]

Thrombocytopenia was seen in 92.3% in our study similar to other studies in India showing consistently low platelet count varying from 13% to 100%. [4-9] This variation could be attributed to different cut offs used in different studies. Leucocytosis (TLC>11000/cumm) suggestive of bacterial infection was seen in 15.3%.

CSF Examination was abnormal in all patients, with mildly raised proteins, mean 80 mg/dl (80-150) and near normal sugar differentiating it from pyogenic meningitis. The mean cell count was on an average 27 cell/cumm with other studies showing a range of 17-200 cell/cumm with lymphocytosis 85% (75-100%) closely resembling viral/aseptic meningitis. [4,9] Other studies with a higher cell and protein count had a CSF picture resembling tubercular meningitis. [7] [Table 3].

In the present study, scrub typhus DNA by PCR was detected in 8 out of the 13 samples. This may be due to delayed presentation; since the DNA in blood is present during rickettsemia period before appearance of antibodies.

In the present study, the outcome was favorable without any complications like other studies [2,3] Being a prospective study geographical distribution, risk factors, time for improvement, complications and course during hospital stay were well documented.

We have used doxycycline and azithromycin-oral and intravenous successfully resulting in dramatic improvement in the form of defervescence of fever, improvement of neurological status and general condition and normalization of platelet count, SGPT and renal parameters. There was no mortality or morbidity in this study unlike others which had mortality from 15-25%. [8,15] Absence of mortality and morbidity in the present study could be due to timely diagnosis with good supportive care. A less virulent circulating strain of O. tsutsugumashi may also be responsible for lesser mortality and morbidity. However, it requires further studies to elucidate this hypothesis.

Conclusion

Hilly areas of Kumaon in Uttarakhand have a poor health infrastructure mainly because of difficult geographic terrain. The population in this region is largely dependent on government hospitals for treatment. A simple algorithm given below would also help the clinician in initiation of treatment and prevention of morbidity and mortality.

Children with clinical features of meningoencephalitis especially in post monsoon season when associated with splenohepatomegaly, raised SGPT, low platelet count and CSF picture suggesting aseptic meningitis must be strongly considered as scrub meningoencephalitis. If diagnostic facility is not available or feasible, Doxycycline or Azithromycin should be promptly started to reduce mortality and morbidity

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Conflict of Interest

All authors disclose that there was no conflict of interest.

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