Hepatic Dysfunction in Typhoid Fever

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ABSTRACT

Background: Hepatic involvement is not uncommon in typhoid fever. This study was conducted to determine the incidence and severity of liver damage in patients admitted with typhoid fever.

Material and Methods: This observational study was conducted from Jan 2005 to Dec 2007 at the Infectious diseases unit, Rashid hospital, Dubai. Only patients with blood culture positive for Salmonella Typhi were included in the study. Liver function test and full blood count done for all patients where as viral hepatitis profile and ultrasound was abdomen done for patients with disturbed liver function test.

Results: A total of 52 patients fulfilled the inclusion criteria. Hepatic manifestation included; hepatomegaly (51.9%), jaundice( 13.4%), raised levels of serum alanine aminotransferase (85%) and in 10% cases the level was more than 10 fold of normal value, aspartate aminotransferase(75%), prothrombin time(53.8%) and in 15.4% cases PT was 3 seconds higher than reference value, alkaline phosphatase (44%) and serum bilirubin (25%); reduced levels of serum albumin (36%). Other manifestations included anemia (55.7%), splenomegaly (36.5%), thrombocytopenia (44%) and leucopenia (6%). Average hospital stay was 11.5±4.3 days. All of the patients were discharged healthy.

Conclusion: In the presence of high grade fever, jaundice and tender hepatomegaly, patients from tropical countries or those who had traveled recently to area of high prevalence of typhoid fever should arouse suspicion of clinical diagnosis of enteric fever. Hepatic dysfunction in these cases, despite its high incidence and serious nature, is transient and responds favorably to appropriate antibiotic therapy.

Key words: Typhoid fever, hepatic dysfunction

INTRODUCTION

Typhoid fever (Enteric fever) is an acute febrile illness that constitutes a major public health problem in many developing countries of the world. This disease has also been increasingly reported from the developed countries. According to Center for Disease Control and Prevention report, there are 21.6 million typhoid cases annually, with the annual incidence varying from 100 to 1000 cases per 100000 population and 600000 deaths occurring per year. The disease predominantly affects children and young adults. In the course of enteric fever, various organs can be involved leading to a wide range of presentation from uncomplicated typhoid fever to a complicated one involving multiple organs. Liver is often involved in typhoid fever, with most patients having only minor elevation of aminotransferases without jaundice. However, in small number of patient the features are clinically and biochemically indistinguishable from other causes of hepatitis. Hepatitis due to Typhoid fever is not only associated with other potentially life threatening extrahepatic complications but relapse rate also is observed higher in these patients those than without involvement of liver. This study was conducted to evaluate the incidence and severity of hepatic dysfunction in Typhoid fever.

MATERIAL AND METHODS

This was a hospital based study conducted from Jan 2005 to Dec 2007 at the Infectious Disease Unit, Rashid hospital Dubai, UAE. Rashid hospital is one of the biggest tertiary teaching hospitals in Dubai accredited by the Joint Commission International (JCI). The study was designed to include demographic (age, sex, nationality, travel history), clinical information and biochemical changes observed in the patients. The patients were specifically questioned regarding past medical history of jaundice, medications, alcohol ingestion and travel abroad. Patients with positive blood culture for S.Typhi were registered for the study, whereas patients with history of chronic liver disease, immunocompromized (HIV/Drugs), positive viral
hepatitis profile, recent intake of hepatotoxic drugs and active alcohol consumer were excluded from the study. Patients with positive blood culture for S. Paratyphi were also excluded from the study.

On admission, blood samples were obtained from all the patients for liver function test (LFT) done by Hitachi Machine 912, full blood count (FBC) done by automated Beckman Coulter machine, blood culture (3 samples), coagulation profile, malaria parasite, urea, electrolytes and blood sugar. Viral hepatitis profile and ultrasound abdomen done for the patients with clinical and or biochemical evidence of hepatic dysfunction. Management was done as per standard guidelines for the management of Typhoid fever and it included antibiotics (mainly Ceftriaxone and Ciprofloxacin) and supportive therapy. The antibiotic therapy was started empirically considering the clinical diagnosis of typhoid fever and likely sensitivity to drugs, and therapy has continued accordingly after receiving the culture and sensitivity report. Data was analyzed by statistical package SAS Enterprise 4.1. A p value <.05 was taken as significant for difference in all statistical analysis.

RESULTS

A total of 52 patients fulfilled the inclusion criteria. Overall, the mean age ± SD of the patients under the study was 27.4±7.89 years (14-45 years) and males outnumbered the females 45(87%) vs 7(13%), there was no significant age difference between males and females.

Table 1. Clinical data of 52 patients with Typhoid fever.

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>No</th>
<th>%age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>45</td>
<td>87</td>
</tr>
<tr>
<td>Females</td>
<td>7</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 2. Biochemical and hematological data of 52 patients with Typhoid fever.

<table>
<thead>
<tr>
<th>Laboratory Parameters</th>
<th>Mean</th>
<th>Range</th>
<th>Normal</th>
<th>Increased</th>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>204.4±362.7</td>
<td>18-1924</td>
<td>8(15%)</td>
<td>44(85%)</td>
<td>-</td>
</tr>
<tr>
<td>AST</td>
<td>136.8±201.5</td>
<td>13(25%)</td>
<td>39(75%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alk. Phosp</td>
<td>19.9±130.5</td>
<td>62-934</td>
<td>29(56%)</td>
<td>23(44%)</td>
<td>-</td>
</tr>
<tr>
<td>T. Bil</td>
<td>1.9±3.8</td>
<td>0.2-18</td>
<td>39(75%)</td>
<td>13(25%)</td>
<td>-</td>
</tr>
<tr>
<td>P. T</td>
<td>14.7±2.1</td>
<td>11.7-25.9</td>
<td>24(46.2%)</td>
<td>28(53.8%)</td>
<td>-</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.4±0.5</td>
<td>1.7-4.5</td>
<td>32(62%)</td>
<td>-</td>
<td>20(38%)</td>
</tr>
<tr>
<td>WBC</td>
<td>6.8±2.5x10^3</td>
<td>1.5-12.8x10^3</td>
<td>45(87%)</td>
<td>4(8%)</td>
<td>3(6%)</td>
</tr>
<tr>
<td>Hb</td>
<td>12.3±1.9</td>
<td>5-15.6</td>
<td>23(45%)</td>
<td>-</td>
<td>29(55%)</td>
</tr>
<tr>
<td>Plates</td>
<td>175.5±102.2x10^3</td>
<td>11-561x10^3</td>
<td>29(56%)</td>
<td>-</td>
<td>23(44%)</td>
</tr>
</tbody>
</table>

Ref. range: ALT-0-41U/L, Alk.Phos-40-129 U/L, T.Bil-0-1mg/dl, Alb.-3.4-4.8gm/dl, PT-11-14 sec, WBC-3.6-11x10^3 cell/ul, Hb-13-18gm/dl, Platelets 150-400x10^3 cell/ul.

Majority of the patients were expatriates who visited or lived in the UAE. Among the study population 26(50%) were from India, 12(23%) Bangladesh, 5(10%) Nepal, 4(8%) Pakistan and 5(10%) from other countries, there was only one patient from UAE. Most of the patients involved in the study were laborers working in construction companies or agriculture fields and history of travel to endemic area was positive in the majority. The duration of illness was 3-14 days before the patients attended the accident and emergency department of the hospital and fever, headache, vomiting, abdominal pain, generalized body pain, loss of appetite were the main symptoms. In some of the patients fever, head ache, abdominal pain, yellowish discoloration of eyes and urine were the presenting symptoms. Toxic and sick appearance, fever, relative bradycardia, anemia, abdominal tenderness, hepatomegaly, splenomegaly and jaundice were the main clinical signs (Table 1).

Liver function test showed raised bilirubin level in 13(25%) patients and 6(12%) of them had bilirubin more than 3mg/dl. Over all, alanine transaminase
(ALT) was above the reference range in 44 (85%) patients but in 5 (10%) patients it was more than 10 times of the reference range. Alkaline phosphatase was noted high in 23 (44%) patients where as prothrombin time was increased in 28 (53.8%) and 8 (15.4%) patients had PT three sec above the reference range. Serum albumin was low in 20 (38%) patients. Hematological changes include normal white cell count in 45 (87%), leucocytosis in 4 (8%) and leucopenia in 3 (6%) patients. Low hemoglobin as well as low platelet count (thrombocytopenia) was observed in 29 (55.7%) and 23 (44%) patients respectively (Table-2). Ultrasound abdomen revealed hepatomegaly in 27 (52%), splenomegaly in 19 (36.5%) and thickening of gallbladder wall suggestive of acute acalculus cholecystitis in 3 (6%) patients. Course of disease remained uneventful in all except in four patients who developed acute acalculus cholecystitis and severe hematological dyscrasias and these patients were managed combinedly by the infectious disease and surgical or hematological team. The mean hospital stay was 11.5 ± 4.3 days (6-22 days). The serial evaluation of physical examination, biochemical and hematological parameters showed return to normal level after recovery from acute illness in all cases.

**DISCUSSION**

The incidence of complication in typhoid fever is reported variably. Parry MC et al have noted complications in 10-15% of cases, the most serious one being GI bleeding, perforation and typhoid encephalopathy, where as Van den Bergh et al has reported the incidence of complications (both in adults and children) in 13-38 percent. Choo, et al has reported anicterus hepatitis, bone marrow suppression, paralytic ileus, myocarditis, psychosis and cholecystis as the most common complications in typhoid fever. Asymptomatic hepatitis is common in typhoid fever and most of the patients having only minor elevation of AST and ALT. Although pathogenesis of hepatitis remains unclear, hepatic insult in typhoid may occur through a variety of mechanisms including local or systemic effects of endotoxin or non specific reactive inflammation in response to ulcerations in the intestine or due to the effect of cytotoxin produced by S. typhi that have infected Kuffer cells.

Jaundice in typhoid fever tends to occur at the peak of fever which differentiates it from viral hepatitis in which case fever usually comes down after the appearance of jaundice. When jaundice is present in typhoid fever hepatitis, cholangitis, cholecystitis and hemolysis will be the most likely cause. Morgestrun et al, has reported incidence of jaundice in 9% of cases of typhoid fever, where as Giltin has reported jaundice in 33% cases. In our study, the presenting symptoms of 13.4% patients were fever and jaundice. Hepatomegaly is usually present in enteric fever after the first week of illness, presumably caused by hypertrophy and hyperplasia of Kuffer cells. In this case series, hepatomegaly was observed in 51.9% patients, a figure higher than reported by Ahmet et al (42%) but consistent with the observation by Rasoolinejad et al (52.3%) We noted enlargement of spleen in 36.5% patients as compared to 26% and 20% reported by Mirsadraee et al and Bhutta ZA respectively.

Abnormal AST and ALT in combination are indicative of a hepatocyte disorder; many investigators used these enzymes for evaluation of hepatic involvement during typhoid fever. The frequency of elevated serum enzyme have been reported by Van den Bergh et al in 26%, Morgenstern et al in 52% and Mirsadraee et al in 22% cases, whereas in this study alanine aminotransferase levels was elevated in 85% of patients. Rise of ALT more than 10 times of normal levels was seen in 5 patients in our study with abnormal PT and serum bilirubin levels that mimicked acute viral hepatitis. El-Newhi et al reported sever hepatic derangement simulating acute viral hepatitis as rare but in this study we observed in 5 (10%) patients. The other important observation in this study was raised alkaline phosphatases (44%) which are quite higher than reported by Rasoolinejad et al (23.3%) but they reported high PT in 63.5% where as we observed increased prothrombin time in 53.8% of patients. Serum albumin level was low in 38% cases which is almost consistent with the report of Ahmet et al (41.9%)%

Hematological derangements are common in typhoid fever. Significant changes include anemia, leucopenia, eosinophilia, thrombocytopenia and sub clinical disseminated intravascular coagulation. Bone marrow suppression and hemophagocytosis are considered to be an important mechanism in producing hematological changes. In our case series, hemoglobin was low in 55.7%, a figure higher than reported by Alam (31%). Leukocyte count was normal in most of our patients although leucopenia is said to be common hematological finding in typhoid fever but we observed leucopenia in 6% cases, continuing the observation of others. Thrombocytopenia was present in 44% cases, whereas it is reported only in 10% cases of typhoid fever by the other studies.

**CONCLUSION**

In conclusion, recognition of typhoid hepatitis is important since it has to be differentiated from other...
conditions such as viral, malarial and amoebic hepatitis. In the presence of high grade fever, jaundice and tender hepatomegaly in patients from tropical countries or with history of recent travel to endemic area should arouse suspicion of typhoid fever. Hepatic dysfunction in these cases, despite its high incidence and serious nature, is transient and responds favorably to appropriate antibiotic therapy.

REFERENCES