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Original Article

Jaundice in typhoid patients: Differentiation from other common causes of fever and jaundice in the tropics

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Abstract

Background: While typhoid fever is common in our environment, presentation with jaundice is unusual. The aim of this study has been to determine the clinical and laboratory features that allow early diagnosis of typhoid fever in patients that present with jaundice and differentiate it from other common causes of fever and jaundice in the tropics.
Materials and Methods: This prospective study was conducted between May 1997 and October 1998 at Center Hopitalier Regional de Hombo Anjuoan, Comoros Islands. Patients with clinical and laboratory evidence of typhoid fever were included. Viral or toxic hepatitis, chronic liver disease, sickle cell disease and other causes of jaundice were excluded by clinical examination and appropriate investigations. Serial evaluation of liver function test and abdominal ultrasound were done. Patients were resuscitated with fluids and electrolytes and treated with appropriate antibiotics. Liver involvement was determined using clinical and laboratory parameters.
Results: Of the 254 patients with confirmed diagnosis of typhoid fever, 31 (12.2%) presented with jaundice. Their mean age was 24.6 ± 9.2SD years. Fever preceded the appearance of jaundice by 8-27 days. In 27 (87.1%) patients, there was hepatosplenomegaly. Serum bilirubin ranged 38 – 165 umol/l with mean of 117 ± 14SD. Conjugated bilirubin ranged 31-150 umol/l with mean of 95 ± 8SD. Serum aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase were raised with mean values of 180, 105 and 136 IU, respectively. Six (19.4%) patients died compared to 12.1% of non-icteric patients.
Conclusion: Typhoid patients may present with varying degrees of jaundice and fever that may be confused with viral, malarial or amebic hepatitis, diseases that are common in the tropics. Physical examination and simple biochemical tests would identify the typhoid patients who should be treated with appropriate antibiotics even before the results of blood culture are available.

Keywords: Hepatitis, jaundice, liver function tests, typhoid fever

Résumé

Arrière-plan: Alors que la fièvre typhoïde est commune dans notre environnement, présentation avec la jaunisse est inhabituelle. L'objectif de cette étude a été pour déterminer les cliniques et les fonctions de laboratoire permettant le diagnostic précoce de la fièvre typhoïde chez les patients qui présentent avec jaunisse et différencient d'autres causes courantes de la fièvre et jaunisse sous les tropiques.
Patients et méthodes: Cette étude prospective a été menée entre mai 1997 et 1998 d'octobre au centre Hopitalier régional de Hombo Anjuoan, Comores. Les patients avec cliniques et preuve de laboratoire de fièvre typhoïde ont été inclus. L'hépatite virale ou toxique hépatopathie chronique, maladie de cellule faucille et autres causes de jaunisse ont été exclus par l'examen clinique et enquêtes appropriées. Série d'évaluation de test de fonctionnement du foie et échographie abdominale ont été effectués. Les patients ont été resuscitated avec des liquides et des électrolytes et traités avec des antibiotiques appropriés. Participation du foie a déterminé l'utilisation clinique et les paramètres de laboratoire.
Résultats: Des 254 patients avec la confirmation du diagnostic de la fièvre typhoïde, 31 (12,2%) présenté avec jaunisse. Leur âge moyen était de ± 24.6 9.2SD ans. La peste précédé l'apparence de l'ictère par 8-27 jours. Dans 27 patients

(87.1%), il n'y avait hepatosplenomegaly. Sérum bilirubine allaient 38-165 umol/l avec une moyenne de 117 ± 14SD. Conjugated bilirubine allaient 31-150 umol/l avec une moyenne de 95 ± 8SD. sérum aspartate aminotransférase, l'alanine aminotransférase et phosphatasique alcaline ont été soulevées avec les valeurs moyennes de 180, 105 et 136 UI, respectivement. Six patients (19,4%) sont morts par rapport à 12,1% des patients non-icteric.
Conclusion: La typhoïde patients peuvent présenter avec différents degrés de jaunisse et la peste qui peut être confondue avec l'hépatite virale, malarienne ou amebic, maladies qui sont courantes dans les tropiques. Examen physique et de simples tests biochimiques devraient identifier les patients de la typhoïde qui doivent être traités avec des antibiotiques appropriés avant même que les résultats de la culture de sang sont disponibles.

Mots clés: L'hépatite jaunisse, tests de fonctionnement du foie, la fièvre typhoïde

Introduction

Typhoid fever continues to be a common problem in developing countries where it is associated with high morbidity and mortality. It usually starts as an acute systemic disease without localization, though one system may and often will dominate the picture. The clinical manifestations of typhoid fever are often non-specific and clinically indistinguishable from other infections, including malaria and other bacterial and viral infections. In many parts of Africa, diagnosis is based entirely on clinical features because conclusive laboratory confirmation of the infection is not usually available.[1] Jaundice is a rare clinical presentation in typhoid fever and its presence may cause diagnostic problems, especially in the tropics where malaria and viral hepatitis are common. Similarly, the high incidence of sickle cell disease in tropical Africa further complicates the picture as a combination of fever and jaundice is also a common form of presentation.[2,3] Typhoid is a disease that is difficult to recognize, yet it is necessary to be aware of the different modes of presentation which may not conform to the classical description of the disease. Several reports have been made on typhoid hepatitis.[4,5] Jaundice in the typhoid patient has also been described.[6,7]

In our hospital, typhoid patients present very late despite having symptoms for several days. Many of these patients have fever and jaundice as the predominant symptoms. We prospectively reviewed 254 patients with typhoid fever. Of these, 31 presented with jaundice and form the subject of this presentation.

The aim of this study has been to determine the clinical and laboratory features that allow early diagnosis of typhoid fever in patients that present with jaundice and differentiate it from other common causes of fever and jaundice in the tropics.

Materials and Methods

This prospective study was carried out at Center Hopitalier Regional de Hombo, Anjuoan. This 250-bedded hospital covers the Island of Anjouan and is surrounded by six district health centers from where patients are referred for treatment. The hospital cares for some 250,000 people including patients from neighboring Islands. The study was conducted between May, 1997 and October, 1998 on patients with confirmatory evidence of typhoid fever. Only patients with jaundice were included in this study. Jaundiced patients that tested positive for malaria parasites or hepatitis-B surface antigen were not included. The study was approved by the hospital ethical committee. History, clinical and laboratory data were recorded in a profoma specifically designed for the study. Definitive diagnosis was made by isolating Salmonella typhi from blood. Where this was not possible demonstration of fourfold rise in serum antibodies to the "O" antigen in serial estimations or, single Widal titre equal to or greater than 160 was considered as an evidence of current infection.[8,9] Bone marrow cultures, which may be positive even when the patient is taking antibiotics, were not done. All typhoid patients were assessed with special reference to the presence of jaundice. In the jaundiced patients, detailed clinical history and physical examinations were made with emphasis on hepatosplenomegaly and stigmata of chronic liver disease. In addition, care was taken to exclude cases of viral or toxic hepatitis, chronic liver disease, sickle cell disease, glucose -6– phosphate dehydrogenase (G-6-PD) deficiency and other causes of jaundice from the history, physical examinations and appropriate investigations.

Investigations performed in the jaundiced typhoid patients include hemoglobin, total and differential leukocytes count, serum electrolytes and urea, total and conjugated serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP). Surface antigen for hepatitis – B virus and blood film for malaria parasites were also performed. Hemoglobin electrophoresis for sickle cell disease was done in appropriate cases. Evaluation of liver function was repeated on days 2, 5 and 8 and at the time of discharge from hospital. Abdominal ultrasound

was also done. Liver biopsy was not performed in our patients. As previously reported by Khosla, a diagnosis of typhoid hepatitis was considered if the patient fulfilled the following criteria (a) Hepatomegaly of more than 14 cm (b) Jaundice (c) Biochemical abnormalities; serum bilirubin > 30.6 umol/l, elevated ALT and AST.[10]

Patients were resuscitated with appropriate fluids and electrolytes. Chloramphenicol was given orally at a dose of 75-100 mg/kg/day in 4 divided doses. The drugs were given intravenously in patients who could not take oral medication. In patients with intestinal perforations, additional gentamicin 3mg/kg/day and metronidazole 50mg/kg/day were given intravenously in divided doses. The perforations were closed in two layers and the peritoneal cavity was lavaged with warm normal saline. Antibiotics were continued for 10-14 days. Data analysis was performed using Epi – info statistical soft were package. Frequencies, tabulations and means were determined. The groups were compared using student t– test and a *P*-value of less than 0.05 was considered to be significant.

Results

During the period of study, 254 patients with typhoid fever had laboratory confirmation of their illnesses of which 31 (12.2%) presented with jaundice. Of the 223 non-icteric patients, only 157 had complete biochemical investigations. Among the jaundiced patients, there were 19 males and 12 females. Their ages ranged from 8 to 46 years with mean of 24.6 ± 9.2 SD years. Salmonella typhi was isolated in the blood of 14 patients while 17 patients showed positive Widal test. The median time between onset of clinical symptoms of typhoid and initiation of specific antibiotics treatment was 11 days (range 5–23 days). The clinical features at presentation are shown in Table 1. The patients presented with high grade fever which preceded the appearance of jaundice by 8 to 27 days. Hepatomegaly ranged from 4 to 16 cm below the costal margin at midclavicular line. Twenty-one patients (67.7%) had hepatomegaly greater than 14 cm. Intestinal perforation (29.0%) was more commonly seen in jaundiced compared to non-jaundice (17.8%) patients. Six patients (19.4%) died compared to 19 (12.1%) of the non – icteric patients ($P < 0.05$). In 16 patients, jaundice gradually disappeared within 2 weeks of initiating specific antibiotics treatment. Duration of hospital stay ranged between 9 and 31 days (mean 14 days). Relapse was seen in 6 (19.4%) patients.

Table 1: Clinical features of typhoid patients with jaundice

Feature	Number	Percentage
Fever	31	100.0
Jaundice	31	100.0
Hepatosplenomegaly	27	87.1
Splenomegaly	4	12.9
Typhoid psychosis	6	19.4
GIT bleeding	3	9.7
Ileal perforation	9	29.0

GIT: Gastrointestinal tract

Hemoglobin levels were between 6 and 13g/d1. Hemoglobin electrophoresis pattern was AA for all the 7(22.6%) jaundiced patients that were tested. Serum bilirubin ranged between 38 and 165 umol/l with a mean of 117 ± 14SD. The conjugated bilirubin ranged between 31 and 150 umol/l with a mean of 95 ± 8SD. Other biochemical abnormalities are shown in Table 2. Surface antigen for hepatitis – B virus and malaria parasites were negative in all the jaundiced patients. They also had no evidence of infestations by entamoeba histolotica. In 22 (71.0%) patients, biochemical parameters returned to normal levels between 12 and 29 days after commencement of treatment. Abdominal ultrasound showed diffuse hepatomegaly with normal biliary channels.

Discussion

The incidence of jaundice in typhoid patients ranges between 4.8% and 17. 6%.[10-12] In our study, jaundice was seen in 12.2%. This wide variation may be due to the severity of the disease in our patients as a result of delay in presentation and diagnosis. Jaundice usually manifests about one week from the onset of fever and improves slowly with recovery of the patient.[4] In 87.1% of our patients there was hepatomegaly, a sign which varies greatly in incidence. Some workers observed hepatomegaly in all icteric typhoid patients.[5,9] As reported by others, jaundice may occur without hepatomegaly and this was the finding in 4 of our patients.[13,14] Hepatomegaly was detected as early as the first week but more often in the second and third weeks and took several weeks to disappear. Hepatic encephalopathy though rare has been reported in typhoid patients.[15] However, a wide range of neuropsychiatric manifestations could be seen in patients with typhoid fever.[16] Neuropsychiatric manifestations were seen in 6 of our patients 2 of whom developed into overt psychosis whose course was independent of fever and jaundice.

Liver function test may show evidence of hepatic dysfunction even in the absence of jaundice. This occurs in 21 – 60% of cases.[12,14] Some workers reported a mild rise in transaminase levels in typhoid patients and suggested that this could

Table 2: Biochemical parameters in patients with or without jaundice

Parameter	Normal value	Jaundiced patients Mean ± SD (Range)	Non-jaundice patients mean ± SD (Range)	Statistical *P*-Value	Remark
Serum bilirubin umol/L					
Total	3-17	117±14 (38-165)	15±4 (3-22)	<0.05	Significant
Conjugated	0-3.4	95±8 (31–150)	1±3 (2-8)	<0.05	Significant
Unconjugated	3.5-13.6	15±6 (4-52)	12±3 (2-19)	<0.05	Significant
Serum proteins g/L	62 – 80	57±6 (47–68)	63±5 (52–77)	>0.05	Not significant
Aspartate aminotransferase IU/L	16-55	180± 18 (71-223)	74± 12 (53–102)	<0.05	Significant
Alanine aminotransferase IU/L	5-46	105± 16(59–168)	60± 8 (36–85)	<0.05	Significant
Alkaline phosphatase IU/L	17-60	136± 19(68-257)	85±15 (42–113)	<0.05	Significant

differentiate such cases from viral hepatitis where increase is marked.[17,18] However, we observed a significant rise in transaminase levels as did others.[4,10] This widespread biochemical evidence of liver dysfunction results from invasion of the liver by Salmonella or from a high concentration of endotoxins which damage the hepatocytes.[10] The bacteria may also proliferate in the hepatocytes and produce hepatic damage by stimulating the synthesis and release of cytokines.[4] Histopathologic study of the liver reveals typhoid nodules, cloudy swelling, ballooning degeneration, moderate fatty change and mononuclear cell infiltrate in few focal areas.[14] In addition, intact bacilli have been demonstrated in the parenchyma of the liver by immunohistochemistry and have been cultured from liver biopsy.[12,19] We did no test for G-6-PD deficiency in our patients. However, we believe that jaundice in our patients was not caused by G-6-PD deficiency. This is because the patients were thoroughly questioned about possible exposure to oxidant agents or previous episodes of jaundice. Similarly, the jaundice in our patients gradually disappeared on continued antibiotics treatment. In most of our patients, conjugated bilirubin constituted more than 80% of the total serum bilirubin [Table 2]. This is unlikely to result from hemolytic episode alone. Indeed, there is increased hemolysis in typhoid fever. However, excretion is the rate-limiting step and is usually impaired as a result of canalicula occlusion by swollen hepatocytes. This may be followed by focal hepatocellular necrosis which can promote rupture of bile canaliculi leading to direct reflux of bile into the hepatic sinusoids, hence the predominant elevation of conjugated bilirubin.[13] Thus 21 (11.2%) patients had typhoid hepatitis using previously described criteria.[10] The presence of comorbid state such as malnutrition and anemia results in a disease with fulminant course because of impaired immune response. The incidence of gastrointestinal hemorrhage and ileal perforation was also higher in our patients than in the non-icteric typhoid patients. Mortality was also significantly higher in the jaundiced typhoid patients. Intestinal perforation is the most important surgical complication of typhoid fever. The presence of jaundice in these patients was associated with higher morbidity and mortality. This is similar to the findings of others who noted that mortality was significantly associated with the presence of jaundice, anemia or malnutrition.[19,20] In general, relapse of typhoid is encountered in 10 – 22% of cases.[21] We found relapse in 20% of our patients as in another report.[10] The early use of effective antibiotics may lead to high rate of relapse presumably because prompt therapy inhibits the development of an adequate immune response.[13]

The clinical presentation of typhoid with jaundice can pose a diagnostic problem especially in the tropics, where jaundice in the febrile patient can be due to malaria, amebic or viral hepatitis. Jaundice has been reported in patients with *Falciparum malaria*.[17] Similarly, workers from Zaire reported Salmonella bacteremia among 206 children many of whom presented with fever and jaundice which was difficult to distinguish clinically from *Falciparum malaria*.[21] A recent study showed that only 2.5% of febrile patients with signs and symptoms of typhoid fever in Cameroon actually had typhoid while about 50% of the patients had malaria.[22] However, in malaria, the fever is abrupt with malaria paroxysm and malaria parasites are seen in a blood film. In areas of high malaria endemicity, the presence of malaria parasites in the blood of a patient with acute febrile illness and jaundice does not necessarily indicate that malaria is the cause of the patient's illness and diseases such as typhoid should be considered.[23-25] Malaria was found in 27% of children who were diagnosed as having typhoid on the basis of positive blood culture and it has been suggested that *Falciparum malaria* predisposes to Salmonella septicemia in children.[26]

In this study, patients presented with fever, jaundice, hepatomegaly and deranged liver function tests. This hepatitis like presentation has been observed by others.[4,7,10] In viral hepatitis, nonspecific prodromal

illness precede the jaundice and the fever usually subsides with the appearance of jaundice while in typhoid, fever persists despite the appearance of jaundice.[10,17,18] A significant rise in serum bilirubin without a corresponding increase in serum ALT is unusual in viral hepatitis but common findings in typhoid as seen in our patients.[18] Wilairatana reported jaundice due to acute viral hepatitis A in typhoid patients and suggested that hepatitis A should be considered in typhoid patients with jaundice because both enterically transmitted diseases may simultaneously occur.[27] The interaction of infections such as typhoid, malaria or viral hepatitis is unknown but may be synergistic and thus lead to more severe liver damage than when the infections act separately. It is a grievous mistake to misdiagnose a treatable systemic disease with liver involvement as viral hepatitis, which has no specific treatment. In the case of typhoid, such mistake can have fatal consequences. The absence of histological examination of the liver is an important limitation in this study. This means that the specific cause of hepatitis in our patients could not be confirmed.

Conclusion

This study concludes that patients with typhoid fever may present with jaundice. This clinical presentation may be confused with viral, malarial or amebic hepatitis, diseases that are common in developing countries where typhoid fever is endemic. Typhoid should be considered in any febrile patient who develops jaundice about a week after the onset of illness and at the peak of fever with or without hepatomegaly. These patients should be treated with appropriate antibiotics even before the results of blood culture are available. In malaria, the fever is abrupt with typical malaria paroxysm and malaria parasites are seen in a blood film, while in viral hepatitis a prodromal illness precedes the jaundice; fever subsides with appearance of jaundice and elevation of serum bilirubin is associated with a corresponding elevation of liver enzymes. Awareness of this unusual form of presentation of typhoid forms the basis for early recognition and treatment, which are vital for a successful outcome.

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