

Original Research Article

Clinical spectrum and outcome of elevated serum transaminases in tropical infections among children aged one month to 18 years in an urban tertiary care centre: a prospective observational study

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ABSTRACT

Background: Tropical infections are common in our country and occur with a variable elevation of transaminases in a majority of them and they pose as a differential diagnosis to the viral infections affecting the liver including COVID-19 and complications like HLH and also paracetamol toxicity. Aim was to study the clinical profile and degree of elevation of liver enzymes in tropical infections in children aged one month to 18 years.

Methods: A prospective observational study of children from one month to 18 years of age with tropical infections in Mehta's multispeciality hospitals, Chennai, India between June 2017 and May 2019 was analyzed. Elevation of liver enzymes was categorized as mild (1-3 fold), moderate (3-20 fold) and severe (>20 fold).

Results: Dengue was the most common infection in our study and the majority (49.07%), followed by enteric fever (78.06%), malaria (27.27%) and leptospirosis (25%), all had a mild elevation of SGOT. Severe elevation of SGOT was seen in 25% of leptospirosis and less than 10% in malaria and none with scrub typhus. SGPT elevation was severe in 50% of leptospirosis. Dengue shock syndrome had a severe elevation of transaminases.

Conclusions: The most common infection was dengue and the majority had mild elevation and those with shock had a severe elevation of transaminases whereas shock was not a feature in leptospirosis even in severe elevation in our study. Though liver enzymes were very much elevated, children recovered without any residual liver damage.

Keywords: Tropical infections, Transaminitis, Hepatosplenomegaly

INTRODUCTION

India being a tropical country, tropical infections are more common. The five most common tropical infections are dengue, leptospirosis, malaria, typhoid and scrub typhus in children. Dengue is the most rapidly spreading mosquito-borne viral disease in the world. In the last 50 years, the incidence has increased 30 fold.¹ Malaria is the most devastating disease of the world, mainly in tropical regions.² In scrub typhus, after an incubation period of 10 to 12 days, the child presents with high-grade fever,

malaise, headache, cough and generalized lymphadenopathy. Typhoid is mainly caused by faeco-oral route, hence it is a major disease in resource-poor settings where sanitation is poor. In leptospirosis, the spectrum varies from asymptomatic to severe disease with multiorgan involvement. They are known to cause a variable range of elevation of transaminases. Not many studies are available either in the pediatric population or from South India especially assessing the severity of transaminitis.

So, in this study, we aimed to study the range of elevation of transaminases in each of the different tropical infections-mild, moderate, severe derangement. Any specific complications associated with the elevation of transaminases will also be studied.

METHODS

The study was a prospective observational study conducted between June 2017 to May 2019. Children from 1 month to 18 years of age presenting with complaints of fever, chills, rigors, abdominal pain, lethargy attending Mehta multispeciality hospitals, Chennai, South India were recruited.

Inclusion criteria

Children of age group 1 month till 18 years of age infected with a tropical infection, irrespective of the initial transaminases level; children with dengue-NS1 positive and/or IgM positive; malaria-MPQBC positive or peripheral smear showing malarial parasites; typhoid-only culture positive; scrub typhus-IgM positive; leptospirosis-MAT positive were included in the study.

Exclusion criteria

Children with underlying liver disease; obese children since they have higher chances of getting NAFLD or NASH; parents who did not give consent for the study; children with co infections were excluded.

Sample size

Sample size was estimated by using the proportion of malaria subjects with abnormal LFT (abnormal SGOT or SGPT) as 10% from the study by pilot study in the same institute using the formula,

$$\text{sample size} = \frac{Z_{1-\alpha/2}^2 p(1-p)}{d^2},$$

where,

$Z_{1-\alpha/2}$: is standard normal variate (at 5% type 1 error) ($p < 0.05$) it is 1.96 and at 1% type 1 error ($p < 0.01$) it is 2.58. As in majority of studies p values are considered significant below 0.05 hence 1.96 is used in formula,

p : expected proportion in population based on previous studies or pilot studies,

d : absolute error or precision, has to be decided by researcher.

$P=10$ or 0.10,

$q=90$ or 0.90,

$d=5\%$ or 0.05.

Using the above values at 99% confidence level a sample size of 237 subjects with tropical disease will be included in the study.

The child was examined thoroughly for vital signs and stabilized accordingly. Then a thorough head-to-foot examination of the child was carried out. General examination was done to look for the presence of petechiae, purpura, rash, eschar, hepatosplenomegaly or evidence of any other source of infection. After doing baseline investigations like CBC, CRP, blood culture and sensitivity, fever investigations to rule out tropical infections like dengue NS1 and IgM, scrub IgM, leptospirosis MAT, blood culture for typhoid and MP-QBC for malaria were done based on the duration of fever and other specific signs and symptoms. The results of the test were analyzed and children who turn out to be positive for any of the tropical infection was taken into our study and details were entered into a pre-structured proforma. Serum transaminases were assessed and checked for elevation. Appropriate treatment was given for the child based on the diagnosis and the child was monitored.

Transaminases were said to be elevated concerning the normal range depending on age as mentioned below in Table 1. Degree of elevation of transaminases was classified as mild (up to 3 times, moderate (>3 to 20 times) and severe (>20 times) of normal (Table 1).

Ethical clearance was obtained from the institutional ethical committee and written informed consent was obtained from the parents of the children who have been recruited for the study.

Statistical analysis

Data were entered into a Microsoft excel datasheet. Categorical data was represented in the form of frequencies and proportions. The Chi square test was used as a test of significance for qualitative data. Continuous data are represented as mean and standard deviation. ANOVA (analysis of variance) was used as the test of significance to identify the mean difference between more than two groups for quantitative data. P value (probability that the result was true) of <0.05 was considered for statistical significance after assuming all the rules of statistical tests.

MS excel and SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) were used to analyze data.

RESULTS

In the present study, between 2017 and 2019 out of a total of 237 children studied, the most commonly observed tropical infection in our hospital was dengue in 172 (72.6%), followed by enteric fever 41 (17.3%), malaria 11 (4.6%), scrub typhus 9 (3.8%) and the least was leptospirosis 4 (1.7%) (Figure 1). There was no

significant association between age and tropical infections. The majority of children with all these tropical infections except dengue were seen in the age group of fewer than five years of age. Dengue was more common in 6 to 10 years of age.

Table 1: Severity of range of transaminases.³

Severity	SGOT	SGPT
Mild	1-3 times	1-3 times
Moderate	3 times-20 times	3 times-20 times
Severe (1000IU/l)	>20 times	>20 times

Normal values SGOT (IU/l): 1 day to 1 year: 22-63; 1 year to 3 years: 20-60; 3 years to 9 years: 15-50; 10 to 15 years: 10-40; normal values SGPT (IU/l): 1 month to 1 year: 12-45; 1 year to 19 years: 15-45.

Concerning other symptoms, there was a significant difference ($p<0.001$) in the mean duration of fever, with fever being for a longer duration with a mean of 8.85 (2.98) days in enteric fever and at the lower side in dengue 5.24 (1.98) days. Vomiting and loose stools were observed for a longer period in enteric fever with a mean of 1.88 (1.68) and fever was least in scrub typhus 0.33 (1.00) (Table 2). Hepatomegaly was seen in all infections but the largest size of liver was seen in leptospirosis. Comparing the severity, among the total 237 subjects, only 16 children required platelet transfusion and only 5 children with dengue who required inotropic support due to persistent shock had higher values of SGOT and SGPT.

SGOT elevation more than SGPT was seen in dengue and leptospirosis however both SGOT and SGPT were significantly elevated in children with shock.

Table 2: Duration of symptoms with respect to the tropical infections.

Symptoms	Group (total duration in days)					Statistical significance
	Enteric fever	Scrub typhus	Malaria	Leptospirosis	Dengue	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Fever	8.85 (2.98)	8.56 (3.3)	6.91 (2.26)	8.25 (4.11)	5.24 (1.98)	<0.001
Vomiting	1.88 (1.68)	0.33 (1.0)	0.91 (1.30)	1.00 (1.41)	0.55 (1.13)	<0.001
Loose stool	2.50 (2.20)	0.67 (1.12)	0.27 (0.90)	1.75 (2.06)	0.34 (0.81)	<0.001
Abdominal pain	1.88 (2.36)	0.56 (1.13)	0.91 (1.30)	1.25 (1.50)	0.96 (1.20)	0.084

Table 3: Association between severity of SGOT elevation with respect to tropical infections.

Groups	SGOT elevation							
	Normal		Mild		Moderate		Severe	
	Count	%	Count	%	Count	%	Count	%
Enteric fever	3	7.32	32	78.05	6	14.63	0	0
Scrub typhus	2	22.22	5	55.56	2	22.2	0	0
Malaria	7	63.64	3	27.27	0	0.0	1	9.1
Leptospirosis	0	0	1	25	2	50.0	1	25
Dengue	12	6.98	81	47.09	78	45.35	1	0.58
Total	24	10.13	122	51.48	88	37.13	3	1.27

$\chi^2=80.814$, $df=12$, $p<0.001$ (GOF test).

Table 4: Association between severity of SGPT elevation and tropical infections.

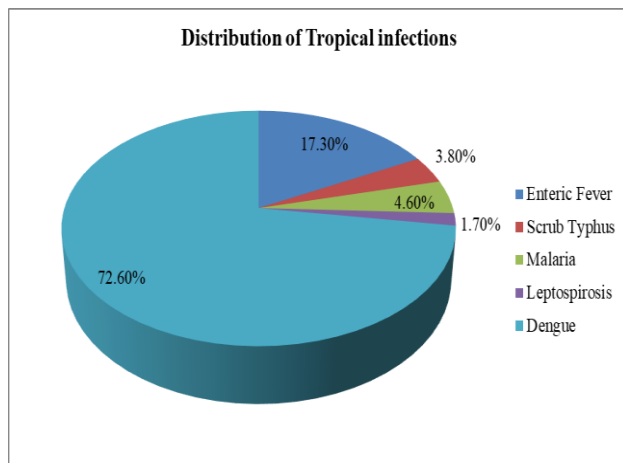
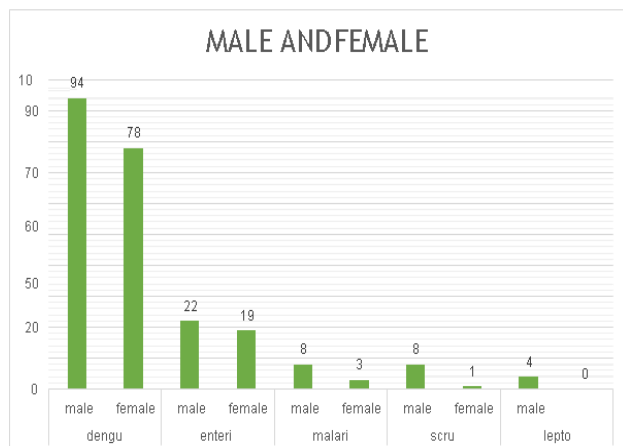
Group	SGPT elevation							
	Normal		Mild		Moderate		Severe	
	Count	%	Count	%	Count	%	Count	%
Enteric fever	18	43.9	19	46.34	4	9.76	0	2.4
Scrub typhus	4	44.4	4	44.4	1	11.1	0	0.0
Malaria	9	81.8	1	9.1	0	0.0	1	9.1
Leptospirosis	1	25.0	0	0.0	1	25.0	2	50.0
Dengue	78	45.35	68	39.53	26	15.12	0	0
Total	110	46.41	92	38.8	32	13.50	3	1.27

$\chi^2=94.077$, $df=12$, $p=0.001$.

Table 5: Comparison of SGOT and SGPT levels among severe and non-severe dengue.

Comparison		SGOT	SGPT
		Median	Median
Dengue	Severe dengue	236	105
	Non-severe dengue	100.5	49
	P value	0.00044	0.00168

Mann-Whitney U test.

**Figure 1: Distribution of tropical infections among hospitalized children.****Figure 2: Gender distribution of five tropical infections.**

SGOT

78.05% with enteric fever, 55.6% with scrub typhus had mild SGOT elevation, whereas 63.6% of children with malaria had normal enzymes. Moderate to severe SGOT elevation was seen in leptospirosis and dengue with shock (Table 3).

SGPT

46.34% of children with enteric fever had mild SGPT elevation and in dengue fever majority 78 (45.35%) had

normal SGPT. In leptospirosis majority (50%) had a severe elevation of SGPT. Significantly more moderate to severe SGPT elevation was seen in leptospirosis and other tropical infections had mild to moderate SGPT elevation and malaria infection had mild SGPT elevation (Table 4).

Significantly higher median SGOT values among severe when compared to non-severe dengue subjects (Table 5) ($p < 0.05$). Also, this difference in SGPT values between severe and non-severe dengue subjects was statistically significant.

DISCUSSION

A study with 237 children having fever and constitutional symptoms attending our hospital, an urban pediatric referral center of the private sector in South India, confirmed to have one of the five tropical infections was assessed for the clinical presentation and severity of transaminases.

Tropical infections

Tropical infections were those that encompassed all diseases that occurred solely or principally in the tropics. In practice, it was often taken to refer infectious diseases, the infections caused by the microbes that thrived in hot, humid conditions causing infections such as enteric fever, dengue, malaria, scrub typhus, leptospirosis and a few others such as leishmaniasis, Chagas and so on, of course with differences in their distribution within this region itself.

Transaminitis

Transaminitis or hypertransaminasemia referred to high levels of transaminases, irrespective of the etiology. The presence of one-third of the reticuloendothelial system mass in the liver, the presence of two circulations-systemic and portal and its role in host defense against microbes were a few reasons why the liver was involved in many systemic infections caused by non-hepatotropic organisms.⁵ Raised transaminases differentiated tropical infections from other systemic infections like urinary tract infections or pneumonia other than mycoplasma infections.

Dengue

Among the 237 children, the majority (72.6%) of the children had dengue with mild hepatomegaly with a mean of 2.04 cm in concordance (88%) with the study by Tambolkar et al.⁶ None of the patients had jaundice, dengue to be anicteric hepatitis. By a study by Promallikit et al the median value of SGOT in persons with shock was 235 IU/l falling into the category of moderate elevation which was significantly higher when compared to children without shock.⁷ The microcirculatory disturbance caused by a shock in liver cells led to acute liver failure and the highest levels were noticed in these patients.⁸ The median SGPT was also higher in children with shock. So, the levels of aminotransferases were higher in children presenting with shock than without shock requiring inotropic support. Intravenous immunoglobulin and platelet transfusions were needed in children with elevated transaminases though the mild elevation of transaminases was observed in 28.5% of cases with shock.

Enteric fever

Enteric fever was seen in the age group of <5 years (51.22%), followed by 6 to 10 years (24.39%). The most common presenting complaint to the hospital was fever and was often prolonged. Other common symptoms observed were abdominal pain, vomiting and diarrhea similar to a study by Geethika et al.⁹ We found that vomiting and diarrhea, the duration of these symptoms were found to be consistently high in enteric fever compared to other tropical infections. Among the 41 children, only two children had complications namely cholecystitis and intussusception. One child with cholecystitis requires cholecystostomy. Moderate elevation of SGOT and SGPT were observed in the majority and relapse in one. The majority (78.05%) of the children and 46.3% had a mild elevation of SGOT and SGPT respectively.

Malaria

In our study, among the 11 children with malaria, 5 children (45.45%) were in age 11 to 15 years. Fever was the consistent finding and one child presented with encephalopathy and seizures due to falciparum malaria. Hepatosplenomegaly was consistently observed in all children with malaria. Mean size of spleen was 2.3 cm. The median value of SGOT and SGPT were the lowest for malaria with 35 and 31 respectively. Though malarial hepatitis was associated with jaundice was a known fact, we had only one child who had seizures and falciparum malaria who presented with clinical icterus. But this was in contrast to the study by Ana et al and Mehta et al where they had 2.5% and 5.2% respectively.^{10,11}

Scrub typhus

Scrub typhus was also common in the age group of fewer than 5 years and prolonged duration of fever next to enteric fever. A study by Vivekanand et al found out that

30% had generalized lymphadenopathy in contrast to our study where only one had generalized lymphadenopathy.¹² The median value of SGOT and SGPT was 89 IU/l and 72 IU/l respectively (mild elevation) and was seen in a majority (55.5%) of our study subjects. SGPT was found to be a predictor of severity in a case series.¹³

Leptospirosis

The mean duration of fever in leptospirosis was 8.25 days and one out of a total of four children presented with acute liver failure. The shock was not a feature in children having transaminases in the range of even several thousand. Categorizing the transaminases, leptospirosis had the highest mean SGOT of 3077 and SGPT of 1456 (severe). Again the reason for elevated SGOT can be accounted to the muscle involvement in leptospirosis with myalgia as the dominant feature.

Limitations

Since the number of other cases of tropical infections was less when compared to dengue, the results of our study cannot be generalized to all tropical infections.

CONCLUSION

To conclude with the aim of the study, to categorize the transaminitis, our study found out that all children with dengue with shock had higher levels of transaminases but not all children with higher transaminases had a stormy course. The range of transaminitis cannot be used to predict the severity of dengue. The majority of the children with enteric fever and scrub typhus had mild derangement. Leptospirosis always had moderate or severe derangement of transaminases. Among the five diseases, the highest elevation of transaminases was noted only in leptospirosis. Though levels were very high, children recovered well without any residual liver damage.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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