Original Article

HEMATOLOGICAL AND BIOCHEMICAL CHANGES IN TYPHOID FEVER

Ali Hassan Abro[1], Ahmed MS Abdou[2], Jawahar L. Gangwani[3], Abdulla M Ustadi[4], Nadeem J Younis[5], Hina Seyada Hussaini[6]

ABSTRACT

Objectives: The hematological and biochemical changes due to multi-organ involvement in typhoid fever are not uncommon. The aim of this study was to determine the frequency and severity of the above changes in adult patients admitted to the hospital because of typhoid fever.

Methodology: This was a hospital based descriptive study conducted at the Infectious Diseases unit and medical wards at Rashid Hospital Dubai, United Arab Emirates, from March 2005 to February 2008. The study was designed to include demographics, clinical information, hematological and biochemical changes observed in each patient. Only patients whose blood culture yielded Salmonella typhi were included in the study. Full blood count, liver function tests, blood culture, urea, electrolytes, malaria parasite and coagulation profile were performed for all the patients, whereas viral hepatitis serology and ultrasound abdomen were limited to those with disturbed liver function tests. The patients with ALT$\geq$ 3 times of normal were screened for viral hepatitis (A, B, & C) serology, whereas the patients' with significant hematological changes were subjected to bone marrow examination.

Results: A total of 75 patients were enrolled into the study. The mean age±SD of the patients under the study were 28.4±8.7 years & males outnumbered the females, 81.3% vs. 18.6%. The most common hematological changes observed were; anemia (61.3%), thrombocytopenia (40%), leucocytosis (10.6%) & leucopenia (4%). Whereas, the biochemical changes included; raised alanine aminotransferase (73.3%), aspartate aminotransferase (62.7%), bilirubin (30.6%), alkaline phosphatase (44%), prothrombin time (57.3) and blood urea (12%), but the serum albumin was found to be low in 40%. The patients with raised ALT had high frequency of thrombocytopenia (p <0.04), raised serum bilirubin (p <0.02), alkaline phosphatase (p <0.01) and prothrombin time (p <0.04). Serum ALT was >10-fold of normal levels in 8%, serum bilirubin was >3mg/dl in 10.3% and prothrombin time was 3 sec above the control in 8% patients. All the patients were discharged in good health once hematological and biochemical changes returned to reference range.

Conclusion: Typhoid fever causes significant hematological changes as well as hepatic dysfunction. The involvement of liver was associated with high frequency of extrahepatic complications. Despite the high incidence and serious nature of the hematological changes & liver involvement, these changes are transient and respond favorably to the appropriate antimicrobial therapy.

KEY WORDS: Typhoid fever, Hematological, Biochemical, Changes.

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Correspondence

Ali Hassan Abro,
Email: ahabro@dohms.gov.ae
momal65@hotmail.com

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INTRODUCTION

Typhoid fever is a systemic bacterial infection caused by Salmonella Typhi, a gram negative rods. The infection is usually acquired through the ingestion of water or food contaminated by the urine or feces of infected

carriers.[1] Typhoid fever constitutes a major public health problem in many developing countries of the world and it has also been increasingly reported from the developed countries.[2] Typhoid fever predominantly affects children and young adults and it is recognized as a major cause of morbidity globally with over 12.6 million cases world wide, and an estimated 600000 deaths annually.[3] Almost 80% of cases and deaths occur in Asia. The attack rate as high as 1100 cases per 100000 populations have been documented in developing countries.[4] 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. Hematological derangements are common in typhoid fever,[5] whereas, hepatic dysfunction has been reported variably from less than 1% to as high as 26%.[6] Clinically significant renal disease in typhoid fever is an uncommon event, occurring in 0-6% of all patients.[7]

This study was undertaken to determine the frequency and severity of the hematological changes, hepatic dysfunction and renal involvement in adult patients admitted to the Rashid hospital because of typhoid fever.

METHODOLOGY

This was a hospital based descriptive study, conducted during the period from March 2005 to February 2008 at the Infectious Diseases Unit and Medical wards, Rashid hospital Dubai, UAE. Rashid hospital is one of the main tertiary care hospitals in Dubai and is Joint Commission International (JCI) accredited. The study was designed to include demographics (age, sex, nationality, and travel history), clinical information and biochemical and hematological changes observed in each patient. The data was entered into a structured proforma separately. The patients were specifically questioned regarding the past medical history of liver diseases, renal diseases, blood disorders, medications, alcohol ingestion and travel abroad. The patients were included in the study when the diagnosis of typhoid fever was confirmed by a positive blood culture for Salmonella Typhi.

Exclusion Criteria: The patients with history of liver diseases, renal diseases, blood disorders, immunocompromized status (HIV/Drugs), positive viral hepatitis serology, recent intake of potential hepatotoxic and/or drugs which can affect blood and biochemical parameters and active alcohol consumer were excluded from the study. On admission, blood samples were obtained from all the patients for liver function test (done by Hitachi Machine 912), full blood count (done by automated Beckman Coulter machine), blood culture (3 samples), coagulation profile, malaria parasite, urea, electrolytes and random blood sugar. The patients with clinical and/or biochemical features of hepatic involvement (ALT> 3 times of normal level), were further subjected to viral hepatitis serology and ultra-sonograophic imaging of the abdomen; whereas bone marrow examination was limited to those patients with severe non responding hematological changes.

The therapeutic intervention was planned as per the standard protocols for the management of typhoid fever. While awaiting the culture and sensitivity results, the empirical antimicrobial therapy was initiated with either Ceftriaxone (2gm/day) or Ciprofloxacin (400 mg IV/ 500mg oral BD), considering the likely antibiotic sensitivity pattern. The antimicrobial therapy was continued accordingly after receiving the culture and sensitivity report. The majority of patients received antimicrobial therapy for the period of two weeks, whereas patients with complicated typhoid fever were treated for three weeks. The patients were discharged from the hospital once hematological and biochemical changes returned to reference range as well as patients became asymptomatic. Data was analyzed by SAS Enterprise Guide 4.1. A p value of <0.05 was taken as significant for difference in all statistical analysis.

RESULTS

A total of 75 patients were enrolled into the study (63 admitted in Infectious Disease Unit, whereas 12 in medical wards) The mean

age±SD of the a patient under the study was 28.4±8.7 years (14-51 years) and males (Most of the study male patients were laborer and living in bachelor sharing accommodation) outnumbered the females 61(81.3%) vs. 14(18.6%), there was no significant age difference among two groups. Majority of the patients were expatriates who visited or lived in the UAE. Among the study population, 38(50.6%) patients were from India, 15(20%) Bangladesh, 9(12%) Pakistan, 5(6.6%) Nepal, 5(6.6%) UAE and 3(4%) from the other counties. The majority (78%) of male patients were laborers, working in construction companies or agriculture fields. The history of recent travel to endemic areas was positive in 82% of the patients. The duration of illness was 3-28 days before the patients attended the accident and emergency department of the hospital. Fever, headache, vomiting, abdominal pain, generalized body pain, loss of appetite, weight loss, diarrhea, were the main symptoms followed by dry cough, constipation, impaired sensorium, yellowish discoloration of eyes and urine. Fever, toxic and sick look, relative bradycardia, anemia, abdominal tenderness, hepatomegaly, splenomegaly and jaundice were the main clinical signs.

The main hematological derangements included; decreased hemoglobin, thrombocytopenia, leucocytosis and leucopenia (Table-I). Serum alanine aminotransferase (ALT) levels were above the reference range in 55(73.3%) patients, which exceeded 3-fold of the upper normal value in 28(37.3%), 5-fold in 14(18.6%) and 10-fold in 6(8%) patients. The other important biochemical changes included; raised aspartate aminotransferase (AST), serum bilirubin, alkaline phosphatase, prothrombin time, blood urea and decreased serum albu-

Table-I: Frequency of Hematological changes observed in Typhoid fever.

Parameter	*No of Pts. (%)*
WBC count (Mean ± SD:7.12+3.69x10^3/ul)	
(Range:1.5-28.8x10^3/ul).	
Normal WBC	64(85.3)
Leucocytosis	8(10.6)
Leucopenia	3(4)
Differential (Absolute count)	
Normal Neutrophils	63(84)
Neutrophilia	9(12)
Neutropenia	3(4)
Normal eosinophils	75(100)
Hemoglobin (Mean ± SD: 12.33±1.78 gm/dl)	
(Range: 5-15.4 gm/dl).	
Normal Hb	29(38.6)
Anemia	46(61.3)
Platelet count	
(Mean ± SD:288.93±146.76x10^3/ul)	
(Range: 11-734x10^3/ul).	
Normal platelets	45(60)
Thrombocytopenia	30(40)

Ref.range: WBC: 3.6-11x10^3 cell/ul, Hb: 13-18gm/dl, Platelets: 150-400x10^3 cell/ul.

Table-II: Frequency of biochemical changes observed in Typhoid fever.

Parameter	*No. of Pts.(%)*
ALT (Mean ± SD: 160.8+244.04 U/L)	
(Rnage: 12-1807 U/L).	
Normal ALT	20(26.6)
Raised ALT	55(73.3)
AST (Mean ± SD: 126.64+161.72 U/L)	
(Range: 10-889 U/L).	
Normal AST	28(37.3)
Raised ALT	47(62.7)
Bilirubin (Mean ± SD: 1.8+4.04 mg/dl)	
(Range: 0.2-31.8 mg/dl).	
Normal bilirubin	52(69.3)
Raised bilirubin	23(30.6)
Albumin (Mean ± SD: 3.46+0.55 gm/dl)	
(Range:1.7-4.8gm/dl).	
Normal Albumin	45(60)
Decreased Albumin	30(40)
Alk. Phosphatase	
(Mean ± SD: 125.28+123.17 U/L)	
(Range: 48-934 U/L).	
Normal Alk.Phosphatase	42(56)
Raised Alk.Phosphatase	33(44)
Prothrombin Time	
(Mean ± SD: 14.73+1.95 sec)	
(Range: 11.7-25.9sec).	
Normal PT	32(42.6)
Raised PT	43(57.3)
Blood Urea (Mean ± SD: 25.21+13.53 mg/dl)	
(Range: 7-67 mg/dl).	
Normal B.Urea	64(84.3)
Raised B.Urea	9(12)

Ref.range: ALT: 0-41U/L, Alk.Phos: 40-129 U/L, T.Bil: 0-1mg/dl,
Alb.: 3.4-4.8gm/dl, AST: 0-38 U/L, B.Urea: 12-40 mg/dl.

min level (Table-II). Serum bilirubin level was >3mg/dl in 8((10.6%) patients, whereas, prothrombin time was 3> sec of the control level only in 6(8%) patients. In comparison to the patients with normal ALT, the patients with increased ALT levels had high frequency of anemia, thrombocytopenia, raised serum bilirubin, alkaline phosphatase and prothrombin time, Table-III & Fig.1. Twenty eight patients were screened for viral hepatitis (A, B and C) serology, four of them were found to be HBV surface antigen positive and only two were HCV antibodies positive. No patient had evidence of disseminated intravascular coagulation.

Hepatomegaly and splenomegaly were the most common findings on ultrasound examination of the abdomen followed by the thickening of the gallbladder wall suggestive of acute acalculus cholecystitis. Three patients underwent bone marrow examination due to severe blood dyscriases and it showed normal cell lineage except for mild increase in megakaryocytes. In addition to the supportive treatment, all the patients received intravenous antibiotics at the time of admission. The mean hospital stay was 10.9±3.9 days (6-23 days). The hospital stay was longer in patients with complicated typhoid fever such as associated hepatic dysfunction than uncomplicated ones, p <0.03. The serial evaluation of physical examination, biochemical and hematological parameters showed return to normal level after recovery from acute illness in all cases. The course of the disease remained uneventful and all the patients were discharged in good health.

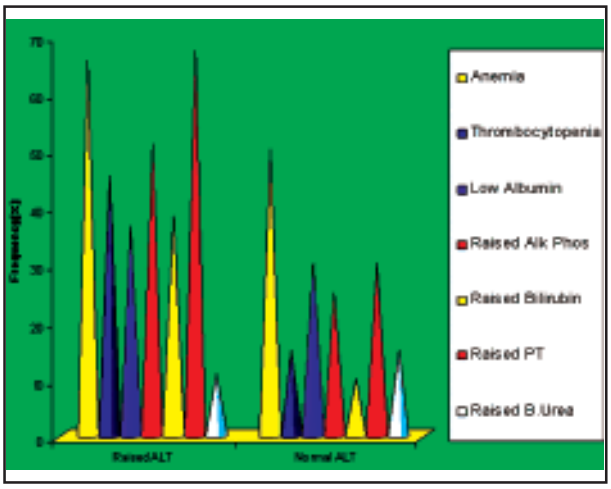

Fig-1: The graph shows the frequency of hematological and biochemical changes associated in patients with raised and normal ALT levels in Typhoid fever.

DISCUSSION

The patho-physiology of typhoid fever is a complex process which proceeds through the several stages.[8] The disease begins with an asymptomatic incubation period of 7-14 days, during which bacteria invade the macrophages and spread throughout the reticuloendothelial system. The first week of symptomatic disease is characterized by progressive elevation of the temperature followed by bacteraemia. The second week begins with the development of rose spots, abdominal pain and splenomegaly. The third week is a week of complications and is marked by a more intense intestinal inflammatory response with associated necrosis which can result in perforation and hemorrhage.[9] The complications in typhoid has been reported variably, Parry MC et al has described

Table-III: Associated hematological and biochemical changes in patients with typhoid fever who had normal or raised ALT

Parameter	*Pts. With normal ALT*	*Pts. With raised ALT*	*p value*
Hemoglobin	12.3±2.1gm/dl	12.3±1.6gm/dl	0.9
WBC	8.5±5.6x103/UL	6.6±2.5x103/UL	0.1
Platelets	290.0±167.4x103/UL	206.7±131.0x103/UL	0.04
T. Bilirubin	0.7±0.6mg/dl	2.1±4.6mg/dl	0.02
Al.Phosph.	112.5±59.3U/L	166.7±136.1U/L	0.01
Proth.Time	14.12±1.2 Sec	14.9±2.1 Sec	0.04
Blood Urea	27.7±13.2mg/dl	24.2±13.4mg/dl	0.3

gastrointestinal bleeding and perforation and encephalopathy as the most serious among the other complications in 10-15% of cases of typhoid fever.[10] Anicterus hepatitis, bone marrow suppression, paralytic ileus, myocarditis, psychosis and cholecystis were the most common complications of typhoid fever in the study by Choo et al.[11]

The hematological changes are common in typhoid fever and these include anemia, leucopoenia, eosinophilia, thrombocytopenia and sub clinical disseminated intravascular coagulation. Bone marrow suppression and hemophagocytosis are considered to be an important mechanism in producing hematological changes.[5] In this case series, 61.3% patients had anemia, a figure higher than reported by Ahmed et al (38%)[12] and Alam (31%),[13] however, lower than observed by Joseph at al (77.8%)[14] and Rasoolinejad et al (79.4%).[15] Leukocyte count was normal in most of the patients which is consistent with the earlier reports.[15] Leucopenia is said to be a common hematological finding in typhoid fever. In this study, leucopenia was observed only in 4% cases, continuing the observation of others,[16] whereas the frequency of leucopenia was observed in 18% and 11.2% by Ahmet et al[12] and Rasoollinad et at[15] respectively. Thrombocytopenia was present in 40% cases, a figure higher than reported by other the investigators (10% and 9.1%).[12,15] In this case series, no patient had evidence of disseminated intravascular coagulopathy, an observation which is also supported by the earlier study.[14] Eosinophilia has been reported in typhoid fever by the previous investigators,[5] whereas, in this study eosinophil count was within reference range.

The liver is commonly involved in patients with typhoid fever. However, severe hepatic derangement simulating acute viral hepatitis is rare.[17] Although pathogenesis of hepatitis remains unclear, hepatic injury in typhoid has several underlying mechanisms including local or systemic effects of specific endotoxin, nonspecific reactive inflammation in response to intestinal ulceration and cytotoxin produced by S.typhi that have infected Kuffer cells.[18] The frequency of liver enzymes elevation in typhoid fever has been reported as 22%, 26% and 52% in various case series.[16,19,20] In this study, we observed a much higher incidence of elevated alanine transaminases levels (73.3%). El-Newihi et al[17] has reported severe hepatic derangement simulating acute viral hepatitis as rare but in this study we observed raised ALT > 10-fold of normal level with prolonged PT and increased bilirubin >3mg/dl mimicking acute hepatitis in 8% patients.

The other important observation in this study was raised alkaline phosphatase (44%) which are quite higher than reported by earlier investigators (23.3%), however, they have reported prolonged PT in 63.5%, whereas, we observed increased prothrombin time in 57.3% of patients[15]. Serum albumin level was low in 40% cases which is almost consistent with the other reports (41.9%).[12] The incidence of jaundice and raised bilirubin level in typhoid fever have been reported variably, Morgestern et al has reported the frequency of jaundice in 9%,[20] whereas Giltin has reported jaundice in 33% cases.[21] In our study, fever and jaundice were the main presenting symptoms in 10.6% of patients. The involvement of liver in Typhoid fever is usually associated with extrahepatic complications,[22] we also had the same observation. Clinically significant renal disease in typhoid fever is an uncommon event and spectrum of renal complication includes mild to severe glumerulonepheritis to acute renal failure.[23] In this case series, none of the patients had significant renal dysfunction except in nine patients whose blood urea level was mildly elevated which returned to the reference range with hydration and treatment of typhoid fever.

CONCLUSION

In conclusion, typhoid fever causes significant hematological changes as well as hepatic dysfunction. The involvement of liver was associated with high frequency of extrahepatic complications. Despite the high incidence and serious nature of the hematological changes

and liver involvement, these changes are transient and respond favorably to the appropriate antimicrobial therapy. Furthermore, the kidneys are involved less frequently and usually do not require specific treatment.

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Authors:

1. Ali Hassan Abro, FCPS, MRCP,
2. Ahmed MS Abdou, FRCPI,
3. Jawahar L Gangwani, FCPS, MRCPI,
   Accident and Emergency Department,
4. Abdulla M Ustadi, M Sc Trop Medicine,
5. Nadeem J Younis, FCPS, MRCPI,
6. Hina Seyada Hussaini, MBBS,

1-6: Infectious Disease Unit,
Rashid hospital,
Dubai,
United Arab Emirates.

Mailing Address:

Ali Hassan Abro,
Infectious Disease Unit,
Rashid hospital Dubai,
P.O. Box: 4545,
Dubai, UAE.