BANGLADESH J CHILD HEALTH 2010; VOL 34 (3): 80-85

Original Articles

A Reappraisal of Clinical Characteristics of Typhoid Fever

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Abstract

Background: Recent reports from developing countries show that the clinical presentation, diagnosis and treatment of typhoid have significantly altered often leading to missed diagnosis. The incidence of complications is also reported to be variable. The consequence of missed diagnosis is immense in terms of burden on limited health resources and patients' suffering. Therefore, its clinical spectrum requires constant reappraisal to update our physicians with current knowledge. This study was carried out to determine the changes in clinical pattern of typhoid fever.

Patients & Methods: A total of 106 children, aged up to 14 years, diagnosed primarily as typhoid fever, were included as study population. The diagnostic criteria were either positive blood culture for Salmonella typhi *or* Salmonella paratyphi *or at least a four-fold rise in antibody titre on Widal test. The study included mode of clinical presentations, treatment received before admission, Widal test findings and culture and sensitivity to antibiotics.*

Results: The mean age of the patients was 5.2 years and males were a little than the females. The mean duration of illness was 11.2±3.3 days. Majority of the patients presented with classical signs and symptoms like step ladder pattern of fever (nearly 70%) coated tongue (69.8%), diarrhoea (49.1%), toxemia (68.9%), relative leucopenia (71.7%), hepatomegaly (55.7%), pain in the right hypochondrium (41.5%) and splennomegaly (18.9%). Very few cases had a typical manifestations. Over 85% of the patients had raised SGPT (>40 IU/L) and 13.8% had detectable jaundice (serum billirubin >3 mg/dl). Widal test demonstrated that about 45% of the patients' 'O' antibody titer increased to 4-fold, 27.4% to 8-fold or more. In case of antibody 'H', 35.8% exhibited 4-fold and 39.7% 8-fold or more increase. Of the 103 cases, 68(66%) were positive for Salmonella typhi. *Majority of the isolated organisms was sensitive to cefixime, ceftriaxone and gentamycin (83%, 84% and 82% respectively). The second line of sensitivity was obtained to amikacin (64.2%), meropenem (50%), ciprofloxacin (46.2%), imepenem (46.2%) and azithromycin (43.4%). The least sensitive drugs were amoxicillin (28.3%), cotrimoxazole (27.4%) and chloramphenicol (22.6%). One-third (33.8%) of the patients had multidrug resistant (MDR) strains. However, No significant association was found between multi-drug resistant (MDR) strains and atypical clinical manifestations.*

Conclusion: *Clinical presentation of most typhoid fever still conforms with the classic pattern. High fever, anorexia, coated tongue, diarrhoea, relative leucopenia and hepatosplenomegaly are still common manifestations of typhoid fever. So, majority of the patients could be treated blindly based on clinical diagnosis. However, treatment should be given with first line of drugs like cefexime or ceftriaxone.*

Key words: *Typhoid fever, classic presentation, atypical presentation.*

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Introduction

Typhoid fever is a systemic infectious disease caused by *Salmonella enterica*, including *S enterica* serotype *Typhi* (*S typhi*) and serotype *Paratyphi* (*S paratyphi*). It is characterized by an acute illness, the first typical manifestations of which are step-ladder pattern of fever,

headache, abdominal pain, relative bradycardia, splenomegaly, and leucopenia[1,2]. Each year, worldwide there are at least 13-17 million cases of typhoid fever, resulting in 600,000 deaths[3]. With the adoption of sanitary and hygienic measures in the developed countries, there has been a marked decline in the incidence of the disease[4], although the disease is still endemic in developing countries. However, its clinical presentation, pathological and biochemical manifestations and antimicrobial sensitivity pattern have changed significantly posing problem to diagnosis and management[5]. Agarwal and associates[6] reported clinical features of typhoid fever to be in conformity with earlier studies[7,8] and noted spleenomegaly in only less than one third of the cases. Multidrug resistant enteric fever is associated with prolonged duration of fever, hepatomegaly, more complication and higher mortality[9-11]. Typhoid fever below five years of age is uncommon and these cases have more complications[12,13].

Durani and Rab[14] reported that classical pattern of step-ladder fever associated with relative bradycardia was not seen in most patients. Twenty-two percent cases had sudden onset of high grade fever and of them majority were clinically diagnosed as septicaemia. Diarrhoea, hepatomegaly and jaundice are not commonly encountered. Diagnoses of viral hepatitis, bronchitis, psychosis, meningitis, myocarditis, polyneuropathy and proximal myopathy were also made based on the presenting signs and symptoms. Neuropsychiatric manifestations were less frequent as compared to 45% cases reported from India[9,12]. In a study Dutta and associates[15] reported that nearly half (46.9%) of the enteric fever cases present with atypical manifestations. Atypical manifestations observed were burning micturation with normal urine examination (15.6%), diarrhooea, isolated hepatomegaly and bone-marrow depression (each 6.2%) in first week. Nearly one-third (31.3%) had multi-drug resistant (MDR) strains and 50% of the cases with MDR strains had atypical presentation[16]. As it results in high morbidity and mortality, reappraisal of presentation, course, complication and treatment is deemed necessary. So, this study was carried out to determine the changes in clinical pattern of typhoid fever.

Materials and Methods:

This descriptive study of 106 cases of enteric fever was done over a period of 14 months from September 2008 to December 2010 at the Central Hospital Ltd, Dhaka. With the permission of the hospital authority, informed consent was obtained from each of the participating subjects. The study was carried out to determine the changes in clinical pattern of enteric fever. Paediatric patients up to the age of 14 years, diagnosed primarily as typhoid fever, were the study population. The diagnostic criteria were either positive blood culture for *Salmonella typhi* or *Salmonella paratyphi* or at least a four-fold rise(1:160) in either 'O' or 'H" antibody titres on Widal test. The variables studied were age, sex, mode of clinical presentations, treatment received before admission and laboratory findings.

Laboratory tests performed were a complete blood count and widal test. The widal test was performed by rapid slide agglutination method using 'O' or 'H' agglutinins. Blood specimens were cultured to evaluate the yield of *Salmonella typhi* or *paratyphi.* Five ml of blood was collected in thioglycolate broth. Culture bottles were incubated at 37^0 C and then bacilli were identified according to standard techniques. Sensitivity status to different antibiotics was studied. Sensitivity of the cultured strains were tested against amoxicillin, cotrimoxazole, chloramphenicol, ciprofloxacin, amikacin, meropenem, imepenem, azithromycin, cefixime, ceftriaxone and gentamycin. The test statistics used to analysis the data were descriptive statistics, Chi-square test or Fisher's Exact Probability test. Spearmen correlation was done to see the relationship between temperature and pulse.

Results:

Out of the 106 patients, 10.4% was below 2 years, 45.3% between 2-5 years and 44.3% 5 years or above 5 years old. The mean age of the patients was 5.2±2.8 years and the youngest and oldest patients were 7 months and 14 years respectively (Table-I). Over half (54%) of patients was male and the rest female. Seventeen percent of patients presented between 5-7 days of onset of illness, 58% between 8-14 days and 25% after 14 days (Fig.-1). The mean duration of illness was 11.2±3.3 days and the shortest and longest durations were 5 and 17 days respectively. Widal test result demonstrated that 44.3% and 27.4% of the cases had 4- and 8-fold or > 8-fold rise of 'O' agglutinin

titers respectively, while 35.8% and 39.7% of cases had 4- and 8-fold or >8-fold rise of 'H' agglutinin titers respectively (Table-II). However, 'O' and 'H' agglutinins for S. *paratyphi* did not show significant increase. Of the 103 patients whose blood was cultured, 68(66%) were found positive for *Salmonella typhi* or *paratyphi* (Fig.-2). Of the 68 culture positive cases, 17(25%) were *S. typhi* and the rest were other species of Salmonella.

Table-I

Distribution of patients by demographic characteristics (n=106)

Demographic characteristics	Frequency	Percentage
Age (years)		
< 2	11	10.4
2 – 5	48	45.3
≥ 5	47	44.3
Sex		
Male	57	54.0
Female	49	46.0

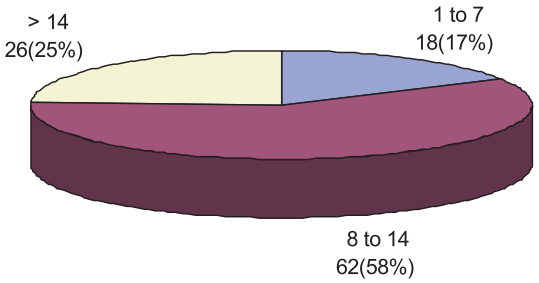

Fig.-1: *Distribution of patients by duration of illness (days)*

Table-II

Distribution of the patients by Widal test findings (n=106)

Widal test	Frequency	Percentage
TO		
Normal	06	5.7
2 fold	24	22.6
4 fold	47	44.3
8 fold or higher	29	27.4
TH		
Normal	08	7.5
2 fold	18	17.0
4 fold	38	35.8
8 fold or higher	42	39.7

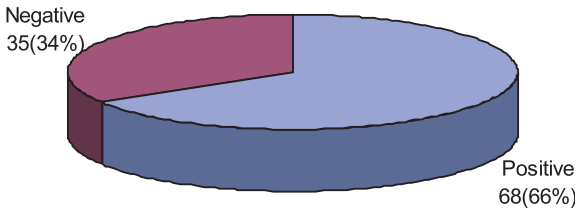

Fig.-2: *Distribution of patients by blood culture findings (n=103)*

Over 70% of the patients had step-ladder pattern of fever, 25.5% intermittent and 3.8% remittent fever (Table-III). About 70% of patients had coated tongue followed by 49.1% diarrhoea, 33% nausea/vomiting, 28.3% loss of appetite, 20.8% cough, 15.1% constipation, 13.2% headache, 12.3% relative bradycardia, 11.3% abdominal discomfort, 6.6% others. Toxemia was the predominant clinical sign (68.9%) followed by hepatomegaly (55.7%), pain in the right hypochondrium (41.5%) and splennomegaly (18.9%). Burning micturation, altered consciousness and dehydration each was found in 3.8% of the cases. Joint pain and muscle pain was negligible. Jaundice and epistaxis were rare (0.9%) (Table-IV). About 72% of the cases exhibited relative leucopenia (6000–11000/mm^3 of blood) and 15.1% absolute leucopenia (<6000/mm^3 of blood). One-third (33%) of the cases was found anaemic (haemoglobin <10gm/dl) and nearly 20% had raised ESR (>50 mm in 1st hour). Out of 29 cases, raised SGPT (>40 IU/L) and raised serum billirubin were found in 25 (86.2%) and 4 (13.8%) cases respectively (Table-V).

Table-III

Frequency of symptoms (n=106)

Symptoms[#]	Frequency	Percentage
Step-ladder pattern of fever	75	70.8
Coated tongue	74	69.8
Chills	05	4.7
Headache	14	13.2
Relative bradycardia	13	12.3
Loss of appetite	30	28.3
Nausea/vomiting	35	33.0
Abdominal discomfort	12	11.3
Diarrhoea	52	49.1
Constipation	16	15.1
Cough	22	20.8

[#]Multiple responses

Table-IV

Frequency of signs (n = 106)

Signs[#]	Frequency	Percentage
Pain in right hypochondrium	44	41.5
Jaundice	01	0.9
Epistaxis	01	0.9
Bleeding per rectum	06	5.7
Burning micturation	04	3.8
Joint pain and muscle cramp	04	3.8
Toxemia	73	68.9
Dehydration	04	3.8
Tachycardia	07	6.6
Splennomegaly	20	18.9
Hepatomegaly	59	55.7
Altered consciousness	04	3.8

[#] multiple responses

Table-V

Hematological and biochemical findings

Haematological and biochemical variables	n	Frequency (%)	Mean	SD
TC of WBC (/mm^3)	106		8539.8	
2869.7				
<6000		16 (15.1)	—-	—-
6000-11000		76 (71.7)	—-	—-
>11000		14 (13.2)	—-	—-
Hemoglobin	106	35 (33.0)	11.9	2.2
<10 gm/dl				
ESR >50 mm	106	21 (19.8)	—-	—-
SGPT >40 IU/L	29	25 (86.2)	—-	—-
Serum billirubin	29	4 (13.8)	—-	—-
>3 mg/dl				

As shown in table VI, the majority of the isolated organisms was sensitive to cefixime, ceftriaxone and gentamycin (83%, 84% and 82% respectively). The second line of sensitivity was obtained to amikacin (64.2%), meropenem (50%), ciprofloxacin (46.2%), imepenem (46.2%) and azithromycin (43.4%). The least sensitive drugs were amoxicillin (28.3%), cotrimoxazole (27.4%) and chloramphenicol (22.6%). One-third (33.8%) of the culture positive cases had multidrug resistant (MDR) strains (resistant to three commonly available antibiotics like amoxicillin, cotrimoxazole and chloramphenicol[16]).

Table-VI

Sensitivity of salmonellae typhoid or paratyphoid to different antibiotics

Antibiotic	Frequency[#]	Percentage
Amoxicillin	30	28.3
Cotrimoxazole	29	27.4
Chloramphenicol	24	22.6
Ciprofloxacin	49	46.2
Cefixime	88	83.0
Azithromycin	46	43.4
Ceftriaxone	89	84.0
Gentamycin	87	82.1
Amikacin	68	64.2
Meropenem	49	46.2
Imepenem	49	46.2

[#] multiple responses

Discussion

The clinical profiles of typhoid fever are diverse and atypical manifestation often makes a serious diagnostic problem, especially in childhood. The present study intended to assess the changing pattern of typhoid fever found mean age of the patients to be 5.2 years and the lowest and highest ages were 7 months and 14 years respectively. Males and females had almost equal representation in the population. The mean duration of illness at presentation was 11.2±3.3 days and the shortest and longest durations were 5 and 17 days respectively.

Majority of the patients in our study presented with step-ladder pattern of fever, coated tongue, toxemia, relative lecopenia and hepatomegaly, which conforms with classical presentation described by Dutta[15]. He studied clinical presentation of 32 bone marrow culture positive patients and described classical typhoid fever to be characterized by insidious onset of sustained fever, severe headaches, malaise, anorexia, a non productive cough (in the early stage of the illness), a relative bradycardia and leucopenia and hepatosplenomegaly. Diarrhoea and abdominal pain are also common manifestations[15]. Very few cases were presented with atypical manifestation. Atypical

manifestations observed were burning micturation with normal urine examination (15.6%), diarrhoea (6.2%) and encephalopathy (3.1%) in the first week, isolated hepatomegaly (6.2%), pneumonitis (3.1%) and bone marrow depression (6.2%). The present study revealed relative leucopenia as the common feature of typhoid fever as more than 70% of the patients had WBC count in the range of 6000-11000/mm^3 and 15% below 6000/mm^3 though majority of them had been suffering from the disease for more than 7 days.

Our study showed that majority (86.2%) of the patients had raised SGPT (>40 IU/L) and 13.8% had detectable jaundice (serum billirubin >3 mg/dl). Morgenstern and Hayes[16] studied the course of liver involvement during the first three weeks of typhoid fever in 20 patients and found almost consistent result with present study. In their study, hepatomegaly was found during the 2nd or 3rd week more often than in the 1st week (36% vs. 11%), whereas jaundice was detectable in 9% of patients after the 1st week.

A four-fold rise in somatic (O) agglutination titres in paired sera during the second week supports the diagnosis of enteric fever, provided vaccine had not been given recently (PHAC, 2005). As more than 70% of our patients exhibited at least a four-fold increase in somatic (O) agglutination titers, they could be considered diagnostic of the disease. Although two-thirds (66%) of the blood culture gave a positive result, they cannot be reliably considered as diagnostic, for sensitivity of blood culture alone is only 50% to 70% (PHAC, 2005). Clegg et al[17]. conducted a study in Papua New Guinea (PNG) in 1992 to re-evaluate the Widal slide agglutination test as a rapid diagnostic test for typhoid fever. This was in response to an apparent increase in the number of false positive Widal slide agglutinations occurring using an 'O' cut-off titer greater than or equal to 40 which was previously shown to be appropriate in 1987. The results of the re-evaluation indicated that the Widal test using a diagnostic cut-off titer of 40 or more lacked specificity and was no longer appropriate for this population and a new 'O' antibody titer of 160 or greater was then recommended as a diagnostic titer for typhoid fever in PNG.

Out of 68 culture positive cases, 23(33.8%) had MDR strains. In South East Asian nations, 5% or more of the strains of the bacteria have already been resistant to several antibiotics[3]. However, cross-tab analysis did not reveal any significant associations between MDR strains and atypical manifestations. Nevertheless resistance to commonly available antibiotics has emerged as a significant problem resulting in protracted illness and increased treatment cost.

Conclusion

The study concluded that the clinical pattern of typhoid fever did not change much from the classic pattern of typhoid fever. Anorexia, coated tongue, diarrhoea, relative bradycardia, relative neucopenia, hepatosplenomegaly are still common manifestations of typhoid fever. Very few cases had atypical manifestation. Atypical manifestations are usually seen in cases of infection acquired by resistant microorganisms. So majority of the patients could be treated blindly based on clinical diagnosis. However, treatment should be given with first line of drugs like cefexime or ceftriaxone. Second and third line of antibiotics can be used only if the isolated organisms are found sensitive to a particular antibiotic.

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