

Original Article**Scrub Typhus Associated Secondary Hemophagocytic Lymphohistiocytosis in Pediatric Intensive Care Unit**Sandip Kumar Singh ^{1*}, Shishir Jha ¹, Rajnish Mishra ², Sajan Kumar Thakur ², Suja Gurung ³, Aliza Bajracharya ⁴¹Department of Pediatrics, Nobel Medical College & Teaching Hospital, Biratnagar, Nepal,²Department of Pediatrics, Lifeline Hospital Pvt. Ltd. Damak, Nepal, ³Intensive care Unit, Dirghayu Guru Hospital and Research Center Pvt. Ltd. Kathmandu, Nepal, ⁴Department of Medicine, Alka Hospital, Kathmandu, NepalArticle Received: 25th September, 2023; Accepted: 20th November, 2023; Published: 31st December, 2023DOI: <https://doi.org/10.3126/jonmc.v12i2.61351>**Abstract****Background**

Scrub Typhus is febrile illness caused by orientia tsutsugamusi and presents with multiorgan involvement. It can cause multiorgan failure resulting in acute respiratory distress syndrome, acute kidney injury and hemophagocytic lymphohistiocytosis. Secondary hemophagocytic lymphohistiocytosis is rare but life threatening clinical condition caused by uncontrolled activation of inflammatory cytokines and accumulation of activated macrophages and lymphocytes.

Materials and Methods

This study is a prospective observational study conducted on children with Scrub Typhus being admitted to Pediatric Intensive care Unit of Nobel Medical College during 12 months period from July 2022 to June 2023. Basic demographic features, clinical presentation, severity and outcome were analyzed. Categorical variables were reported as frequencies, and continuous as mean \pm SD. Independent sample t-test and chi square test was used for comparison of means and categorical variables.


Results

A total of 32 children with scrub typhus were included. Common age group was >10 years. Fever, hepatosplenomegaly, rash and respiratory distress were common clinical features. Among 32 cases, 7 (21.87%) had Encephalitis, 10 (31.25%) developed acute respiratory distress syndrome, 13 (40.62%) had Shock, and 9 (28.12%) developed secondary hemophagocytic lymphohistiocytosis. Among 9 children with scrub typhus associated secondary hemophagocytic lymphohistiocytosis, all of them had Hyperferritinemia, Hypofibrinogenemia, and Hypertriglyceridemia. Hemophagocytosis was identified in (55.55%) in bone marrow biopsies. 1 patient succumbed to multiorgan failure.

Conclusion

Secondary hemophagocytic lymphohistiocytosis should be considered in children with Scrub typhus requiring Intensive care support. Early recognition and prompt treatment can result in good outcome in children with Scrub typhus associated secondary hemophagocytic lymphohistiocytosis.

Keywords: Hemophagocytic lymphohistiocytosis, Prognosis, Scrub Typhus

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Introduction

Scrub Typhus presents with acute febrile illness with multiorgan involvement and presence of painless eschar. After incubation period of 9-11 days, when bacteria invade vascular endothelium, it causes widespread perivasculitis leading to capillary leakage, edema, tissue hypoperfusion and ischemic injury to multiple organs [1]. In a study done in Nepal, almost 26% of scrub typhus patient were in pediatric age group [2]. Scrub typhus can have multiple complications, one of them is rare but life threatening condition called secondary hemophagocytic lymphohistiocytosis (HLH).

HLH is caused by uncontrolled activation of inflammatory cytokines and accumulation of activated macrophages and lymphocytes [3]. It is characterized by fever, splenomegaly, cytopenias, hypertriglyceridemia, raised ferritin, low fibrinogen, bone marrow evidence of hemophagocytosis and raised sCD25 levels with low NK cell activity [4]. Other supportive criteria include CSF pleocytosis, transaminitis, hypoalbuminemia, hyponatremia and elevated D-dimer.

Though many cases of scrub typhus and scrub associated secondary HLH were reported in last few years but only few case reports are described in pediatric age group. This study will be conducted to find out the incidence, clinical markers, laboratory parameters, complications and outcome of scrub typhus associated HLH in children admitted to PICU.

Materials and Methods

This is a prospective observational study conducted on children with Scrub Typhus associated secondary HLH admitted to Department of Pediatrics (PICU) of Nobel Medical College and Teaching Hospital during 12 months period from July 2022 to June 2023. This study was started after acquiring approval from the Institutional Review Committee of Nobel Medical College (IRC). Nobel medical college is a tertiary referral center located in Biratnagar, Nepal. Department of Pediatrics consists of 63 bedded pediatric ward and 15 bedded level III pediatric intensive care unit. In a study done by Rathi N.B. et al., about 2-3% of associated HLH cases were reported secondary to scrub typhus in children in a tertiary hospital [6]. We calculated sample size of 31, using sample size formula $[N = Z^2pq/d^2]$ (where $q = 1-p$) and margin of error 5%. However, we intended to include all the cases being admitted as Scrub Typhus in Pediatric Intensive care unit during the study period and consenting to participate in this study. A well designed

proforma containing various parameters under study was used to collect data.

Primary objective of this study was to determine incidence, demographic features and complications of scrub typhus associated secondary HLH in pediatric intensive care unit. Secondary objectives was to describe common clinical presentation, evaluate clinical and laboratory markers of severity and to describe outcome (Duration of Hospital/PICU stay, Need of vasoactive agents, need of respiratory support, mortality). All children from 6 months to 15 years of age with scrub typhus infection (IgM antibody for scrub typhus positive by ELISA) being admitted to PICU were included in the study. Children with other causes of febrile illness like other infectious diseases, malignancies, or rheumatological condition were excluded from the study. Children who were clinically suggestive of scrub typhus but IgM for Scrub typhus negative by ELISA were also excluded.

Scrub typhus was suspected when children had acute febrile illness with rash, history of outdoor play, presence of eschar or in any children with undifferentiated fever. All these children were screened for IgM antibodies against scrub typhus using ELISA method. Additional tests like malaria rapid diagnostic test, dengue serology, leptospirosis serology, typhoid serology, Hepatitis B and C, urine and blood culture was done to rule out other endemic infections. Among these children with scrub typhus, HLH was suspected, in those who had persistent fever, cytopenias, and worsening of clinical condition despite optimal treatment. HLH was diagnosed using HLH 2004 criteria and five out of 8 parameters were sufficient for the diagnosis of HLH [5].

Detailed history and physical examination was done. Relevant investigations were done to find organ involvement and diagnose secondary HLH. PRISM III score of children was documented at admission and daily SOFA score and worst SOFA score was documented. Bone marrow aspiration was done to look for features of hemophagocytosis. Children was treated with anti rickettsial antibiotics, other supportive treatment was given. Shock was managed with fluids, inotropes and VIS score was documented. Respiratory support was provided using NIV/HFNC/Mechanical ventilation. If child had no improvement after 48 hours of starting anti-rickettsial antibiotics, or if patient had clinical deterioration, child was managed with steroids (dexamethasone/methyl prednisolone) and/or IVIG. Outcome was documented in form of improved, death or leave against medical advice (LAMA).



Data was entered in MS Excel and analyzed using SPSS 20. Categorical data was analyzed in terms of number and percentages. Quantitative data was expressed as mean (SD) or median (IQR). Identification of predictors of scrub typhus associated secondary HLH was done through univariate followed by multivariate analysis.

Results

A total of 32 children were included in our study. Among them, 19 were male (59.37%) and 13 (40.62%) were female. We found six (18.75%) cases between 1-5 years of age, 10 (31.25%) cases between 5-10 years of age and 16 (50%) cases were above 10 years of age. Mean age of patients was 11.2 years. There was seasonal trend in admission of cases to PICU, maximum number of cases peaking during June to October month. Fever was found in all (100%) cases, hepatosplenomegaly (68.75%), respiratory distress (71.87%) in cases, hypotension at time of admission (40.62%), neurological involvement in form of encephalopathy or seizure (21.87%), rash (43.75%) of cases, Acute kidney injury (21.87%) and Eschar was seen in (21.87%) of cases. Laboratory parameters showed leukocytosis in 95% of cases, 68% cases showed neutrophilia and 62% cases showed thrombocytopenia. Mean (SD) CRP level was 76 (34) mg/l, ESR 55 (36) mm in the first hour and mean PCT was 8.6 ng/ml. Transaminases were raised in 78%, deranged coagulation profile in 38%, hypoalbuminemia in 82%, 36% had hyponatremia and 56% had hyperferritinemia. Serum LDH was elevated in 36% cases and 7.14 % had elevated troponin. Out of 32 children, 30 (93.75%) were scrub typhus IgM positive, two (6.25%) were scrub PCR positive.

Table 1: showing common clinical presentation of scrub typhus

Symptoms	Number (%)
Hepatosplenomegaly	22 (68.75%)
Respiratory distress	23 (71.87%)
Eschar	7 (21.87%)
Neurological Involvement	7 (21.87%)
Rash	14 (43.75%)
Shock	13 (40.62%)
Acute Kidney Injury	7 (21.87%)
Myocarditis	3 (9.37%)
MODS (Multi-organ Failure)	14 (43.75%)

Among 32 children with scrub typhus, 9 cases (28.12%) developed secondary HLH. Among them, 6 were male (66.66%) and 3 (33.33%)

were female. We found two (22.23%) cases between 1-5 years of age, 4 (44.44%) cases between 5-10 years of age and 3 (33.33%) cases were above 10 years of age. Mean age of patients was 10.6 years. Common clinical presentation was fever (100%) and hyperferritinemia (100%), followed by organomegaly (87%), thrombocytopenia (92%) of cases. Bone marrow evidence of Hemophagocytosis was seen in 5 children (55.55%).

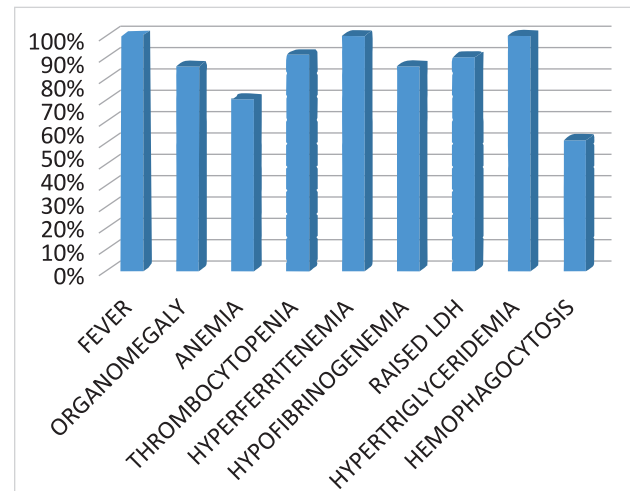


Figure 1: Showing common clinical presentation in children with scrub typhus associated secondary HLH

Mean serum ferritin in children with secondary HLH was 952 ± 155.60 ng/ml, mean platelet count was $32,400 \pm 16,300$, mean serum LDH was 855 ± 166 IU/L and mean serum triglyceride level was 310 ± 96 mg/dl. All these parameters were significantly higher in children with scrub typhus associated secondary HLH as compared to children without secondary HLH (Table 3). Similarly, children with secondary HLH has higher requirement of mechanical ventilation (44.44% vs 10.52%, p value 0.0448) and required longer duration of PICU stay (9.5 ± 2.8 vs 5.5 ± 1.8 , p value <0.0001).

Table 2: Showing laboratory markers of severity in children with scrub typhus associated secondary HLH

Lab parameters	Scrub Typhus without secondary HLH	Scrub Typhus with secondary HLH	P value
Serum Ferritin	386 ± 88.60 ng/ml	952 ± 155.60 ng/ml	< 0.0001
Platelets	$86,000 \pm 11,200$	$32,400 \pm 16,300$	< 0.0001
Serum LDH	220 ± 55 IU/L	855 ± 166 IU/L	< 0.0001
Serum Triglycerides	176 ± 68 mg/dl	310 ± 96 mg/dl	0.0002

Among children with scrub typhus, 78.12% required respiratory support (28% required CPAP, 32% required HFNC and 24% required mechanical ventilation), 13 (40.62%) had shock and 3.12% required renal replacement therapy in



form of hemodialysis. All children received either Doxycycline or Azithromycin, if scrub typhus was suspected. Azithromycin was preferred in children < 8 years of age. 4 (12.5%) children required dual therapy. Azithromycin was added to Doxycycline, if there was clinical deterioration after 48-72 hours of starting Doxycycline (esp. in cases with Scrub Encephalitis). Among children with scrub typhus associated secondary HLH 3 children were (33.33%) managed with intravenous immunoglobulin and methyl prednisolone and 6 (66.66%) were managed with only methyl prednisolone. Multiorgan failure was seen in 14 children (43.75%). One children (3.12%) expired, who had multiorgan failure, DIC and secondary HLH, one children (3.12%) went on LAMA due to financial issues and other children (93.75%) were discharged after complete recovery. Mean duration of PICU stay was 6.5 days.

Discussion

Scrub typhus is an acute febrile rickettsial infection and present with multiorgan failure. Our study showed seasonal trend in admission of cases to PICU, maximum number of cases peaking during June to October month, similar to study done by Manish et al [7]. Majority of children in our study were more than 5 years of age, which may be due to their outdoor activities compared with the younger ones. In our study, fever was seen in all cases, other common presentation were hepatosplenomegaly (68.75%), respiratory distress (71.87%), shock (40.62%), neurological involvement in form of encephalopathy or seizure (21.87%), rash (43.75%), acute kidney injury (21.87%) and Eschar in (21.87%) of cases. These findings were similar to study done by Gurnathan et al [8] where hepatosplenomegaly (80.6%), encephalopathy (18.5%), AKI (10.8%) were similar to our study but incidence of Eschar was higher in this study (55.5%). This could be due to known phenomenon in patient with scrub typhus in Asia as they are dark skinned. Moreover eschar is less likely to be reported by patients and needs careful physical examination to find it.

Most cases in our study showed leukocytosis (95%), neutrophilia (68%), thrombocytopenia (62%), transaminitis (78%), hypoalbuminemia (82%), hyponatremia (36%), and hyperferritinemia (56%). This findings were similar to study by Nallasamy K and Giri PP et al. [9,10] where thrombocytopenia was seen in 82%, hypoalbuminemia (77%), transaminitis (47%) and hyponatremia (62%). Mean (SD) CRP level was 76 (34) mg/l, ESR 55 (36) mm in the first hour and

mean PCT was 8.6 ng/ml in our study, similar to study by Giri PP et al. [10] where mean ESR was 86.2 mg/l. In our study 40.62% developed shock and 21.87% developed Encephalopathy. Giri PP et al [10] also reported similar findings, shock (60%) and Encephalopathy (43%) of cases. Though AKI was seen in 21.87% of our cases but renal replacement therapy was needed in only 1 case, this could be due to early diagnosis and early use of anti rickettsial antibiotics.

In the present study, half of the patient experienced multiorgan failure (43.75%) and 9 (28.12%) experienced secondary HLH. So secondary HLH should always be considered in children with scrub typhus with multiple organ involvement in PICU. Common clinical presentation was fever (100%) and hyperferritinemia (100%), followed by organomegaly (87%), thrombocytopenia (92%) of cases. Similar findings were seen in study done by Jin Y et al.¹¹ where bicytopenia, hyperferritinemia and coagulopathy was seen in all cases. Bone marrow evidence of Hemophagocytosis was seen in 5 children (55.55%). This could be due to early bone marrow aspiration in our study. Mean serum ferritin in our children with secondary HLH was 952 ± 155.60 ng/ml, mean platelet count was $32,400 \pm 16,300$, mean serum LDH was 855 ± 166 IU/L and mean serum triglyceride level was 310 ± 96 mg/dl. All these parameters were significantly higher in children with scrub typhus associated secondary HLH as compared to children without secondary HLH (Table 3). These findings were similar to study by Jin Y et al. [11] where all children had markedly high ferritin (>1500 ng/ml), high triglycerides, low fibrinogen and 66.7% of children had high serum LDH (>1000 U/L). Similarly, children with secondary HLH has higher requirement of mechanical ventilation (44.44% vs 10.52%, p value 0.0448) and required longer duration of PICU stay (9.5 ± 2.8 vs 5.5 ± 1.8 , p value <0.0001). As multiple organ involvement, ARDS, coagulopathy coexist with secondary HLH, they require mechanical ventilation support and longer PICU stay.

All patients in present study were treated with anti rickettsial antibiotics and immunomodulatory therapy (Methyl prednisolone \pm IVIG) if required, along with supportive care. Steroids is used in combination with IVIG to treat cases of scrub associated HLH. Hyperinflammation is treated with corticosteroids, which are cytotoxic for lymphocytes and inhibit the expression of cytokines and the differentiation of dendritic cells [3,4]. Furthermore, IVIG is also effective in hyperferritinemia [12]. In our study 3 (33.33%) of children with



secondary HLH was managed with intravenous immunoglobulin and methyl prednisolone and 6 (66.66%) were managed with only methyl prednisolone. In the current study, 1 child (3.12%) expired, who had multiorgan failure, DIC and secondary HLH, one child (3.12%) went on LAMA due to financial issues and other children (93.75%) were discharged after complete recovery. Study by Jin Y et al. [11] also showed low mortality (16.7%) in scrub associated secondary HLH. These results demonstrated that anti-rickettsial treatment and the use of immunomodulatory therapy is highly effective in the treatment of scrub typhus-associated HLH contrary to familial HLH, where mortality is very high. This study has important limitations. This was a single center study with small sample size owing to uncommon complication of scrub typhus and lack of genetic testing and molecular studies for diagnosis of secondary HLH.

Conclusion

Scrub typhus is common cause of multiorgan failure in pediatric intensive care unit. HLH should be suspected, in those who had persistent fever, cytopenias, worsening of clinical condition despite optimal treatment and requiring Intensive care support. Early recognition, prompt treatment and management with immunomodulators can reduce mortality in children with scrub associated secondary HLH.

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Conflict of interest: None

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