PREDICTORS OF INTESTINAL PERFORATION IN CHILDREN WITH TYPHOID FEVER

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ABSTRACT

Typhoid fever is a major public health problem globally; the greater burden however occurs in the developing countries because of lack of potable water and proper waste management. The disease is associated with a high mortality rate especially in those with enteric perforation or intestinal hemorrhage. The goal of this study was to identify the clinical and laboratory factors that predict the development of enteric perforation in children with typhoid fever.

This study was a retrospective case control analysis of children admitted for typhoid fever without or without enteric perforation over a three year period in a newly established teaching hospital in Kannur. Forty seven children with typhoid fever and enteric perforation (cases) were compared with 94 controls (those without typhoid fever but without enteric perforation). Multivariate analysis using logistic regression was applied to all the factors that were initially significantly associated with enteric perforation. Male sex (Odd Ratio, OR=3.10, p=0.003); inadequate treatment (OR=3.03,P< 0.001); short duration of illness (OR=2.36,P=0.030); neutrophilia (OR=2.92,p=0.013) and elevated ESR (OR=1.07, P=0.041) were found to have independently contributed to development of perforation in children with typhoid fever. This study has attempted to outline the factors that may predict typhoid ideal perforation in children, thereby helping in recognition of high risk cases and drawing up of screening tool to facilitate effective and prompt management.

KEYWORDS: Children, clinical, laboratory, perforation, predictors, typhoid

INTRODUCTION

Typhoid fever is a systemic illness caused by infection with Salmonella typhi, a gram negative bacillus, found only in humans (1). Although it is a major public health problem globally, the greater burden occurs in developing countries where most population neither have adequate and potable water nor proper waste disposal methods (1, 2). According to World Health Organization (WHO) and United Nation Children Fund (UNICEF) report, as at 2010, more than one billion people, especially those living in developing countries, do not have access to safe water (2).

The annual incidence of typhoid fever ranges from 10.2 to 50.3 per 100,000 population in most parts of the developing countries (3). The disease is associated with high mortality rate especially

in those with enteric perforation and intestinal bleeding (3). WHO estimated that the annual global incidence of typhoid fever is about 21 million cases with about 1-4% mortality. Adesunkanmi et al, reported a mortality of 24% among children and adolescents with typhoid perforation in a tertiary hospital in a south western Nigeria.

Few studies have attempted to describe the risk factors for enteric perforation in adults with typhoid fever. To the best knowledge of the authors, relatively little is known about factors predictive of enteric perforation in children with typhoid fever. Prompt identification and management of these factors may ultimately reduce the high morbidities and mortality associated with cases of childhood typhoid fever.

MATERIALS AND METHODS

The study was a retrospective case- control analysis of children aged two months to fifteen years who were admitted for typhoid fever with or without perforation over a 3 year period (January, 2008-December, 2010) at University Teaching Hospital, Kannur. Diagnosis of typhoid fever was made based on the clinical presentations as well as isolation of Salmonella typhi from the blood, stool or urine of the child using standard microbiological procedures (6).The clinical criteria used included persistent fever (fever duration longer than 7 days) and at least two of the following - constipation or diarrhea, anorexia, abdominal pain, abdominal rigidity, relative bradycardia and alteration in the level of consciousness (7). In addition to the haematological and microbiological investigations such as complete blood count, blood, stool and urine culture, all the children with acute abdomen had plain abdominal radiograph as well as abdominal radiography as well as abdominal ultrasonography for evidence of intestinal perforation such as the presence of air under diaphragm, free abdominal fluids and multiple air fluid levels. In most cases, abdominal radiography was done in erect position; however, for those who were unconscious, it was done in supine position.

The cases were children admitted with typhoid fever and radiological and surgical evidences of enteric perforation; either on admission or during the period of hospitalization. Children with traumatic or nontraumatic intestinal perforation not due to typhoid fever, such as ruptured appendix, abdominal tuberculosis, HIV were excluded from the study. The controls were children with clinical and microbiological evidence of typhoid fever but with no clinical, radiologic and surgical evidence of intestinal perforation.

The information collected from the patient's files were: age, gender, socioeconomic status of the parents, clinical symptoms, physical signs, hematologic, microbiologic, radiologic and operative findings where applicable, management and treatment outcome. In addition, treatment before admission into the hospital either at home or in the referral hospital was documented for all the patients. Those who received antibiotics that were presumably effective against Salmonella typhi at correct dose and for at least 3 days before presentation were considered as having adequate therapy prior to presentation. Chloramphinicol, Amoxicillin, Ciprofloxacin and Cephalosporins were taken as effective chemotherapeutic agents against Salmonella typhi (9).

The interval between the onset of first symptom and presentation in our hospital was defined as the duration of illness prior to admission with duration of illness less than or equals 14 days taken as short duration (7).The socioeconomic status of the parents was based on the occupation and the highest level of education of the parents.

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The two groups (cases and control) were compared in terms of their socio-demographic characteristics (age, sex, socioeconomic class), clinical symptoms and signs including duration of illness prior to presentation, adequacy of therapy before presentation, presence of high fever (temperature > 38.5) and hepatosplenomegaly. In addition the two groups were compared based on their laboratory findings such as haematocrit, complete blood counts and differentials, serum AST and ESR. These blood indices were selected because they are commonly deranged in complicated enteric fever.

The data were analyzed using SPSS version 17. Tests of association between the variables and the presence of enteric perforation were performed with chi-squared and student's t test for categorical and continuous variable respectively. Variables with statistically significant association with perforation were further analyzed with logistic regression modelling to identify the independent predictive factors of intestinal perforation in children with typhoid fever. Results of logistic regression were presented with Odds Ratio (OR) and 95% Confidence Interval (CI). Statistical significance was established when P values where <0.05 or Confidence Intervals excluded unity.

RESULTS

During the study period a total of 193 children with blood, stool and or urine culture positive for Salmonella typhi were managed in the PICU of the hospital. One hundred and forty one of these children, comprising of all the 47 cases (those with enteric perforations) and 94 controls (those without enteric perforations who were selected at random) were included in the study. The rate of typhoid fever perforation was 24.4%. Seventy-eight (55.3%) of the children studied had Salmonella typhi isolated from their blood, forty five (31.9%) from the stool and twenty seven (19.1%) from the urine. Nine (6.4%) had positive blood and urine culture.

Table 1
Comparison of the socio-demographic characteristics between the cases and the control

Socio-demographic characteristics	Cases $n = 47$	Control $n = 94$	Total $n = 141$	χ^2	P
Sex				8.941	0.003
Male	34 (72.3)	43 (45.7)	77		
Female	13 (27.7)	51 (54.3)	64		
Age group (in years)					
1–5	5 (10.6) ·	17 (18.1)	22	1.320	0.251
> 5–10	35 (74.5)	51 (54.3)	86	5.381	0.020
> 10	7 (14.9)	26 (27.7)	33	2.848	0.091
Socio-economic class					
Upper class (I-II)	9 (19.1)	23 (24.5)	32	0.505	0.477
Middle class (III)	7 (14.9)	28 (29.8)	35	3.725	0.054
Lower class (IV-V)	31 (66.0)	43 (45.7)	74	5.133	0.023

The 47 children with surgically confirmed enteric perforation (cases) comprised of 34 males and 13 females with a male to female ratio of 2.6:1. Their ages range from 26 to 184 months with a mean standard deviation (SD) of 96.51 (31.30) months. Also, 94 children whose blood, stool, and or urine were positive for Salmonella typhi organism but had no clinical or radiological evidence of enteric perforation who were selected as control were comprised of 43 males and 51 females (the ratio female to male 1.2:1). The mean (SD) age of the control was 93.56(39.70) months, ranging from 22 to 180 months. Although the mean (SD) age of the cases was higher than the control; the difference was not significant statistically (t=0.45, p=0.657). However, significantly higher proportion of males had perforation as 34 (44.2%) of the 77 males compared with 13 (20.3%) of the 64 females had enteric perforation (x2=8.941, p=0.003).

Table 2
Comparison of the clinical features between the cases and the control

Clinical features	Cases $n = 47$	Control $n = 94$	Total $n = 141$	χ^2	P
High fever (T > 38.5°C)	45 (95.7)	85 (90.4)	130	1.541	0.214
Abdominal pain	47 (100.0)	89 (94.7)	136	1.270	0.260
Constipation	12 (25.5)	19 (20.2)	31	0.517	0.472
Diarrhea	28 (59.6)	42 (44.7)	70	2.780	0.095
Vomiting	30 (63.8)	65 (69.1)	95	0.143	0.706
Inadequate pre-hospital treatment	39 (83.0)	58 (59.8)	97	6.607	0.010
Short duration of symptoms	19 (40.4)	21 (21.6)	40	5.043	0.025
Rebound tenderness	47 (100.0)	34 (36.2)	81	49.644	< 0.001
Hepato-splenomegaly	33 (70.2)	69 (73.4)	102	0.160	0.690

Tables 1-3 compare the sociodemographic characteristics, clinical features and the laboratory findings between the cases and the control. From Table 1, significantly higher proportion of cases were males, school aged and from lower social class (p=0.0003, 0.020 and 0.023, respectively). Also, as shown in Table 2, more cases had short duration of illness (onset of illness to presentation <_ 14 days), inadequate treatment before presentation to our unit and rebound tenderness (p=o.o25, 0.010 and <0.001, respectively). The duration of illness before presentation among the cases ranged from five to 21 days, with a mean (SD) of 9.03 (2.12) days, where as that of the control ranged from 6 to 28 days, and a mean (SD) of 14.77 (4.22) days. The average duration of illness in cases was significantly shorter than that of the control (t =8.78, df = 139, p <0.001). Table 4 shows that neutrophilia (p =0.011), elevated ESR (p <0.001) were significantly associated with enteric perforation.

Table 3
Comparison of the laboratory findings between the cases and the control

Laboratory findings	Cases $n = 47$	Control $n = 94$	Total $n = 141$	χ^2	P
Severe anemia	8 (17.0)	16 (17.0)	24	0.000	1.000
Neutrophilia	15 (31.9)	13 (13.8)	28	6.439	0.011
Leucopaenia	10 (21.3)	22 (22.7)	32	0.081	0.776
Leucocytosis	10 (21.3)	27 (28.7)	37	0.898	0.343
Elevated serum Creatinine	6 (12.8)	8 (8.5)	14	0.634	0.426
Elevated serum AST	23 (48.9)	41 (42.3)	64	0.358	0.550
Elevated ESR	19 (40.4)	17 (17.5)	36	8.225	0.004
Air under the diaphragm	35 (74.5)	0 (0.0)	35	89.165	< 0.001
Air fluid level	43 (91.5)	34 (36.2)	77	38.683	< 0.001

Severe anaemia (packed cell volume < 15%), leucopaenia (total white blood cell count < 2000/ccml of blood), leucocytosis (total white blood cell count > 11,000/ccml of blood), neutrophilia (neutrophils > 60% of total WBC), elevated serum creatinine (serum creatinine > 110 micromol/L), elevated AST (serum Aspartate aminotransferase > 35 IU/L), elevated ESR (erythrocyte sedimentation rate > 15 mm/hr).

Table 4
Socio-demographic data, clinical features and laboratory findings independently associated with enteric perforation in children with typhoid fever using logistic regression analysis

Variables	95 % CI	OR	P
Male	1.46–6.61	3.10	0.003
School age children	2.43–5.14	2.47	0.086
Low social class	1.71–7.49	0.44	0.101
Rebound tenderness	0.00		0.997
Inadequate treatment	0.09–0.46	3.03	0.000
Short duration of illness	1.13–10.75	2.36	0.030
Neutrophilia	1.25–6.28	2.92	0.013

95% CI = 95% Confidence Interval, OR = Odd Ratio.

Multivariate analysis using logistic regression was applied to all the factors that were significantly associated with enteric perforation. As presented in Table 4, male sex (OR =3.10, P =0.003); inadequate treatment (OR =3.03, P <0.001); short duration of illness (OR =2.36, P=0.013) and elevated ESR (OR =1.07, p =0.041) were found to have independently contributed to the occurrence of perforation in children with typhoid fever.

In term of mortality, six of the 47 children (12.8%) with typhoid perforation and two of the 94 children (2.1%) without perforation died. Significantly higher proportion of children with intestinal perforation died($x2$ =4.787, df =1, p =0.029).

DISCUSSION

Enteric perforation in children with typhoid fever is still is a major health problem in our environment, with a rate of 24.4% in the children we studied. This rate is within the quoted 10-30% rates reported in many studies in developing countries (1, 5, 7, and 8). In this study, some socio-demographic characteristics, clinical features and laboratory findings were found to be significant independent predictors of enteric perforation in children with typhoid fever.

The finding of a male gender as an independent factor for enteric perforation in children is in concordance with some previous studies (8, 10). Hosoglu et al found that significantly more males than females (M:F =4:1) had perforation (7).The explanation for this observation, however, remains unclear.

None of the infants in this study had enteric perforation. This is consistent with previous observation that enteric perforation is rare in infancy: with reported rate of less than 1% in many studies (3, 4). Perhaps their poor immunological state may be responsible for this. The older children possibly would have had multiple exposures to Salmonella typhi organisms over time.

Although, significantly higher proportion of our cases where school aged children, (p =0.020), when further analyzed as independent risk factors for perforation, the factor was not significant. This contrast with the finding by Bulter et al, who concluded that older age is a significant risk factor to intestinal perforation (11).

Clinical features such as high grade fever, abdominal pain and hepatomegaly were common among children with typhoid fever; either with or without enteric perforation. This agrees with previous studies (1, 3, 5, 7). Rebound tenderness which indicate peritoneal irritation from soilage, was seen in about one-third (36.2%) of the children without radiological evidence of enteric perforation. These patients could have had minimal perforation.

Inadequate treatment prior to admission in our hospital independently predicted perforation in the children studied. If adequate and prompt treatment has been sought or initiated at the referral center; perhaps, some of these children would not have developed intestinal perforation. It has been reported that the timing, dosage and duration of antimicrobial therapy in typhoid fever are important in limiting morbidities such as intestinal bleeding and perforation (12).They must be commenced early following outset of symptoms, at appropriate dose for adequate period. It is however worrisome that in most parts of the developing countries, delay presentation as well as antibiotics abuse and misuse still predominates.

The causes of delayed presentation of typhoid fever in third world countries are due to inadequate health seeking behavior (13) and the presence of endemic malaria infection which is clinically similar to typhoid fever especially in the early stages. Inadequate therapy can also lead to emergence of multidrug resistant strains of Salmonella typhi, which may cause atypical presentation (14).

A short duration of symptoms was also found to predict perforation. In this study, the mean duration of symptoms in cases was significantly shorter than that of the control. This is similar findings by Khan et al. and supports the hypothesis that the disease pathogenesis in children with typhoid perforation is fulminant (15). The damage in the Payer's patches, which is associated with the inflammatory response of the host as well as the virulence of the organisms, is associated with intestinal ulceration, haemorrhage, necrosis and perforation (16).

The findings of neutrophilia and elevated ESR as predictors of enteric perforation are consistent with several previous studies, which reported that leucopoenia is more common in patients with uncomplicated typhoid fever, while leukocytosis and neutrophilia are more common in those with intestinal perforation or cholecystitis (4).

CONCLUSION

This study, although retrospective in nature, has attempted to outline those factors that predict typhoid ileal perforation in children. This will ultimately help in recognition of high-risk cases and drawing up of screening tool to facilitate effective and prompt management.

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