Evaluation of clinical and laboratory profile of typhoid fever in Nepalese children- A hospital-based study

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Abstract

Background: Typhoid fever caused by bacteria *Salmonella* typhi is endemic in developing countries like Nepal where water and sanitary conditions are questionable. It disproportionately affects children with varied clinical presentations ranging from a mild illness with low grade fever to severe life threatening complications. Hence this study was carried out to improve the understanding of this disease process in the area, enable prompt diagnosis and effective management of patients to decrease the mortality from typhoid fever.

Objective: To study the clinical and laboratory profile of typhoid fever in infants and children with possible gender differentiation.

Methodology: A total of 74 infants and children with fever for ≥5 days were enrolled for this study. Positive blood culture for S. typhi and/or Widal agglutination test 1:160 or more dilution for O and /or H antigen, clinical symptoms, signs and the results of laboratory investigations were recorded and the number and percentage noted, with respect to different ages.

Results: Mean±Standard Deviation of age was found to be 7.6±3.9. The male to female ratio was 1.4:1 with most of the patients belonging to lower middle class. Headache, anorexia and irritability were statistically significant symptoms for typhoid fever. On the analysis of the signs according to age, there were no significant differences in the frequency of any signs in the three age groups. Most of the symptoms were similar in both sexes. In all the three age groups, fever with abdominal distention and hepatomegaly was the most common presentation.

Conclusion: Typhoid fever should be suspected and investigated in all children with short and long duration fever without localizing signs. Early diagnosis and institution of appropriate antibiotics therapy is of paramount importance in the management of typhoid fever.

Keywords: Fever, Infants, Typhoid fever.

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Introduction

Typhoid fever is an infectious disease caused by gram negative bacteria *Salmonella* enteric serovar typhi (S.typhi). In developed countries, the incidence of typhoid fever is less than 15 cases per 100,000 populations, with most cases occurring in travelers; whereas in developing countries the estimated incidence rate ranging from 100-1,000 cases per 100,000 populations.[1]

It is endemic in developing countries where water supplies and sanitation are sub-standard.[2] Humans are the only natural reservoir of the organism. Direct or indirect contact with an infected person is a prerequisite for infection. The infected person sheds the bacteria in stool and urine. Ingestion of food or water contaminated with S. typhi from human feces is the most common mode of transmission.[3]

Assessment of a child presenting with fever is always a challenge to most pediatricians. Typhoid fever is one of the common causes of fever in children with varied presentation and significant difference in the signs and symptoms compared to adults. Population-based studies from South Asia indicate that age specific incidence of typhoid fever is highest in children under 5 years of age, in association with comparatively higher rates of complications and hospitalization.[1]

The gold standard of the diagnosis of typhoid fever is a positive result of culture from the blood, urine or stool.[1] The classic Widal agglutination test is one of the most utilized diagnostic tests for typhoid fever, especially in developing countries.[4] In a country like Nepal where typhoid fever is endemic and the infrastructure for prompt laboratory diagnosis and management is not available at the all levels of health care system, it is largely diagnosed on the basis of clinical signs and symptoms in the outpatient clinics. This often leads to over or under diagnosis of typhoid fever.

Hence the present study was conducted with the aim to evaluate clinical and laboratory profile of typhoid fever in infants and children in order to improve the understanding of the disease process in the area and enable early and effective management of

patients to decrease the morbidity and mortality from typhoid fever.

Materials and Method

The present study was a hospital-based, prospective and a cross-sectional study that was carried out at Department of Pediatrics, Nepalgunj Medical College and Teaching Hospital (NGMCTH) from December 2013 to December 2014 on 74 subjects that were selectedusing purposive sampling technique. The inclusion criteria considered were the infants and children with fever for ≥5 days, those with positive blood culture for S. typhi and/or Widal agglutination test 1:160 or more dilution for O and/or H antigen. Children suffering from other systemic illness like congenital heart disease, tuberculosis, malignancy, terminal stage of any disease or protein energy malnutrition (PEM>Grade 3 as per Indian Academy of Pediatrics classification)[5] or whose guardians refused to give consent were excluded from the study.

After obtaining ethical approval from Institutional Review Board (IRB) of NGMCTH, a written consent was taken from parent/guardian of the subject. Detailed history and physical examination for fever, hepatomegaly, splenomegaly, bradycardia, anemia etc. was done according to a pre-designed proforma. Socio-economic status was graded according to modified Kuppuswamy's scale.[6]

All patients included in this study underwent complete blood investigation to estimate the total and differential leukocyte count, hemoglobin level and serum transaminases (ALT, AST) by using fully automated complete analyzer, Nihon Kohden Ceitac E. Widal test was done by using semi-quantitative tube agglutination (titration) method in patient with history of fever of >7 days duration. The titre of the patient was taken as the highest dilution of the serum sample that gave a visible agglutination. Titre of 1:160 or more dilution for O and/or H antigen was considered positive. Blood culture and sensitivity test was done in all cases by collecting 5 ml of venous blood was and incubated overnight at 37°C in brain heart infusion broth.

All the variables regarding the clinical symptoms, signs and the results of laboratory investigations were recorded and analyzed using SPSS version 17. The findings were tabulated in percentage and mean±standard deviation (SD) was calculated. The statistical analysis using Chi-square was carried out and a p-value <0.05 was considered statistically significant.

Results

A total of 126 cases with fever for ≥5 days were studied. Out of these 126 cases, 74 cases fulfilled the inclusion criteria and were enrolled in the study. Most of the patients were in the age group of 5-15 years (69%) followed by 1-5 years (27%) **(Table 1)**. Mean±SD of age was found to be 7.6±3.9. The male to female ratio was 1.4:1.

The socioeconomic status was graded as per modified Kuppuswamy's scale. None of the patients was from upper socioeconomic status. Eighteen (24%) cases belonged to upper middle, 30 (41%) cases from lower middle class and 26 (35%) cases from lower socioeconomic status **(Fig. 1)**.

The signs and symptoms of typhoid fever were analyzed according to age. Headache, anorexia and irritability were statistically significant symptoms for typhoid fever ($p<0.05$). The most frequently observed signs were abdominal distention, splenomegaly and hepatomegaly. Coated tongue was found only in the age group 5-15. Rose spots were not observed in any of the cases. On the analysis of the signs according to age, there were no significant differences in the frequency of any signs in the three age groups **(Table 2)**.

Most of the symptoms were similar in both sexes. Almost all the signs and symptoms were more common in males as compared to females. Abdominal distention was significantly more in females as compared to males with a p-value of 0.01 **(Table 3)**.

In all the three age groups, fever with abdominal distention and hepatomegaly was the most common presentation found in 23 (30.4%) patients followed by fever with abdominal distention and splenomegaly that was seen in 21 (28.4%) patients and the least was fever with abdominal distention and hepato-splenomegaly that was found in 10 (13.2%) patients **(Fig. 2)**.

Relative bradycardia was present in 4 cases in the age group 5-15 and absent in other age groups **(Table 4)**.

A total of 16 (21.6%) patients had leucocytosis. All of the infants showed leucocytosis whereas only 5 (25%) patients in age group 1-5 and 8 (15.7%) in age group 5-15 had leucocytosis, which was statistically significant with p-value of 0.002. Leucopenia was not observed in any patient **(Table 5)**.

Table 6 depicts differential leukocyte count in different age groups. Anemia was found in 39 (53%) patients. Mean hemoglobin percentage of all cases involved in the study was 10.7% with SD of 1.9 **(Table 7)**. Serum transaminases (ALT, AST) were found within the normal range in all the cases.

Table 1: Distribution of patients according to age and gender

Age group (years)	Gender				Total (n=74)	
	Female (n= 31)		Male (n= 43)			
	No.	%	No.	%	No.	%
Infants	1	3.2	2	4.7	3	4.0
1-5	4	12.9	16	37.2	20	27.0
5-15	26	83.9	25	58.1	51	69.0
Male: Female = 1.4:1						

Table 2: Distribution of clinical symptoms and signs according to age

Signs and symptoms	Infants	1-5 years	5-15 years	P-value
Pain abdomen	--	5	21	0.2
Headache	--	3	40	0.000*
Vomiting	2	12	15	0.1
Constipation	--	4	14	0.4
Diarrhea	3	12	3	0.000*
Cough	--	5	7	0.4
Anorexia	--	12	40	0.008*
Rose spot	--	--	--	--
Sick looking	3	15	33	0.3
Restless	1	5	8	0.7
Irritable	3	16	7	0.000*
Coated tongue	--	--	7	0.2
Abdominal distension	2	13	33	1
Abdominal tenderness	--	7	21	0.5
Splenomegaly	3	9	28	0.2
Hepatomegaly	1	11	27	0.8
Icterus	--	2	9	0.5
Cyanosis	0	2	1	0.3
Pallor	0	5	14	0.6

***Statistically significant (P-value <0.05)**

Table 3: Distribution of clinical symptoms and signs according to gender

Signs and symptoms	Male (n= 43)		Female (n= 31)		%age	P-value
	No.	%	No.	%		
Pain abdomen	13	30.2	13	41.93	35.1	0.3
Headache	23	53.5	20	64.51	58.1	0.3
Vomiting	18	41.9	13	41.93	41.9	0.5
Constipation	10	23.3	8	25.80	24.3	0.7
Diarrhea	13	30.2	5	16.12	24.3	0.2
Cough	6	13.9	6	19.35	16.2	0.5
Anorexia	29	67.4	23	74.19	70.3	0.5
Rose spot	--	--	--	--	--	--
Sick looking	29	67.4	22	70.96	68.9	0.7
Restless	11	25.6	3	9.67	18.9	0.2
Irritable	20	46.5	6	19.35	35.1	0.2
Coated tongue	2	4.7	5	16.12	9.5	0.1
Abdominal distension	23	53.5	25	80.64	64.9	0.01*
Splenomegaly	23	53.5	17	54.83	54.1	0.9
Hepatomegaly	21	48.8	18	58.06	52.7	0.4
Icterus	5	11.6	6	19.35	14.9	0.4
Cyanosis	2	4.7	1	3.22	4.1	0.8
Pallor	14	32.6	5	16.12	25.7	0.1

***Statistically significant (P-value <0.05)**

Table 4: Distribution of relative bradycardia in different age group

Relative bradycardia	Age		
	Infants	1-5 Years	5-15 Years
Present	--	--	4
Absent	3	20	47
Total	3	20	51
%age	--	--	7.8

Table 5: Distribution of leucocytosis in different age groups

Age group (years)	Number	%age	P-value
Infants (n=3)	3	100	0.002*
1-5 (n=20)	5	25	
5-15 (n=51)	8	15.7	
Total (n=74)	16	21.6	

***Statistically significant (P-value <0.05)**

Table 6: Differential leukocyte count in different age group

Age group (years)	Mean neutrophil	Mean eosinophil	Mean basophil	Mean monocyte	Mean lymphocyte
Infants	61.3	2	--	0.3	26
1 to 5 years	62.8	0.8	0.2	0.7	33.8
5 to15 years	65.4	1.5	0.1	0.8	33.1

Table 7: Frequency of anemia

Anemia	Frequency	Percent	Hemoglobin (gm/dl)	
Present	39	53	**Mean**	**SD**
Absent	35	47	10.7	1.9

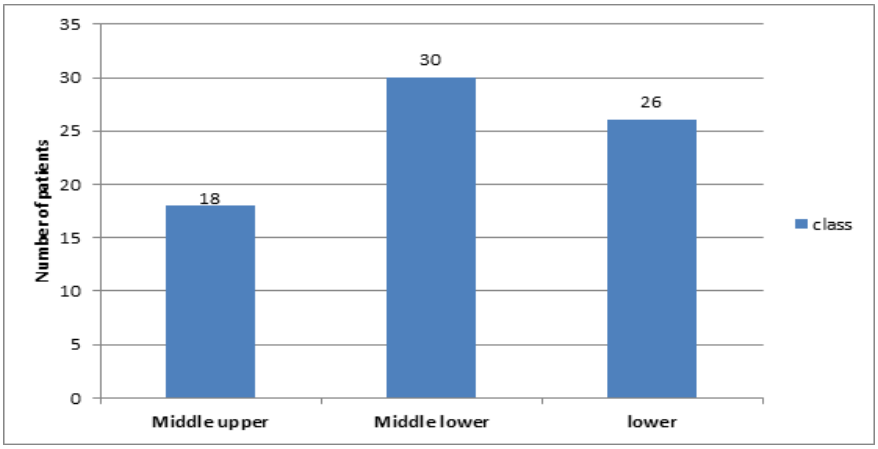

Fig. 1: Distribution of patients according to socioeconomic status

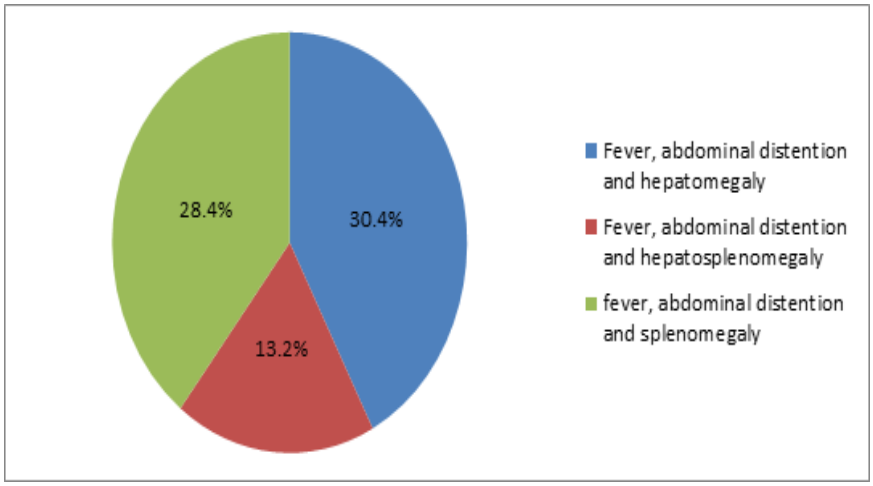

Fig. 2: Distribution of common clinical signs with fever

Discussion

We carried out a unicentric study of culture and Widal positive pediatric typhoid fever cases highlighting the clinical features and laboratory profile. Typhoid fever is a common cause of fever persisting for ≥5 days. It is an important cause of community acquired septicemia with high morbidity and mortality. Spread of this disease is through faeco-oral route facilitated by poor environmental hygiene, unhygienic food, contaminated water and polluted environment.

Due to the poor water supply and sanitary conditions, it continues to be a major public health problem in developing countries like Nepal, being compounded by emerging resistance to antibiotics that were effective earlier.

In the present study, the mean age of presentation was 7.6 years, which correlates well with the study conducted by Malik and Malik[7] in Malaysian population where the mean age of presentation was also found to be 7.6 years. On analysis of all the cases, it was found that majority of the subjects' belonged to older age group i.e. 5-15 years. This group constituted 69% (n=51) of all cases. This is in accordance to the general concept of typhoid fever as a disease of school aged children.

In our study, the male to female ratio was 1.4:1.This correlates with other studies conducted in Ganesh et al[8] and Sen and Mahakur[9] with male to female ratio of 1.29:1 and 1.1:1 respectively. The male predominance in our study is thought to be due to fact that, boys are more exposed to external environment, may consume unsafe water or food and hence are more prone to be infected. Moreover, in a male dominated society like Nepal, male child receives more attention than female child. This may be a cause of more number of male children receiving faster medical attention.

As observed with other studies, fever was the most common presenting symptom with mean temperature was 102.6°F with SD of 1.72. Anorexia was the second most common presenting symptoms found in 52 (70.3%) patients which was found to be statistically significant (p=0.008). This was similar to studies conducted by Raj C[10], Chandrashekhar et al[11] and Gosai et al[12]. In this study, headache was significantly more common in age group of 5-15 years seen in 40 (54.1%) patients which is comparable to studies conducted by Lefebvre et al[13], Joshi BG et al[14] and Khan et al[15]. On the contrary, a study conducted in Nepal by Singh et al[16] showed headache in 72.4% patients. This study recruited more number of cases above 5 years. This disparity could be due to the fact that children of younger age group may not appreciate headache or may not be able to report it as a symptom.

Vomiting was found overall in 29 (41.9%) subjects in the present study which is similar to the other studies conducted by Ganesh et al[8] and Patankar and Shah[17]. Abdominal pain was found in total 28 (37.8%) children in the present study. Previous studies conducted in Nepal by Singh et al[16] and Joshiet al[14] observed 33.3% and 22.5% of children complaining of pain in abdomen respectively. Diarrhea was found in 18 (24.3%) patients and was significantly more in the age group of 1-5 years (p=0.000). Similar findings were observed in studies conducted by Ganesh et al[8], Patankar and Shah[17], Chandra shekhar et al[11] and Chowta N[18]. Constipation was found in 18 (24.3%) patients, was more common in older children (5-15 years) and was not statistically significant. A study conducted in Nepal by Joshi et al[14] found constipation in 15% of the patients. Cough was found in 12 (16%) subjects in the present study and both genders were equally affected. This coincided with other studies conducted by different authors in India and Nepal.[11,14] Coated tongue was found in 7 (9.5%) children and all subjects were from 5-15 years of age group. This is in sharp contrast with other studies from various parts of world which showed higher incidence of coated tongue.[8,10,12,19] Abdominal distention was found in 48 (64.9%) patients in the present study and was the most common sign. No other studies confirm the same. Also it was statistically

significantly more common in females (p=0.01). A study conducted by Worku B[19] showed 40% of children having abdominal distention and was found to be more common in female as compared to males, the reasons for which could not be explained.

Splenomegaly was present in 40 (54.1%) patients in the present study. Hepatomegaly was found in 39 (52.7%) children; which was in line with studies of Raj C[10] and Gosai et al[12]. Most of the studies showed hepatomegaly to be more common than splenomegaly but present study found the frequency of splenomegaly higher than hepatomegaly. Rose spots were not observed in any cases in contrast to other studies. This could be due to the fact that rose spots are difficult to identify in dark skinned patients.

Relative bradycardia was found in 4 (5.4%) children in our study; all cases were in the age group of 5-15 years, which is in contrast with the studies conducted by Gosai et al[12] and Worku B[19]. Another study conducted by Ganesh et al[8] showed relative bradycardia in 15.2% cases seen mainly in children more than 5 years of age, which rightly correlates with the present study.

Leucopenia was not observed in any patient instead leucocytosis was found in 16 (21.6%) patients in the present study. 100% children up to 1 year group, 25% in 1-5 years age group and only 15.7% in 5-15 age groups had leukocytosis. Most of the studies observed more leucopenia than leucocytosis.[8,12,14,19] In the present study, leucopenia was not observed which could be due to the fact that almost all the patients who presented to us had taken antibiotics for few days of. In the region where this study was conducted, there is a liberal and wide spread use of antibiotics by medical shops without prescription of registered doctors. Eosinopenia was found in 31.4% of children. Similar observation was found in a study conducted by Chandrashekar et al[11] where it was observed in 38.4% of children.

Anemia was found in 39 (53%) patients in the present study. A study conducted by Raj C[10] showed anemia in 41.8% of patients and Lefebvre et al[13] in their study found anemia in 78% of children, which were in accordance with present study.

In the present study, S. typhi was isolated from blood culture of only 2 patients. The poor yield could be due to use of antibiotics prior to culture the blood. Clinically it was also found that chloramphenicol was more sensitive than ceftrixone and cefotaxime though not proven by sensitivity test. It could be due to over prescription of third generation cephalosporins in fever cases and also due to the fact that, in Nepal antibiotics can be purchased over the counter without prescription of registered clinicians. On the other hand the increasing response to chloramphenicol could be due to decreased use of this medicine in febrile patients.

Limitations of the study

1. Studies with longer periods and with the larger sample size are recommended as the present study was carried out for the short period with small sample.
2. Further studies including antibiotic sensitivity testing, treatment and follow-up of patients have to be carried out to provide a better understanding of this entity in order to improve future patient care.

Conclusion

The above study shows that typhoid fever continues to be a major health problem in a developing country like Nepal which has poor water supply and sanitary conditions. To avert the increasing morbidity and mortality from typhoid fever, clinicians and health workers need to work together to raise awareness about thorough hand washing before eating or preparing food and proper sanitary disposal. Typhoid fever should be suspected and investigated in all children with short and long duration fever without localizing signs. Early diagnosis and institution of appropriate antibiotics therapy is of paramount importance in the management of typhoid fever. Antibiotic sensitivity testing may be an added tool in this era of resistant strain emergence.

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