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Hepatic Involvement with Typhoid Fever

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SUMMARY

Salmonella typhi has been reported to cause hepatic involvement. One hundred and eight patients with positive blood cultures for salmonella typhi were studied to evaluate the incidence of liver involvement, 34 of these showed evidence of liver involvement. These patients were studied to identify characteristic features of typhoid hepatitis which may help in early diagnosis.

No specific clinical features were found consistently and liver function tests showed wide variation. Other biochemical abnormalities occurred due to vomiting and renal involvement. Liver biopsy done in 11 patients showed normal lobular architecture and non-specific changes. Fifteen patients had resistance to conventional antibiotics but responded to second line chemotherapy. Patients with fever and liver involvement should be thoroughly investigated for typhoid fever.

INTRODUCTION

Typhoid fever is common in Pakistan and is a major health problem[1]. It is a systemic illness and can effect any organ in the body and cause damage[2,3]. Classical presentation described in text books is no longer commonly seen. Atypical and unusual presentations cause diagnostic difficulties[3-5].

Salmonella hepatitis is one of its rare and unusual presentations[6,7]. It simulates other diseases involving liver, especially in endemic areas[2,28]. It is important to differentiate between them as the treatment differs. A profile of 34 patients with typhoid fever and hepatic involvement is presented here to identify characteristic features contributing to early diagnosis.

PATIENTS AND METHODS

We studied clinical features of 34 patients who had positive blood cultures for salmonella typhi and also showed clinical, biochemical, and/or histological evidence of liver involvement.

Typhoid patients with positive blood cultures, but without liver involvement were excluded. Those patients who had a typhoid like illness with a positive widal test but negative culture were also excluded.

RESULTS

Thirty four patients with positive cultures and liver abnormalities were seen over a period of four years (October 1987 to December 1991) in the Division of Medicine and Gastroenterology at the Shaikh Zayed Hospital, Lahore.

The symptoms, physical signs, hematological values, liver function tests, and other biochemical tests are shown in Tables 1-6.

Twenty two patients were males and 12 were females. Ages ranged between 12 and 44 years (mean age 28 years) (Table 1).

Table 1: Dermographic features.

Total No. of patients	34
Male	22
Females	12
Male:Female	1.8:1
Mean age in years	28
Age range yrs	12-44

All patients presented with fever and also had vomiting and abdominal pain (Table 2).

Onset of fever was rapid in 66% and gradual in 34% of patients. The duration of illness ranged from 4-33 days. Majority had prolonged duration of illness prior to admission (Table 2).

Other clinical features like relative bradycardia, jaundice, hepatomegaly and splenomegaly were not present consistently (Table 3).

Table 2: Symptoms.

Symptoms	*Percentages*
Fever	100%
Onset	
i. Gradual	34%
ii. Rapid	66%
Duration	4-30 days
Type	
i. Continuous	89%
ii. Remittent	11%
Vomiting	100%
Abdominal pain	100%

Table 3: Clinical features.

Clinical features	*Mean*	*Range*
Pulse	100/min	70-130
Temperature	38.4 ° C	34-40.5 ° C
Pallor	75%	
Jaundice	45%	
Hepatomegaly	70%	
Splenomegaly	57%	

Most patients became anemic during their illness (Table 4). ESR fluctuated from normal to very high. Leucopenia was seen in 8 patients, thrombocytopenia in 5, and 4 patients showed significant prolongation of prothrombin time (Table 4).

Hyponatremia was a feature in all patients, serum potassium was found to be low or at lower limit of normal (Table 4). These biochemical features were attributed to vomiting seen in all patients. Six patients developed renal failure which reverted to normal after recovery from illness. Fifty seven percent and sixty percent of patients had proteinuria and hematuria, respectively regardless of development of renal failure (Table 5).

Table 4: Hematological features and biochemical data.

	Mean	*Range*
Haematological		
Hb gm%	9.0	5.0-13.2
ESR mm in 1st hour	35	8-130
TLC/mm^3	7.0	3.6-13.2
Platelets/mm^3	1,70,000	40,000-3,85,000
PT sec.	15	13.5-18
Biochemical		
Serum Na^+ mEq/L	128	125-130
Serum K^+ mEq/L	3.2	2.9-3.8
BUN mg/dl	42	8-86
Creatinine mg/dl	1.8	0.6-7.2
Liver function tests		
Bilirubin mg/dl	3.9	2.4-20.8
SGOT U/L	92	19-300
SGPT U/L	126	45-301
Alk. Phos x normal	2.7	1-1.6
Albumin gm/dl	3.4	2.3-4.0
Widal tests		
TO	1:80	1:120-1:320
TH	1:160	1:160-1:320

Table 5: Urine analysis.

Urine	*No. of Patients*	*Percentage*
Protein	19	57
RBC	20	60
WBC	6	18
Granular casts	27	81

The picture of liver function tests was widely variable. Some patients showed normal serum bilirubin whereas in others it was more than 20 mg/dl. Generally, the illness was more severe when there was hyperbilirubinemia.

The levels of alkaline phosphatase varied widely but did not correlate with the degree of hyperbilirubinemia. The levels of SGPT and SGOT ranged from normal to 300 U/L and these did not correlate with the severity of disease, degree of hyperbilirubinemia or the level of alkaline

Table 6: Reports of liver involvement in typhoid fever (in percentage)

Study	*No. of patients*	*Jaundice*	*Hepatomegaly*	*Abnormal LFTs (%)*	*Abnormal liver histology*
Stuart and Pullen 1946	360	3.6	25	NR*	NR
Rowland 1961	530	1.1	NR	NR	NR
Gulati et al. 1968	98	0	0	NR	NR
Ramachandran et al. 1974	58	7.6	29	-	-
Wicks et al. 1974	243	1.6	NR	NR	NR
Diem et al. 1976 ..	15	26.6	40	93.3	100
Samantray et al. 1977	500	0	48	NR	NR
Nasrallah and Nassar 1978	104	23	33	47	NR
Singh et al. 1978	460	1	NR	NR	NR
Johnson and Aderele 1981	117	6	27	5	NR
Gupta et al. 1985	125	5.6	8.8	5.6	NR
Khosla et al. 1988	36	8.3	55	55	40
Arif et al. 1990	9	66	77	100	44
Ishaq et al. 1990	30	0	63	NR	NR

*Not recorded.

phosphatase (Table 4). Serum albumen was frequently found to be in the lower range.

Widal test became positive in all patients (Table 4). The titres of 1:160 for flagellar component (TH) were more sensitive than somatic component (TO). Blood cultures were positive for salmonella typhi in all the patients.

Liver biopsy was done in 11 patients. Normal lobular architecture was present. Non-specific changes like fatty change, bile stasis, bile plugs, mononuclear infiltration in portal areas, foci of hepatic inflammation and necrosis, kupffer cell hyperplasia and acidophil bodies were seen.

Twenty three patients remained in the hospital for more than two weeks. Average hospital stay was 25 days. Total duration of illness varied from 16-47 days. A delayed response to therapy for 10 days or more was seen in 40% of patients. Fifteen patients had S. typhi resistant to chloramphenicol, amoxycillin and cotrimoxazole and were in vitro sensitive to ofloxacin, nor-floxacin and cephalosporins like cefotaxime, ceftazidime. Forteen pateints were given ofloxacin and 1 received cefotaxime.

Response with ofloxacin was earlier as compared to that of chloramphenicol. Improvement was seen in all the patients clinically as well as biochemically.

DISCUSSION

Involvement of liver in typhoid fever occurs commonly[8,9]. In our study, no definite clinical picture or biochemical profile was present. Similar results have been reported by our department[28] and by other authors[5,11].

Hepatomegaly was found in 70% of our patients (Table 3). This incidence is a little higher than previously reported which may be due to the fact that we studied only those typhoid patients who showed involvement of liver.

Jaundice was present in 15 patients (45%). Jaundice has been reported in patient with typhoid fever[11,12,29]. These patients have to be differentiated from viral hepatitis since both diseases are common in endemic areas. In viral hepatitis, jaundice usually precedes the febrile illness, whereas in typhoid fever, it usually occurs at the height of fever. Transaminases are much higher in viral hepatitis.

Similar variation in liver function tests and other biochemical profile was documented as reported earlier (Table 6). According to the presented clinical and biochemical profile, no definite association could be made as in past studies[4,5,28].

The exact mechanism of hepatic damage in typhoid fever is not clear. This complication is more commonly seen in malnourished people belonging to lower socio-economic group[12].

Bacteremia may be the cause of liver damage but as hepatic lesions persist during the pyrexial period and during defervescence, hepatic damage could be secondary to intestinal ulceration[11].

Other possible factors considered to cause liver damage in typhoid fever are endotoxic damage to hepatocytes[14], ascending cholangitis[5], consumptive coagulopathy[13,27,31], localized intravascular coagulo-

pathy and arteritis[16].

Demonstration of salmonella typhi within the liver by indirect immunofluorescence strongly suggests the possibility of the damage caused by locally released endotoxins from proliferating organisms and by local inflammatory reactions[26].

Immune complexes and high ratio of antitrypsin to C_3 have been seen in typhoid fever and significantly more frequently in patients with hepatitis[18].

Salmonella hepatitis is seen more frequently in patients with depressed cellular immunity[19] and recovery from the illness has been correlated with development of cell mediated immune response[20].

Other associated abnormalities in typhoid have been reported e.g., myocarditis[4,30], haemolysis[24], thrombocytopenia[22], consumptive coagulopathy[27,31], and an haemorrhagic state due to liver dysfunction and clotting factors deficiency[25]. Significant thrombocytopenia, and prolongation of prothrombin time was seen in 5 and 4 patients respectively. Nephritits[21,22] and haemolytic uremic syndrome[23] have also been reported. Most of our patients had urinary abnormalities e.g., proteinuria, haematuria and granular casts indicating renal damage (Table 5).

Liver biopsy may be considered to confirm the diagnosis. Involvement of liver has been seen in all patients by some workers[8,9]. Fluorescein stained bacilli can also be seen in the liver and other tissues[26]. We did liver biopsy in 11 of our patients and all showed involvement of liver, histologically.

In summary, this study shows that clinical features of salmonella hepatitis are variable and do not constitute a specific pattern. There should be high index of suspicion of typhoid fever in patients with high grade fever and disturbed liver functions. Cultures of blood and bone marrow are strongly recommended and where possible, liver biopsy should be done.

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