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Clinical Patterns of Typhoid Fever in Children in Zimbabwe

IC Chikanza[1,2]*, TA Mazodze[3], K Nathoo[4] and CML Olweny[5]

[1]*International Arthritis and Hypermobility Centre @ Harley Street Clinic, London WIG 7AF, UK*

[2]*Department of Medicine, Catholic University, Harare, Zimbabwe*

[3]*Department of Pediatrics and Child Health, University of Zimbabwe, Harare, Zimbabwe*

[4]*Department of Pediatrics and Child Health, Harare Teaching Hospital, Harare, Zimbabwe*

[5]*Uganda Cancer Institute, Upper Mulago Hill Road Kampala, Uganda*

***Corresponding Author:** IC Chikanza, International Arthritis and Hypermobility Centre @ Harley Street Clinic, London WIG 7AF, UK and Department of Medicine, Catholic University, Harare, Zimbabwe. E-mail: i.c.chikanza@btinternet.com

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Abstract

The clinical, serological, hematological and biochemical features of bacteriologically proven typhoid fever were assessed prospectively in 218 children in Zimbabwe over a 3 year period. The most predictive clinical features most useful in diagnosing pediatric typhoid fever, were fever with relative bradycardia, abdominal pain and diarrhea. Though there was a high incidence of complications, treatment with chloramphenicol was associated with a good outcome. Hepatic involvement occurred in 28% (61), 3.7% (8) had myocarditis, 14.7% (32) had renal complications, 8% (6) developed gastrointestinal complications whilst neuropsychiatric manifestations occurred in 55.5% (121) of cases. For the Widal test, H titres were a more sensitive indicator of infection, being found in 57,3% of culture positive cases compared with 33.5% for O. The relapse rate was 1.8% whilst the mortality rate was 0.45%.

Keywords: *Typhoid Fever (TF); Widal Test (WT); Children*

Introduction

Enteric fever {generically called typhoid fever (TF)} remains endemic in the developing world [1]. Advances in public health and hygiene have led to its virtual disappearance in the developed world. The causative organism is *Salmonella enterica serovar typhi* (*S. typhi*), a gram negative bacterium and *S. paratyphi A* {which causes less severe disease}, less commonly, *S. paratyphi B* and *S. paratyphi C*. About 14.3 million cases of typhoid {76.3%} and paratyphoid fevers were diagnosed 2017 [15]. Higher fatality rates were observed in children and older adults, as well as generally, in cases from lower-income countries [15]. We do not have accurate typhoid cases estimates on incidence and mortality rates in Zimbabwe.

The spectrum of the disease pattern has continued to alter over the last 4 decades. The introduction of chloramphenicol and subsequently amoxicillin and fluoroquinolones coupled with improvements in the socio-economic status amongst other factors might have played a role [2]. A number of reports on the clinical aspects of TF based on retroprospective analysis of mainly adult cases have been

published [3-5]. None have looked prospectively at the clinical patterns in the paediatric-age group. In fact most of the studies of TF in adults (with the exception of that of Gupta., *et al*, Gulati., *et al*, Huckstep) have been retrospective [3-5]. The incidence of complications and outcome as well as the spectrum of clinical features appear to be different in children when compared to adults [6]. This prospective study in children with bacteriologically proven TF was designed to prospectively assess the clinical, hematological, biochemical and serological parameters during the course of TF.

Materials and Methods

All children under 13 years of age admitted over a 3 year period into Harare and Parirenyatwa Hospital and Wilkins Infectious Disease Hospital with bacteriologically proven TF were prospectively studied. A detailed history and physical examination were done on admission. Clinical progress, temperature and physical examination were recorded. Investigations on admission included: hepatitis B serology, weekly hemogram (total and differential WBC and platelet counts), serum urea and electrolytes, liver function tests, complement and immune complex levels, urinalysis, blood/urine/stool cultures, electrocardiogram and WT. The hemogram, urea and electrolytes were done weekly. Patients were treated with chloramphenicol 30 - 50 mg/kg/day orally for 21 days and the response to therapy was assessed. Relapse of TF was defined as the recurrence of symptoms and re-isolation of organisms by culture after discontinuation of therapy. Patients were followed up after discontinuing antibiotics with cultures of urine, stool and blood at 72 hours, 2 weeks, 1 month and 4 months.

Results

A total of 218 children (101 males and 117 females), maximum age 13 years, were studied. There were two neonates who were treated with amoxycillin. The average duration of illness before admission from onset of symptoms was 16.6 days (range 3 - 35). On admission the commonest symptoms were fever, cough, diarrhea, abdominal pain, acute confusional state and headache (Table 1). The most frequent clinical signs were: pyrexia, relative bradycardia, pallor, toxic psychosis and abdominal tenderness (Table 2). Unusual manifestations were of cardiac, hepatic, renal and neuropsychiatric nature.

Myocarditis manifested clinically with undue tachycardia, feeble pulse, muffled heart sounds and cardiac decompensation as well as ECG changes of low voltage complexes and changes in the PR interval and QTc interval, ST segment displacement and non-specific T wave changes in many leads as described by Goldman [13] occurred in 3.7% of cases. Echocardiograms were not performed due to lack of equipment. All patients recovered on the institution of anti-heart failure measures and chloramphenicol therapy. Relative bradycardia i.e. a low pulse in relation to fever, occurred in 61.9% (135) of cases. Renal impairment occurred in 14.7% (32) of cases. Four patients

Symptom	Number	% Frequency
Fever	184	84.4
Loss of weight	131	60.1
Diarrhea	127	58.3
Abdominal pain	110	50.5
Cough	93	42.7
Headaches	87	39.9
Malaise	85	39
Vomiting	54	24.8
Constipation	51	23.4

Table 1: *Clinical symptoms on admission showing the percentage frequency of occurrence of symptoms in decreasing order of frequency.*

Clinical Sign	Number	% Frequency
Pyrexia	212	97.2
Bradycardia	135	61.9
Abd. tenderness	133	61
Neuropsychiatric	121	55.5
Anemia	103	47.2
Hepatomegaly	69	31. 7
Pulmonary crepitations	44	20.2
Splenomegaly	38	17.4
Edema	24	11
Jaundice	8	3,7
Heart failure	8	3,7

Table 2: *Pattern of clinical signs in order of decreasing percentage frequency.*

developed pre-renal azotemia whilst 10 cases had nephrotic syndrome. Typhoid glomerulonephritis associated with periorbital and peripheral edema, uremia casts of various types, hematuria, proteinuria, oliguria (with anuria in 30%), hypertension, ASOT < 200 U/L, low complement 3 levels and high levels of immune complexes (assayed using a Clq-based assay technique) was found in 14 cases.

Four of the cases had hemolytic uremic syndrome with thrombocytopenia, acute hemolysis and acute renal failure not associated with G6PD deficiency. All patients made a good recovery with treatment. Neuropsychiatric features occurred in 55.5% (121) of cases. The distribution of the various manifestations is shown in table 3. Lumbar punctures done on 20 patients with meningism, stupor and convulsions revealed no CSF abnormalities. There were no cases of typhoid meningitis. All patients recovered with treatment. Mild to severe hepatic injury was found in 28% (61) of cases. Hepatic involvement with jaundice (bilirubin > 40 umol/l), elevated AST > 600 U/L and ALP > 700 U/L as well as abnormal blood clotting profile were seen in 8 cases. Liver biopsies were not done as all the patients recovered with treatment. Mild elevations of bilirubin and hepatic enzymes were found in 53 cases. Tender hepatomegaly was a feature in the 61 cases of whom 12 had splenomegaly. Hepatitis B serology was negative in all the cases. Acute colitis with endoscopically proven ulceration which was macroscopically indistinguishable from ulcerative colitis occurred in 2 cases whilst fatal ileal perforation occurred in 5 cases of whom 3 presented with profuse blood in stool whilst one later had a fatal ileal perforation.

Clinical Sign	Number	% Frequency
Delirium	96	44
Meningism	12	5.5
Convulsions	4	1.8
Psychosis	3	1.38
Myoclonus	2	0.92
Stupor	2	0.92
Spasticity	1	0.46
Hypotonicity	1	0.46

Table 3: *Distribution of neuropsychiatric features in order of decreasing frequency.*

Other features included paralytic ileus (3 cases) in the face of normal serum potassium. Stool cultures were positive in 61% (133), blood 59.2% (129) and urine 5.5% (12). On admission, significant O and H titres of > 1:160 were found in 33.5% (73) and 57.3% (125) respectively. The relapse positivity rate was 1.8% (4).

Discussion

This study prospectively looked at the manifestations and complications of typhoid fever in children in Zimbabwe. At the time of the study chloramphenicol was widely used to treat TF. The majority of patients in this study had fever (84.4%) and it tended to be intermittent simulating malaria. Low grade fever (temperatures of < 38°C) was found in 10% of cases, a figure in agreement with the work of Gupta., *et al.* [5]. These findings contrast with those of other workers [4,5,7]. Manson-Bahr reported that intermittent fever was not compatible with a diagnosis of TF [8]. The step ladder pattern of temperature stressed in earlier studies, was rare in this study being found in only 2.1% of cases [9,10]. Diarrhea (58.3%) was more common than constipation (23.4%). The incidence of colitis was very low (0.92%) in children and this contrasts sharply with the high incidence of about 20% in adults with TF [11]. Furthermore children had a low frequency (0.45%) of gut perforation. Gupta., *et al*. found an incidence of 9.6% in adults [5]. Children may be more resistant to developing this complication or that the use of corticosteroids in Gupta's series probably accounted for the higher incidence to gut perforation. Relative bradycardia was seen in 61.9% of children. This is comparable with the figure in adults of 50% [7]. Watson stressed that bradycardia never occurred in the first week of illness [12]. We found it in the first week in children. In our experience it constituted a useful adjunctive clinical sign that helped to exclude other causes of fever. The pathogenesis of this bradycardia is still uncertain. All children with myocarditis recovered fully. Table 4 shows the comparative incidence of complications in children in our series and those from another series with adult patients [5]. At the time of the study, chloramphenicol was widely used to treat TF in Zimbabwe. Currently, Ciprofloxacin is the commonly used antibiotic. However, in Harare now, 20% of typhoid cases show resistance to ciprofloxacin. So, 1:5 TF cases will require treatment with the more expensive antibiotics such as azithromycin.

Complication	Adults (%)	Children (%)
Neuropsychiatric	16	55.5
Hepatic Injury	5.6	28
Renal Impairment	0	14.7
Myocarditis	13.6	3.7
Bowel Perforation	9.6	0.45
Rectal Bleeding	8.8	0.91
Mortality	8.8	0.45

Table 4: *Comparative % complication rate in adults (Gupta., et al. 1985) and children in this study.*

Conclusion

There are differences in the incidence of unusual manifestations of TF in children and adults. Children tend to have a more severe illness and have an increased tendency to developing neuropsychiatric, renal and hepatic manifestations but surprisingly respond well to treatment. They also have a low mortality compared to adults. The most prevalent clinical features suggestive of TF were pyrexia with relative bradycardia, abdominal tenderness and diarrhea rather than constipation. Stool and blood cultures were more frequently positive than urine cultures. For the WT, the H titre was a more sensitive indicator of infection than O titre.

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