FULMINANT HEPATIC FAILURE WITH TYPHOID FEVER IN CHILDHOOD

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ABSTRACT

Although hepatic dysfunction has been described among adults with typhoid, there are few reports of significant hepatic functional impairment in children with typhoid. Of 355 children with culture proven typhoid seen at the Aga Khan University Hospital, hepatomegaly was noted in 118 (33%) and isolated right hypochondrial tenderness in 30 (8.5%). The liver function tests were normal in 78% and 47% of these children respectively and significant hepatic dysfunction was seen only in 26 (7.3%). However, children with typhoid and significant hepatic dysfunction had higher mortality ($P < 0.001$) and two patients presented with a picture of fulminant hepatic failure with fatal outcome (JPMA41: 123, 1991).

INTRODUCTION

Although hepatic dysfunction in typhoid fever has been recognized for nearly a century[1], significant hepatic dysfunction is uncommon[2]. There have been sporadic case reports in adults[3-5] of hepatic derangement in typhoid, but very little is known about potential hepatic involvement with typhoid in children. We present our experience of hepatic dysfunction in culture proven typhoid fever among children at the (AKUR), Karachi.

PATIENTS AND METHODS

Since early 1986, the department of paediatrics at AKUR has employed the following protocol for investigating suspected typhoid fever in children. A complete blood count and blood culture are obtained in all cases with suspected typhoid fever. A bone marrow aspirate for culture is also taken if there is a history of prolonged illness (15 days) or antibiotic administration for _ 72 hours prior to presentation. A stool culture is obtained if there is concomitant diarrhoea at presentation. Liver function tests (total and direct biirubin, alanine transaminase (SGPT) and alkaline phosphatase) are performed if there is hepatomegaly or right upper quadrant tenderness. We retrospectively analysed the case records of all children presenting to AKUH with culture proven typhoid fever between January 1986 and December 1989. Children with confirmed typhoid were identified from the admission records of the paediatric ward and a log book of blood and body fluid cultures maintained by the microbiology laboratory at AKUH. The case records were specifically analysed for mode of presentation, clinical features and laboratory evidence of hepatic dysfunction, course of the illness and presence of complications. The ‘t’ test and chi square analysis were employed for data analysis as appropriate.

RESULTS

A total of 355 children with culture proven (blood and/or bone marrow cultures) typhoid were studied. Amongst these visible icterus was unusual and only seen in six (1.7%) children. One hundred and eighteen (33%) children presented with hepatomegaly. Of these 56 (47.5%) also had associated tenderness in the right hypochondrium on palpation. Forty nine (13.8%) children presented with

splenomegaly. Thirty (8.5%) children were tender on palpation in the right hypochondrium but had no discernible hepatosplenomegaly. All children (n= 148) with hepatomegaly and/or tenderness in the right hypochondrium had liver function tests done at adniission. There was poor correlation between hepatomegaly and impairment of liver function tests. Of 118 children with hepatomegaly who had liver function tests performed at admission, 92 (78%) revealed values well within the normal range. Similarly 14/30 (47%) children presenting with only right hypochondrial tenderness had normal liver function tests. Significant hepatic dysfunction (defined as hepatomegaly ± right hypochondrial tenderness and elevation of SGPT 80 _ lu/i) was seen in 26 children. The mean SGPT in children with hepatic dysfunction was 129.6 ± 49.1 lU/i (range 80-301 IU/1).

TABLE I. Comparison of children with typhoid according to hepatic dysfunction.

	Hepatic Dysfunction	Normal Hepatic function
Number of children	26	329
Age (Yrs)	5.9 ±3.8	7.0 ±4.1
Sex ratio (M:F)	16 : 10	189 : 140
Duration of illness (days)	12.2 ±7.7	12.0 ±12.8
Toxicity (%)	14 (54%)	134 (41%)
Mortality (%)	4 (15.4%)	3 (0.9%)

Note: Values are mean ± SD

Table I shows the clinical characteristics of children with typhoid and hepatic dysfunction, in comparison with typhoid patient without any obvious hepatic involvement. Children with hepatic dysfunction were slightly younger and a higher percentage were toxic at admission. The mortality in children with hepatic dysfunction was significantly higher than in those without hepatic impairment p2 = 26.1, PczO.00l). The mean time, todefervescence of children with typhoid and hepatic dysfunction was 6.6 ± 2.7 days and only one (3.8%) child relapsed.

TABLE II. Comparison of liver function parameters in children with drug sensitive and multi-ple-drug-resistant typhoid.

Typhoid	Drug Sensitive Typhoid	Multiple Drug Resistant
Number of children	284	71
Hepatomegaly (%)	84 (29.6%)	34 (47.9%)
Jaundice(%)	4 (1.4%)	2 (2.8%)
Serum bilirubin (mg/dl)	0.8 ±0.9	1.0 ±1.7
SGPT(IU/l) (Alanine transaminase)	68.4 ±53.5	73.3 ± 57.5
Alkaline phosphatase (IU/l)	176.7 ±86.2	211.0 ±225.9

Note: values are mean ±SD

Table II shows the comparison of clinical and laboratory features of children with drug sensitive and multiple-drug-resistant (MDR) typhoid, with reference to liver function. A significantly greater number of children with MDR typhoid had hepatomegaly ($X2 = 10.7$, $P < 0.01$) but the number of children with elevation of SGPT (50 IU/l) was equal in both groups (57% and 53% respectively). There was a wide spectrum of clinical hepatic derangement in the patients, ranging from mild elevation of SGPT in 56 (16%) children with typhoid, to fulminant hepatitis in a few. We present the case reports of two children with typhoid who died and also showed evidence of hepatic dysfunction.

Case 1: This eight months old male infant weighing 6.8 kg, was admitted as an emergency with hyperpyrexia and a history of a purulent discharge from the left ear for 72 hours. He had been unwell for nearly 30 days with intermittent bouts of diarrhoea and a low grade fever for nearly 20 days. On examination he was febrile 41°C had a heart rate of 120/min and a respiratory rate of 60/mm. His breathing was acidotic and peripheral perfusion was poor. The pupils were equal bilaterally but non-reactive and the anterior fontanelle was normal. The liver was 5 cm palpable below the right coastal margin and the spleen was also 1 cm palpable. Investigations showed Hb 7.9 g/dl, Hct 22.2%, WBC 23600/cu mm, neutrophils 87%, lymphocytes 9%, monocytes 2%, eosinophils 2%, peripheral film showed toxic neutrophilia with left shift and malarial film was negative. APTT was 114 sec (control 34 sec), PT was 92 sec (control 13 sec), platelet count 15000/cu mm, blood glucose 185 mg/dl, sodium 134 meq/l, potassium 2.5 meq/l, chloride 101 mecijl, bicarbojiate 10.9 meqJl, serum biirubin 3.3 mg/dl (direct 1.6 mg/dl, indirect 1.7 meq/l), SGPT 90 IU/1 and serum ammonia 242 mcg/dl. Arterial blood gas showed pH 7.437, PCO2 14.6 torr, P02 148 torr and base deficit 10.2 meqJl. The chest Xray showed slight cardiomegaly with bilateral pulmonary venous congestion consistent with congestive cardiac failure. The child was resuscitated in the emergency room, given fresh frozen plasma and placed on cefotaxime 80 mg/kg/day IV. However, despite these resuscitative measures, he went into cardiorespiratory arrest two hours after admission from which he could not be resuscitated. An autopsy was refused by the parents. Blood cultures taken at admission grew Salmonella paratyphi B resistant to ampicillin, chioramphenicol and trimethoprim-sulfa and sensitive to cefotaxime, aztreonam and ofioxacin.

Case 2 : This was a 3 yrs 8 months old child who presented to the emergency room at AKUH with generalized tonic clonic seizures for 30 minutes. He had developed a high grade fever 12 hours prior to referral and had had one bloody mucoid stool. In the past he developed hepatitis A seven months earlier, from which he had recovered uneventfully. He was also diagnosed to have severe iron

deficiency anaemia at that stage for which he had received a blood transfusion and oral iron supplements. On examination the child weighed 12.2 kg, had a temperature of 390C and was in grade III coma. His heart rate was 124/mm, respiratory rate 50/mm with deep respirations, blood pressure 85/70 mm Hg. His pupils were equal and reactive, there were no signs of papilloedema or meningeal irritation but the plantar reflexes were upgoing. He had generalized tonic clonic seizures in the emergency room with facial twitching. Investigations revealed a Hb 11.2 g/dl, Hct 36%, WBC 21800/cu mm, neutrophils 80%, lymphocytes 15%, monocytes 4% and eosinophils 1%. Peripheral blood film showed neutrophiia with left shift and toxic granulation. Blood sugar was 24 mg/dl, sodium 125 meqJl, potassium 3.5 meq/l, bicarbonate 12.5 meciJl, BUN 12 mg/dl, serum creatinine 0.8 mg/dl, calcium 8 mg/dl and serum Osmolality 257 mosm/l. Serum bilirubin was 2.4 mg/dl (direct 0.4 mg/dl, indirect 2.0 mg/dl), SGPT 132 lU/i, alkaline phosphatase 364 IU/l and serum ammonia 212 mcg/dl. Prothrombin time was 25 sec (control 13 sec), partial thromboplastin time 60 sec (control 33 sec) and fibrin degradation products <10 mcg/ml. Blood gas showed pH 7.375, PCO2 26.1 torr, P02 196.5 torr and base deficit 7.8 meq/I. Cerebrospinal fluid and stool examination were normal. The child was given 25% dextrose intravenously followed by an infusion of 10% dextrose with electrolytes. Phenobarbitone 20 mg/kg was given as a loading dose iv. alongwith Diazepam i.v. to control seizures. Ampicillin (200 mg/kg/day) and chioram phenicol (100 mg/kg/day) were administered intravenously. Lactulose (1 mI/kg/dose) was given by nasogastric tube. When his condition continued to deteriorate, fresh frozen plasma was given and i.v. cefotaxime (100 mg/kg/day) was added. Despite supportive measures the child continued to deteriorate and died 30 hours after admission. Blood and bone marrow cultures taken at admission subsequently grew Salmonella typhi which was sensitive to all drugs. An autopsy was refused by the parents.

DISCUSSION

Our data reveals a group of children with typhoid and clinical features of significant hepatic dysfunction. Both of our patients demonstrated features of acute hepatic failure i.e. jaundice, hepatomegaly, impairment of liver function tests and the coagulation profile and hyperammonaemia. Our second case presented with features suggestive of Reye's syndrome but turned out to have typhoid. Early administration of steroids have been recently shown to have a beneficial effect in patients with fulminant, life threatening typhoid[6], but it is uncertain if the use of dexamethasone might have made any difference to our patients. Although we do not have data on hepatitis serology on the two patients reported, the clinical picture was unlike that of acute viral hepatitis. Our experience of the general features of typhoid in our patients is somewhat similar to that of Gross et al[7] who found hepatomegaly in 24% of children alongwith moderate elevation of SGPT (mean 104 IU/1). However, our patients population reveals a lower incidence of hepatomegaly in comparison to the 88% reported among children with typhoid from Thailand[8]. The number of children presenting with overt jaundice is also comparable to Gross and Thisyakorn[7,8]. However, we performed liver function tests on only those children with clinical features suggestive of hepatic involvement, and it is possible that subclinical hepatitis and asymptomatic elevation of hepatic enzymes and may have been missed. Indeed, close monitoring and investigation of outbreaks of typhoid in Israel[9] and Texas[10] reveals elevation of hepatic enzymes in over 90% of the cases, without any overt signs of hepatic dysfunction. In a few cases the clinical picture of typhoid closely simulates acute hepatitis. This is similar to the experience of Singh et al[11] who reported similar findings among adults with typhoid in South India. The pathogenesis of hepatic dysfunction in typhoid fever remains unclear. The typhoidal Salmonella strains proliferate in the reticuloendothelial system and several studies have demonstrated hepatitis in patients with typhoid, alongwith morphological evidence of liver damage such as cholangiohepatitis[12] or non-specific

reactive hepatitis[13]. Recent immunofluorescent studies of liver biopsy specimens of typhoid patients reveal intact Salmonella bacilli[14]. Thus it is possible that direct cellular damage by cytotoxins released by the typhoidal organisms in the liver may be an important mechanism in the pathogenesis of hepatic dysfunction. An alternative possibility is that circulating endotoxins in typhoid may act as mediators for typhoid hepatitis in the liver[15]. It is however, more likely that endotoxins enhance local inflammatory responses at the tissue sites of Salmonella typhi multiplication[16]. Thus it is likely that hepatic dysfunction in typhoid is multifactorial in nature. Factors which determine the propensity for varying degrees of hepatic dysfunction in typhoid, remain to be elucidated. Our observation of a higher mortality among children with hepatic dysfunction and typhoid is intriguing. It is possible that the degree of hepatic derangement indirectly reflects the virulence of the infecting typhoidal strain. The higher incidence of hepatomegaly among children infected with MDR typhoidal Salmonella strains may also be indicative of a greater propensity for the organisms to proliferate in the reticuloendothelial system. The rapid onset of a severe form of typhoid with concomitant features of fulminant hepatic failure, as in the two cases reported, may indicate infection with a particularly virulent typhoidal strain. It is important to note however, that in many parts of the world typhoid is likely to occur in the same environmental conditions that promote the spread of viral hepatitis, and it is conceivable that occasional dual infections can occur[17]. Repeated episodes of viral hepatitis or malaria[18] in some children may predispose them to overt hepatic dysfunction if they develop typhoid. In summary we find that a small but important subgroup of children with typhoid develop significant hepatic dysfunction. In our experience this was also associated with higher mortality among children. Typhoid can present in childhood with a clinical picture suggestive of fulminant hepatitis and should be considered in the differential diagnosis when evaluating such patients.

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