RESEARCH BRIEF

Clinical Profile of Scrub Typhus in Children and its Association with Hemophagocytic Lymphohistiocytosis

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Objective: To study the clinical profile of children with scrub typhus and its association with hemophagocytic lymphohistiocytosis. **Methods**: Children presenting with unexplained fever and multi-systemic involvement between May to December 2011 were tested for scrub typhus using IgM ELISA kits. Occurrence of Hemophagocytic lymphohistiocytosis in IgM positive cases of scrub typhus was studied. **Results**: Of the 35 children with unexplained fever and multi-systemic involvement, 15 children (9 boys) tested positive for scrub typhus. Thrombocytopenia, hypoalbuminemia and raised hepatic transaminases were observed in all children. Out of seven children evaluated for hemophagocytic lymphohistiocytosis. 3 met the criteria for hemophagocytosis. Two children (one with hemophagocytic lymphohistiocytosis) died. **Conclusions**: Scrub typhus is a common cause of unexplained fever in children in northern India. Hemophagocytic lymphohistiocytosis can occasionally complicate scrub typhus in children.

Keywords: *Infectious vasculitis, Rickettsial disease, Hemophagocytosis.*

Scrub typhus is an acute febrile illness caused by infection with *Orientia tsutsugamushi*. It is characterized by focal or disseminated vasculitis and perivasculitis, involving the lungs, heart, liver, spleen, and central nervous system. It is reported from many countries in the world [1], and recent reports from many parts of India highlight its endemicity in India [2].

Hemophagocytic lymphohistiocytosis syndrome (HLH) is a rare but potentially fatal clinical syndrome resulting from dysregulated activation and proliferation of lymphocytes. Infections are important triggers for hemophagocytosis [3]. There are few case reports of scrub typhus associated HLH in children [4,5]. We report our experience with pediatric scrub typhus at a hospital in Northern India, and highlight its association with HLH.

METHODS

This study was done from May 2011 to December 2011 at a tertiary care pediatric hospital in northern India. Children admitted with unexplained fever and evidence of multi-systemic involvement were prospectively enrolled and followed-up till discharge from hospital. Clearance was obtained from the Institutional Ethics Committee. A total of 35 children were tested for scrub typhus using the IgM ELISA (In Bios International, Inc.) assay. Additionally, blood culture, urine culture, malaria rapid diagnostic test, malarial smears, leptospira serology, and WIDAL tests were done in all children.

The diagnosis of hemophagocytosis was established using the criteria proposed by Henter, *et al*. [6]. For this study, we could use only six among the eight characteristics because of the unavailability of natural-killer (NK) cell activity assessment and sCD25 quantification. Supportive evidence for HLH included cerebral symptoms with moderate pleocytosis and/or elevated protein and elevated transaminases, bilirubin and LDH [7]. Categorical variables were reported as frequencies, and continuous as mean± SD (parametric) or median and ranges (non-parametric).

RESULTS

Based on clinical suspicion, a total of 35 admitted children were tested for scrub typhus. Samples of fifteen children (9 boys) tested positive for scrub typhus. The children reported from the states of Himachal Pradesh, Haryana, Punjab and Uttar Pradesh, besides Union Teritory of Chandigarh. All these children (median age 78 months, range 24-140 months) presented during the months of July to October. The median (range) duration of fever was 7 (3-22) days. The other presenting features were: sensorial changes (11), vomiting (10), seizures (9), rapid breathing (8), edema (7), cough (5), rash (5), bleeds (2) and jaundice in two children. On examination, hepatosplenomegaly was

TABLE I FINDINGS ON EXAMINATION AND INVESTIGATIONS IN CHILDREN WITH SCRUB TYPHUS

Clinical features	*No. (%)*	*Investigations*	*No. (%)*
Hepatomegaly	14 (93)	TLC >15 $\times 10^9$/L	7 (47)
Splenomegaly	13 (87)	Platelets < 150 $\times 10^9$/L	15 (100)
Rash	10 (67)	Platelets < 50 $\times 10^9$/L	7 (47)
Edema	9 (60)	Serum albumin < 25 g/L	15 (100)
Petechiae	7 (47)	Serum Na <135 mmol/L	8 (53)
Raised intracranial pressure	5 (33)	Serum creatinine (>1 mg/dL)	3 (20)
Wheeze/crepts	7 (47)	Hb* (gm/L)	91 ± 21
Lymphadenopathy	6 (40)	AST** (IU/L)	145 (108-1479)
Eschar	2 (13)	ALT** (IU/L)	96 (60-1131)
Meningeal signs	5 (33)	CSF cells** (No./mm^3)	40 (20-60)

**Data as mean±SD, **data as median (range), TLC- total leukocyte count, Hb- Hemoglobin, AST-Aspartate aminotransferase (IU/L), ALT-Alanine aminotransferase (IU/L).*

found in nearly all the children. The characteristic '*eschar*' was found in only 2 children (***Table* I**). Thrombocytopenia, hypoalbuminemia and elevated tranaminases were observed in all children. Half the children had hyponatremia. Eleven children underwent CSF examination; eight had raised CSF proteins and five had pleocytosis (lymphocytic in 3, neutrophilic in 2).

Doxycycline was the drug used in 10 children and azithromycin in the rest. The median (range) time to defervescence was 6 (3-9) days. Two children with proven scrub typhus died. The mean (range) hospital stay of the survivors was 11 days.

Seven children were evaluated for HLH; five of these underwent bone marrow examination. Three children met the criteria for HLH (***Table* II**). All children with HLH had prominent hepatosplenomegaly. One of these 3 children died and the diagnosis was established only post mortem. No clinical or laboratory feature could reliably distinguish these children from those who did not develop hemophagocytosis.

DISCUSSION

In our series hepatosplenomegaly was seen in nearly all children with scrub typhus, two-thirds had evidence of rash and fluid leak, clinical pulmonary manifestation were seen in half, and CNS manifestation occurred in one-third of the children. Being a tertiary care referral center, our patient series may not be a true reflection of the disease spectrum in the community. However, scrub typhus was diagnosed in children hailing from five North Indian states. This data extends the previous observations [8], and suggests that scrub typhus is possibly endemic in Northern India.

In a study of thirty children with scrub typhus from Thailand, most children presented during the rainy season and lymphadenopathy (93%), hepatomegaly (73%), eschar (68%), conjunctival hyperemia (33%), maculopapular rash (30%), and splenomegaly (23%) were the commonest signs. Eleven patients had interstitial pneumonitis and one patient had meningitis [9].

Most children in our series did not have the characteristic eschar. Eschars have been reported to be

TABLE II PROFILE OF THREE CHILDREN WITH SCRUB TYPHUS-INDUCED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Age(y)/ sex	*Fever duration(d)*	*Clinical features and Examination findings*	*AST/ALT (IU/L)*	*TG (mg/dL)*	*Albumin (g/L)*	*Ferritin (ng/mL)*
7/M	7	Tachypnea, pallor, edema, hypotension, wheeze on auscultation	136/60	286	22	2640
9/F	10	Skin bleeds, altered sensorium, seizures, jaundice, lymphadenopathy, edema, hypotension,wheeze on auscultation	439/74	846	17	19706
6.5/F	8	seizures, altered sensorium, rash, rapid breathing, jaundice, edema, hypotension	112/51	286	17	644

AST-Aspartate aminotransferase (IU/L), ALT-Alanine aminotransferase (IU/L), TG- Triglycerides(mg/dL).

WHAT THIS STUDY ADDS?

- The atypical clinical manifestations with increased propensity for secondary hemophagocytosis in children with scrub typhus is highlighted in this series from Northern India.

rare in previous studies from this region [10]. The variation in cutaneous immunity and possible previous exposure to the pathogen in indigenous populations have been cited as a possible explanations for the absence of an eschar in scrub typhus [10]. In a study from Korea, among 208 adults with scrub typhus, factors independently associated with the severe complications were; the absence of eschar, WBC counts >10, 000/mm^{3,} and albumin ≥3.0 g/dL [11]. Response to appropriate treatment is often described as 'dramatic' with early defervescence [9]. However, in our series, the median time to defervescence was 6 days, possibly reflecting the severity of involvement in our patients.

Despite the recognition of HLH in rickettsial infection, till now only few case reports of acquired HLH in scrub typhus are available in children [4,5,12]. We diagnosed HLH in 3 of our 7 children with scrub typhus evaluated for HLH. This suggests that HLH may not be uncommon in children with severe scrub typhus. Understanding this would drive us to evaluate the children earlier for acquired HLH, treating which could change the outcome of severe scrub typhus. For patients with reactive HLH associated with pathogens other than EBV, supportive care and treatment of the underlying infection is associated with recovery in 60%-70% [13]. Two of the three children in our series recovered with the control of infection. One child with scrub typhus and HLH died before the diagnosis could be suspected or established.

The current study is limited because of its single-center origin and small sample size. Another drawback is the lack of confirmation of the diagnosis using the gold standard micro-immunoflurosence assay. Larger multi-centric studies are thus required to elaborate on the endemicity of scrub typhus in India and its spectrum of manifestations. To optimize outcomes of children with severe scrub typhus, co-existing HLH needs to be suspected early and investigated promptly. Treatment protocols for ricketssia-induced HLH in children need evaluation in future studies.

Contributors: SN: conceptualized the study, organized the data, analyzed, interpreted the data, and prepared the first draft; SLG: data acquisition, data analysis and interpretation, manuscripts revision SK: helped in data collection and analysis; KA: coordinated the laboratory testing and analysis of results; SS: conceptualized the study, revised drafts for important intellectual content and approved the final manuscript. All authors contributed to the final version of manuscript.

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