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Clinical and laboratory predictors to differentiate severe dengue from scrub typhus in children

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ABSTRACT

Background: Objective of study was to compare the clinical features and laboratory parameters at admission and differentiate severe dengue from scrub typhus in children.

Methods: Retrospective analysis of case records and comparison of clinical and laboratory parameters at admission of all children with a diagnosis of severe dengue and scrub typhus was done.

Results: A total of 72 children were included (severe dengue =40; scrub typhus =32) during the study period. The mean (SD) age of children with severe dengue and scrub typhus was 7.9(3.8) and 11.8(5.8) years, respectively. Majority of children with severe dengue presented with hypotension, 21(52.5%) vs 3(9.4%) in scrub typhus. Children with severe dengue had a relatively low ANC $(2.6\pm1.97x10^3/\text{mm}^3 \text{ vs } 3.9\pm2.06x10^3/\text{mm}^3)$, low platelet count $(50.23\pm35.55x10^3/\text{mm}^3 \text{ vs } 140\pm95.0x10^3/\text{mm}^3)$ and low mean ESR at 1hour $(8.1\pm6.82\text{mm vs } 33.88\pm13.79\text{mm})$ than scrub typhus.

Conclusions: Compared to scrub typhus, severe dengue was significantly associated with hypotension, lower ANC, ESR and platelets.

Keywords: Eschar, Fever, Low ESR, Rash, Thrombocytopenia, Scrub typhus, Severe dengue

INTRODUCTION

Globally 390 million dengue infections per year are reported, of which 96 million manifests clinically carrying high morbidity. Dengue viruses (DV) belong to the family flaviviridae and is transmitted by vectors Aedes aegypti and Aedes albopictus. Scrub typhus (ST) is another hemorrhaegic fever caused by Orientia tsutsugamushi that is spread by the bite of trombiculid mite. ST is increasingly recognized in tropical countries contributing upto 50% of patients with undiagnosed acute febrile illnesses. In many parts of India, these two infections together comprise more than half of all acute undifferentiated febrile illnesses, more so in south Indian states due to the favorable tropical climatic conditions. Their similar clinical features and laboratory findings

often pose diagnostic difficulty for the treating physician. Early diagnosis of the illnesses is life saving to improve patient outcomes and promote timely public health interventions. In this retrospective study we have compared the clinical features and laboratory parameters of children with severe dengue and scrub typhus and attempted to derive the parameters that differentiate severe dengue from scrub typhus.

METHODS

This retrospective study conducted over a period of 1 and ½ year (January 2015 to June 2016) in the department of pediatrics of PSG Institute of Medical sciences and research, a tertiary care teaching hospital in South India. Case records of all children (≤18 years) discharged with a

diagnosis of severe dengue and scrub typhus were identified, and those who had a serological confirmation were included for analysis. Severe dengue was diagnosed based on revised WHO criteria and included in the study.⁵ Children with or without warning signs, without serological confirmation were excluded. The data was recorded on specified data collection form. The data included demographic parameters, clinical features, and laboratory parameters (CBC, RFT, LFT, serology, culture if any). The serological diagnosis of Dengue fever was based on dengue IgM-ELISA (Panbio dengue IgM & IgG capture ELISA) where values <9 PanBio ELISA units were considered negative, 9-11 equivocal, and more than 11 positive, as per the manufacturer's instructions). Similarly, serological diagnosis of scrub typhus was based on scrub typhus detectTMIgM ELISA system. Children with SD were treated with normal saline, monitored for complications and treated according to the physician's discretion. Children with ST were treated with antibiotics and offered symptomatic care for the illness. The Institution's Human ethical committee approved the study.

Statistical analysis

Kolmogorov-Smirnov test was used for testing normality of the data. Normally distributed continuous variables were compared using *t*-test and non-parametric variables using Wilcoxon signed-rank and Mann-Whitney U tests. Chi-square analysis was done for comparisons of proportional data among groups. Multiple logistic regression models were used to assess the association of severe dengue and scrub typhus with relevant clinical and laboratory parameters.

RESULTS

A total of 7926 children got admitted as inpatients during the study period of which 6737 children were admitted for evaluation of fever. 747 children were serologically confirmed as dengue fever of which a total of 40 children were diagnosed with severe dengue fever with mean $(\pm \text{SD})$ age 7.9 (± 3.80) years, and male: female ratio was 1.1:1. The mean $(\pm \text{SD})$ duration of fever at admission was $4.5(\pm 1.13)$ and the mean $(\pm \text{SD})$ duration of hospital stay was 5.58 (± 1.13) as in Figure 1.

Among children with severe dengue, 31(77.5%) had vomiting, 27(67%) had abdominal pain and 23(57.5%) had oliguria as presenting complaints. A majority of them (31; 77.5%) had evidence of plasma leakage, and 17(42.5%) had skin and mucosal bleeds at admission. None of the children had any alternate provisional diagnosis at admission other than severe dengue based on the clinical presentation.

A total of 32 children were serologically diagnosed as scrub typhus with mean $(\pm SD)$ age of 11.8 (± 5.83) years, and male:female ratio was 2.2:1. The mean $(\pm SD)$ duration of fever at admission was 7.34 (± 2.46) days. Of

32 children, 14 (43.8%) presented with vomiting and 11 (34.4%) presented with abdominal pain at admission. On examination, 5 (15.6%) had maculopapular rash and 15 (46.9%) had hepatosplenomegaly. Only 8 (25%) were found to have eschar to support the clinical diagnosis of scrub typhus. Other clinical parameters are presented in Table 1.

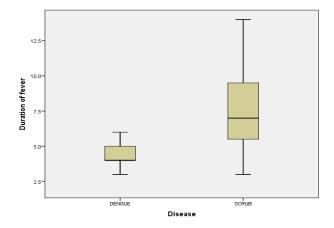


Figure 1: Mean duration of fever among children with severe dengue and scrub.

Table 1: Comparison of clinical features in children with severe dengue and scrub typhus at admission.

	Severe dengue (n=40)	Scrub (n=32)	p- value
Age#	7.97±3.8	11.8±5.83	0.001
Gender(M:F)	1.1:1	2.2:1	NS
Duration of fever at admission#	4.5±1.13	7.34±2.46	<0.001
Vomiting	31(77.5%)	14(4.38%)	0.007
Myalgia	17(42.5%)	8(25%)	NS
Rash	6(15%)	5(15.6%)	NS
Abdomen pain	27(67.5%)	11(34.4%)	0.009
Oliguria	23(57.5%)	3(9.4%)	< 0.001
Respiratory distress	7(17.5%)	3(9.4%)	NS
Skin/mucosal bleeds	17(42.5%)	2(6.3%)	< 0.001
Haematemesis	2(5%)	2(6.3%)	NS
Edema/plasma leakage	31(77.5%)	3(9.4%)	< 0.001
Hypotension	21(52.5%)	3(9.4%)	< 0.001
Hepatomegaly	37(92.5%)	15(46.9%)	< 0.001
Spleen	nil	15(46.9%)	< 0.001

[#]Expressed as Mean ±SD, NS-Non significant

We compared the clinical and laboratory characteristics among children with severe dengue and scrub typhus as shown in Table 2. We found that the mean age at presentation and duration of fever was higher among scrub typhus compared to severe dengue, 7.97±3.8 years

vs 11.8 ± 5.83 years (p = 0.001) and 4.5 ± 1.13 days vs 7.34 ± 2.46 days (p<0.001), respectively. A greater proportion of children with dengue presented with vomiting, abdominal pain, oliguria, skin bleeds, edema and hypotension. There existed a statistically significant difference in the proportions of the above-mentioned variables between both groups (p<0.05). Interestingly erythematous rash was present in equal proportions between both groups (15% vs 15.6%, p = 0.14).

Table 2: Comparison of lab parameters in children with severe dengue and scrub typhus at admission.

	Severe dengue	Scrub typhus	p- value
Hemoglobin [#] (g/dL)	13.3 <u>+</u> 1.70	12.24 <u>+</u> 1.63	0.003
Hematocrit#	41.45 <u>+</u> 5.78	37.6 <u>+</u> 5.14	0.001
TLC #(x10 ³ /cu.mm)	5.19 <u>+</u> 3.03	7.64 <u>+</u> 3.45	0.002
ANC [#] (x10 ³ /cu.mm)	2.6 <u>+</u> 1.97	3.9 <u>+</u> 2.06	0.002
Platelet [#] (x10 ³ /cu.mm)	50.23 <u>+</u> 35.55	140 <u>+</u> 95.0	< 0.001
ESR#	8.1 <u>+</u> 6.82	33.88 <u>+</u> 13.79	< 0.001
SGPT [#]	138.75 <u>+</u> 213.75	91.9	0.31

[#] Expressed as Mean ±SD

The mean haemoglobin (and hematocrit) values were higher among children with dengue (13.3±1.7 vs 12.24 ± 1.63 , p = 0.003). The white blood cell (WBC) count and absolute neutrophil count (ANC) were markedly different in both groups. The children with dengue had a relatively low WBC count and ANC $(5.19\pm3.03\times10^3/\text{mm}^3, 2.6\pm1.97\times10^3/\text{mm}^3 \text{ respectively})$ on comparing children with scrub. The platelet count at admission was lower in children with dengue when compared to scrub typhus (50.23±35.55x10³/mm³ vs $140\pm95\times10^{3}$ /mm³, p<0.001). Also, the mean Erythrocyte Sedimentation Rate (ESR)at 1hour was lower in children with dengue fever compared to scrub $(8.1\pm6.82 \text{mm vs } 33.88\pm13.79 \text{mm}, \text{ p}<0.001)$. The mean serum Alanine Transaminase (ALT) levels were higher in children with severe dengue compared to scrub typhus (138.75±213.75 vs 91.9IU/L). But this difference did not achieve statistical significance (p = 0.19).

From the data obtained at admission, variables between these two illnesses that had statistically significant difference were applied to a logical regression model. We found a high probability of severe dengue compared to scrub typhus was associated independently with hypotension, lower ANC, low ESR and platelets as in Table 3. With a probability cut-off of >90%, the predictive model gave a sensitivity of 100%, specificity of 87.5%, positive predictive value of 88.8% and negative predictive value of 100%, for dengue compared to scrub typhus with ANC 0.93 (0.79-0.99) as shown in Figure 2.

Table 3: Multivariate logistic regression between severe dengue vs scrub typhus.

Variable	Unit of change	Multivariate OR (95% CI)	p- value
ANC	2x10 ³ /cu. mmincrease	1.98 (1.18-3.30)	0.012
Platelet count	40000/cu. mmdecrease	2.47 (1.63-4.23)	< 0.001
ESR	6mm decrease	5.69 (2.88-15.97)	< 0.001

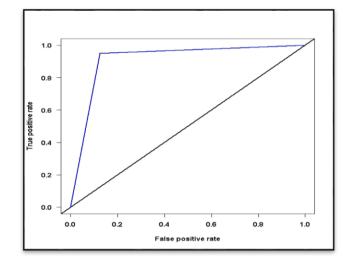


Figure 2: Receiver operating characteristic (ROC) curve of the multivariate logistic regression model for severe dengue vs scrub typhus.

DISCUSSION

Dengue fever and scrub typhus caused by different vectors present in similar demographic distribution and clinical features. Any delay in recognition of these infectious diseases results in significant morbidity and mortality as well. Management of severe dengue is largely supportive with emphasis on fluid resuscitation and hemodynamics monitoring, whereas in scrub typhus the early initiation of antibiotics is mainstay.

Making the correct diagnosis with the available preliminary investigations while awaiting confirmatory test results might help in better management and relieve parent's anxiety. In this retrospective study we attempted to compare the clinical and laboratory parameters between these two similar diseases at initial presentation to the health care facility.

The mean age at presentation of children with severe dengue was less as compared to scrub typhus (7.9 \pm 3.80 vs 11.8 \pm 5.83) and the mean age at presentation of the latter was comparable to that reported previously by Kumar M et al.6

The male:female ratio of children with severe dengue was less than that of scrub typhus (1.1:1 vs 2.2:1). This difference in gender ratio could probably due to similar exposure risk for mosquito bites in-doors and higher prevalence of chigger exposure while playing outdoors by boys. A similar observation was made by Bhat NK et al, who documented a higher male to female ratio (1.44:1) in scrub typhus. Among the symptoms and signs between the study groups at presentation, mean duration of fever, abdominal pain, edema, oliguria and hypotension were strikingly different. Though these differences have been witnessed in children with scrub typhus in previous studies their incidence was much lesser in the present study, when compared to children with severe dengue.⁷

In our present study, there was significant difference in clinical features among the study groups. Children with severe dengue had a short mean duration of fever (4.5 +/-1.13 vs 7.34 +/- 2.46 days) at presentation. Majority of children (77.5%) with severe dengue in our study presented with vomiting and edema. Two third had abdominal pain and oliguria and almost half of them presented with skin bleeds and hypotension at admission. Almost ninety percent of children presented with significant hepatomegaly and none had splenomegaly. Pothapregada S et al, in his clinical profile of children with dengue also observed a similar occurrence with fever (94.6%) being the commonest symptom and persistent vomiting as the frequent warning sign (75.1%).8 Among children with scrub typhus, almost half of them had hepatosplenomegaly. Clinical features like rash, edema, respiratory distress, oliguria was less observed in children with scrub typhus. Only twenty-five percent of children with scrub typhus had eschar in our study population. Rose W et al, found 40.8% of their children having the characteristic eschar at the presentation but most studies project a lesser percentage.9 Babu et al, in their prospective study found only 34.6% of serologically confirmed scrub typhus to have eschar.¹⁰ Absence of eschar could be secondary to previous exposure to ricketssial antigen and variation in cutaneous immune response and that could be possible reason for absence of eschar in majority of our study children.

In our study, we found that the striking difference in clinical parameters between the two groups was hypotension, lower ANC, low ESR and significantly low platelet values and thus provides the best ability to differentiate between severe dengue fever and scrub typhus. ANC has been statistically high in children with scrub typhus than severe dengue. The predominance of lymphocytes with leucopenia and severe thrombocytopenia might be an additional pointer to the diagnosis of severe dengue. In the guideline of Indian academy of pediatrics on ricketssial diseases, marked leukocytosis with the shift to the left in later stages, raised ESR and thrombocytopenia were laboratory features suggestive of these infections, as noted in children with ST in the present study. 11 Liver dysfunction

has been observed in children with severe dengue and scrub typhus. ¹² Similar to the present study, Kumar J et al noted a 10-fold increase in the mean serum ALT levels in children with DF and could be used in differentiating these diseases. ¹³

Few limitation of our study is the retrospective model, small sample size and restricted to a hospital – based population. The observation and predictive model may not be applicable to differentiate other febrile illnesses in children and the clinical utility the model needs to be tested prospectively and also validated. In a resource limited setting among endemic areas, our predictive model could be utilized to differentiate hemorrhagic fever due to scrub typhus and severe dengue, helping to initiate appropriate treatment.

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Institutional Ethics Committee

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