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AN OBSERVATIONAL STUDY OF 14 NEONATES WITH SCRUB TYPHUS

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Abstract
Scrub typhus is a rickettsial infection causing pneumonia, myocarditis, bone marrow suppression, Disseminated Intravascular Coagulation and multi-organ failure. Presentation in neonates is rare. We conducted this study on neonates diagnosed as scrub typhus, discuss their clinical presentation and review the literature. The neonates admitted in a tertiary care centre with clinical diagnosis of sepsis were enrolled for the study. Clinical presentation, epidemiology, risk factors, laboratory findings and treatment were recorded. Diagnosis was confirmed by IgM ELISA test and the clinical response to Doxycycline was noted. Anemia, thrombocytopenia and coagulopathy were seen in all neonates. Eschar was not noticed in these cases. Mortality was high (57.1%). Scrub typhus, a sepsis mimicker needs early evaluation and a trial of Doxycycline in suspected neonates my save lives. Polymerase Chain Reaction confirmation and epidemiological surveillance is necessary to standardize antibody kits and controlling endemic.

Keywords: Neonatal scrub typhus, IgM ELISA, rickettsia, coagulopathy

Background

Scrub typhus in neonates is rare, with only around 25 cases reported so far in literature. The first case of neonatal scrub typhus was reported by Wang and colleagues in 1992. [1] The word “scrub” refers to a type of vegetation that maintains the chigger-mammal relationship. Scrub typhus, a rickettsial infection also known as tsutsugamushi disease is an acute febrile disease caused by Orientia tsutsugamushi which is a small gram negative, obligate intracellular organism.[2] O tsutsugamushi is transmitted to humans by the bite of the larva of trombiculid mites(chiggers)which are almost microscopic. Scrub typhus is a multisystem disorder often mimicking bacterial sepsis in newborn, posing challenges in diagnosis. Hence, we aim to do a pilot study on the morbidity and mortality associated with neonatal scrub typhus in our Neonatal Intensive Care Unit (NICU).

Materials and methods

The neonates admitted in NICU at Govt. Rajaji Medical College, Madurai in Tamil Nadu, India from December 2021 to April 2022 with clinical diagnosis of sepsis were enrolled for the study (n=290). We conducted this study during an epidemic of scrub typhus in adult and pediatric population in our locality. Since World Health Organisation criteria for diagnosis of scrub typhus applies to adults and it is not validated for neonates [3], we have done scrub typhus evaluation only in those neonates satisfying any of the following criteria: (a) Neonates with fever, rash, conjunctival injection and hepatosplenomegaly or eschar alone at time of presentation; (b) Neonates with severe sepsis (sepsis plus one of the following: cardiovascular organ dysfunction, acute respiratory distress syndrome (ARDS), or two or more other organ dysfunctions (renal, neurologic, hematologic, or hepatic), Disseminated intravascular coagulation (DIC), septic shock (sepsis with cardiovascular dysfunction (hypotension or reliance on a vasoactive drug to maintain blood pressure, or two of the following: metabolic acidosis, elevated arterial lactate, oliguria, or prolonged capillary refill))[4]; (c) Parents or care takers with recently diagnosed scrub typhus; (d) Stable neonates progressing to severe sepsis clinically and/or with raising C-Reactive protein despite receiving culture sensitive antibiotic. The following groups of neonates were excluded from enrolment: (a) Stable neonates with culture positive sepsis responding to antibiotics; (b) Congenital anomalies; (c) Known metabolic disorders diagnosed during fetal period and/or in previous siblings; (d) Primary immunodeficiency disorders. Clinical presentation, epidemiology, risk factors, laboratory findings and treatment were recorded. IgM Dengue, malarial parasite and TORCH profile were sent. Diagnosis was confirmed by IgM ELISA test (In Bios International Inc., Seattle, WA) and the clinical response to Doxycycline was noted.

Results

290 neonates were enrolled for the study. 23 neonates were evaluated for scrub typhus of which 14 were diagnosed with scrub typhus. 6 among the 23 neonates were evaluated for scrub typhus due to failed response to culture sensitive antibiotic which they received for a mean duration of 6.5 days. Mean age at presentation was 16.36 days (SD-4.19). Of the 14 neonates, 11 were term and 3 were preterm babies. They presented with clinical features mimicking sepsis. 71.4% of neonates presented with fever, 57.1% had seizure, 28.5% had abdominal distension and 100% had orogastric bleed and hepatosplenomegaly. Eschar was not seen in any of the neonates.

Shock was seen in 71.4% and respiratory failure in 50% of neonates. DIC and MODS were seen in 85.7% and 50% of neonates respectively.

Anemia, thrombocytopenia and coagulopathy were seen in all neonates. Leukocytosis was seen in 57.1%, acute kidney injury in 35.7% and deranged liver function tests in 28.5% of neonates. Hyponatremia was seen in 71.4% of neonates. 21.4% of neonates had perinatal asphyxia. Blood culture was positive for 10 neonates (4-Klebsiella pneumonia; 1-Candida; 1-Coaguase negative staphylococci; 1-Non fermenting gram negative bacilli; 3-Escherichia coli).

IgM Dengue, malarial parasite and TORCH profile were negative in all neonates. 5 (35.7%) neonates had minimal pleural effusion on X-ray, 11 (78.6%) had ascites on ultrasonography abdomen and neurosonogram revealed cerebral oedema in 6 (42.8%) neonates. IgM scrub typhus screening done in all mothers were negative. Clinicohematological, biochemical and radiological profile of neonates are shown in figures 1-2.

Six neonates were discharged in a stable condition after intravenous Doxycycline therapy (4.5mg/kg/day in 2 divided doses) for 7 days while eight neonates (57.1%) expired due to complications. The discharged neonates were followed up for a period of 6 months and found to be alive and healthy.

Discussion

Vasculitis is the basic mechanism responsible for skin rash, micro vascular leakage, edema and tissue hypo perfusion, DIC and end-organ ischemic injury. [2,5] Incubation period of the disease ranges between 6-21 days.[6] There are 3 possible routes of infection in neonates-transplacental infection, perinatal blood borne transmission and postnatal infection.

Most newborn present with respiratory distress, fever, decreased oral intake, abdominal distension, hepatosplenomegaly, seizure and lethargy mimicking neonatal septicemia. [1,7] It affects almost all systems. Neonates may develop complications such as shock, seizures, encephalopathy, pleural effusion, pneumonitis and respiratory failure. Paramanantham et al observed hyponatremia, hypoalbuminemia, elevated hepatic transaminases and elevated blood urea as biochemical findings in their case report.[8] 71.4% of cases in our study showed hyponatremia.

In a report by Samad TE involving 7 neonates with scrub typhus, all babies had fever.[9] Deglurkar et al, in their study involving 7 neonates reported fever in all their cases.[10] In our study, fever was present in 71.4% of the cases. According to Megan et al, thrombocytopenia occur in one quarter to one third of neonates and total leukocyte and platelet counts are mostly normal. [5] We observed thrombocytopenia in all our cases as reported by Samad TE and Deglurkar et al. Thrombocytopenia might be due to concurrent sepsis induced bone marrow suppression. While Samad TE and our study report hepatosplenomegaly in all the cases, Deglurkar et al observed the same in 85% of the cases. The pathognomonic finding of eschar was seen in 28.6% of cases by Samad TE. Eschar begins as a small-papule at the site of chigger bite, enlarges, undergoes central-necrosis and acquires a black crust with surrounding erythema, resembling a cigarette burn.[11] Eschar was seen in none of the neonates in our study similar to as reported by Deglurkar et al.

Affected babies had complications such as shock in 57.1% as reported by Samad TE, 29% as reported by Deglurkar et al and 71.4% in our study. Respiratory failure was seen in 42.9% of cases by Samad TE, 57% by Deglurkar et al and 50% in our study. DIC was seen in 28.6% of cases by Samad TE, 14.3% Deglurkar et al and 85.7% in our study. MODS was seen in 28.6% of the cases by Samad TE, 43% by Deglurkar et al and 50% in our study. The high incidence of complications in our study maybe attributed to concurrent sepsis and sick neonates in our study population.

Various serological methods are the mainstay for diagnosis of scrub typhus [12-14]. Indirect immunofluorescence antibody (IFA) test is considered as the reference standard but is expensive, requires considerable training, and is not easily available in resource-poor countries. Enzyme-linked immunosorbent assay (ELISA) is the most preferred and widely used method now. ELISA that uses recombinant p56-kDa type-specific antigen to detect IgM antibodies against O tsutsugamushi has good sensitivity and specificity, is easy to perform, and indicates recent infection. We used IgM ELISA (InBios International Inc., Seattle, WA) at our institute with diagnostic optical density cutoff of 0.5, and this test has sensitivity and specificity of 93% and 91% respectively. [13,14] Molecular tests like nested (Polymerase Chain Reaction) PCR targeting the 56 kDa gene, 47 kDa gene, and 16 S rRNA are rapid and has high specificity but low sensitivity. [3,13]

Department of Health Research-Indian Council of Medical Research (DHR-ICMR) guidelines for diagnosis and management of rickettsial disease in India recommends (a) Doxycycline in the dose of 4.5 mg/kg body weight/day in two divided doses for children below 45 Kg or (b) Azithromycin in the dose of 10 mg/kg body weight for five days. [8] Good supportive therapy is very essential. Doxycycline-resistant strains have been reported and rifampicin may be considered in such situations. [3] In complicated cases, intravenous therapy with azithromycin, chloramphenicol, or fluoroquinolones is recommended. [12, 15]

A compilation of various scrub typhus case reports (n=12) available in literature reported a mortality rate of 25% while in our series it was 57.1%.[9] The overlapping symptoms in association with bacterial sepsis might have delayed the diagnosis in our study population.

Surveillance was carried out in our hospital premises and surroundings by District public health officer but no chiggers were detected. Prevention is based on avoidance of chiggers that transmit O tsutsugamushi, accomplished by insect repellents and by the use of protective clothing impregnated with benzyl benzoate. Various vaccines were developed and tested. However, no single antigen has been identified that induces protection against all of the antigenically diverse strains of O tsutsugamushi.[1]

Limitations

Being a pilot study, we limited our study to a selective population among neonates with severe clinical sepsis and those who presented with classical symptoms described for scrub typhus. All neonates with early symptoms of sepsis were not screened. We did not use PCR due to constraints of availability, high cost and long reporting time. Awaiting PCR report prior to treatment initiation was practically not possible for us. Only intravenous Doxycyline was used as first line drug and alternatives like oral Azithromycin was not used in our study because of gastric bleed in our neonates and other reported side effects like pyloric stenosis.[16]

Conclusion

In neonates presenting with fever, thrombocytopenia, hepatosplenomegaly, seizure and coagulopathy, scrub typhus should be included as a differential diagnosis for early intervention and better prognosis. Scrub typus can coexist with bacterial sepis in neonates. Early evaluation with IgM ELISA and PCR test with initiation of anti-scrub treatment is required to reduce mortality. Further studies incorporating PCR and IgM ELIS in all neonates with features of sepsis is needed to know the incidence and early clinical presentation of scrub typhus. IgM ELISA may be recommended in all neonates with neonatal sepsis during an epidemic of scrub typhus.

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Legends

Figure 1 – Clinicohematological profile of neonates

Figure 2 – Biochemical and radiological profile of neonates