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Salmonella hepatitis as a typical presentation of typhoid fever, its impact and prognosis

Hulal Saleh Sahib¹ Shaima'a Dakhel AbdulHassan¹

¹Department of pediatrics, College of Medicine, University of Al-Qadisiyah, Diwaniyah, Iraq

Abstract

Aim of the study: First, to determine the clinical presentation, biochemical features, and prognosis of *Salmonella* hepatitis and second, to know if there is any risk factor of enteric fever or its complications.

Background: Enteric fever is still a common health problem with a significant morbidity and mortality with high occurrence rates in countries with poorly-established health systems. In patients, all organs can be affected including liver, hepatic dysfunction is not uncommon presentation of enteric fever.

Patients and methods: In endemic areas, fever and liver-based features should alarm the medical personals for the incidence of typhoid because it can mimic other diseases occurring commonly in these areas, like acute viral hepatitis, amoebic hepatitis or malaria, in our study total number of patients were 120 case all diagnosed with enteric fever on clinical and laboratory finding (increasing titer of Widal test and positive typhoid IgG and IgM of *Salmonella typhi* rapid test device)

Results: The clinical features of typhoid fever in the study: fever 100%, hepatomegaly 18%, hepatosplenomegaly 4%, jaundice 27%, headache 32%, anorexia 40%, vomiting 1%, elevated ALT 25%, AST 18%, Alkaline phosphatase ALP 16%, lactose dehydrogenase LDH 24% and abnormal PT 25%. Fever, jaundice, and normal or abnormal liver enzymes must hint for the incidence of typhoid hepatitis.

INTRODUCTION

The enteric fever that is well-known as typhoid fever is one of the main endemic diseases in countries with poorly-established health systems. The gram negative bacterium; *Salmonella enterica* serovar *typhi* (*S. typhi*), is the causative agent of this disease (1). The disease causes pyrexia, collapse, and spleen and lymph node-based features that could last for long time. Because prolonged immunity is not well established for this bacterium, *S. typhi* may induce repeated episodes of infection (2). The disease causes around 26.9 million cases with 1% of death tolls annually. Mostly, these cases are recorded in Asia (1). *Salmonella* infections are acquired through ingesting the organism, most often from food, but waterborne, person-to-person and animal-to-person transmission can occur (3). Poor sanitary conditions, lack of safe drinking water, illiteracy, ignorance, and low standards of personal, group and community hygiene-all contribute to this adverse state of affairs. The proliferation of the bacterium is started in the lymphatic tissues of the intestine with swelling in the Peyer patches. Then, the bacterium is disseminated via blood stream to reach other multiplication sites such as spleen, liver, and lymph nodes. Persistent bacteremia and symptoms then are followed (2). Reinfection of the intestine occurs as organisms are excreted in the bile. Bacterial emboli produce the characteristic skin lesions (rose spots). Symptoms in children may be mild or severe, but children younger than age 5 years rarely have severe typhoid fever (4). Children appear suddenly to be ill with headache, distention with abdominal cramps, unusual constipation followed by diarrhea within 48hrs later, noticed high fever, and toxic reactions. During the prodromal stage, physical findings may be absent, or there may merely be some abdominal distention and tenderness, meningismus, mild hepatomegaly, and minimal splenomegaly (5). Involvement of the liver due to this disease is usual with rare effects similar to viral hepatitis (6).

A special problem is the occurrence of typhoid hepatitis. Typhoid hepatitis is one of the atypical presentations of typhoid fever and can be defined as reversible involvement of liver during the course of typhoid fever. In endemic areas, fever and liver-based features should alarm the medical personals for the incidence of typhoid because it can mimic other diseases occurring commonly in these areas, like acute viral hepatitis, amoebic hepatitis or malaria (7,8). Bacterial cultivation from blood or tissue samples is considered as the main method to diagnose the disease with an accuracy rate ranges from 40% to 60% for the blood samples in the beginning of the disease. Positive results from stool and urine may not be recorded only after 1 week of the disease occurrence.

Bacterial cultivation from blood may be unsuccessful due to over-the-counter use of antibiotics in developing countries leading to false negative results. Highly accurate methods such as bacterial cultivation from bone marrow are not commonly used for diagnosis as it is considered as an invasive for sample collection (1). Error-based results due to lacking the sensitivity and specificity of Widal test against *S. typhi* H and O antigens may reduce the reliance on such diagnostic methods. Interestingly, developed monoclonal antibody-related techniques increase the trustfulness in the results. Moreover, polymerase chain reaction methods also add completely better picture via speed and accuracy of the results when testing for the presence of bacteremia (3). Although the development in the methods used for the detection of this bacterium, clinical-based diagnosis is still an affordable method in many developing countries. Successful treatment of children depends on the early diagnosis using appropriate methods leading in most cases to be managed at home with some oral antibiotics that could be followed up for prognosis. However, some cases may need further care in hospitals using parenteral antibiotic intervention especially when having prolonged vomiting, severe diarrhea, and abdominal distention. Providing adequate amounts of oral and parenteral fluids and electrolytes plus giving antipyretics, acetaminophen at 10-15mg/kg every 4 to 6hrs PO when required, are considered the main strategies in dealing with these cases. To prevent the occurrence of any complications, antibiotics are required to be used for such cases (1).

Preventive measures include proper hand washing with disinfectants after defecation and before consumption of food. These measures will help in breaking the transmission of typhoid thus reducing the burden of disease (6). The use of antibiotic is followed by variable relapsing rates especially when utilizing chloramphenicol (5-15%) or amoxicillin (4-8%) in comparison with higher successful rates when using quinolones and third generation cephalosporin (1).

PATIENTS AND METHODS

This study was performed at Al-Diwaniya maternity and children teaching hospital from the 1st of January 2016 to the 30th of December 2017. The total number of patients involved in our study were one-hundred twenty, (1.5-16yr.) all of them were diagnosed with enteric fever on clinical and laboratory finding (increasing titer of Widal test and positive typhoid IgG and IgM of *Salmonella typhi* rapid device). All patients were evaluated with full history (age, gender, time of presentation, residency, past

history of chronic disease), and were examined for organomegaly. Liver enzymes were performed (ALT, AST, ALP, LDH) and PT for all patients. Limitation of study was inability to perform blood culture because of most of the cases exposed to antibiotic therapy prior to admission.

RESULTS

Study group involve 120 patients with clinical presentation of typhoid fever & +ve results of both Widal test with increasing titer & typhoid IgG/IgM rapid test device, an in vitro-based immunological method for the identification of IgG and IgM in blood, serum, or plasma of human beings. There were female 55 (46%), male 65 (54%). The median age was 9.5yr (Range from 1.5 to 16yr), urban 63(52%), rural 57(48%)

All patient presented with fever, Fever & headache ~32%, Fever & Jaundice ~27%, fever & anorexia ~40%, Fever & Vomiting ~1% Figure2. On clinical examination jaundice 26%, hepatomegaly (HM) 18%, hepatosplenomegaly (HSM) 4% Figure3. Abnormal biochemical tests present in most of typhoid patients, elevated ALT 25%, AST 18%, Alkaline phosphatase ALP 16%, lactose dehydrogenase LDH 24% and abnormal PT 25% Figure4. In our study 109(90.8%) improved, 9cases (7.5%) prolonged hospitalization, one (0.8%) end with hepatic encephalopathy & death and one (0.8%) end with fulminant hepatic failure Figure5.

Table1- Residence & Sex

Residence & Sex	Number		Percent
Residence	Urban	63	52%
	Rural	57	48%
Sex	Male	65	54%
	Female	55	46%

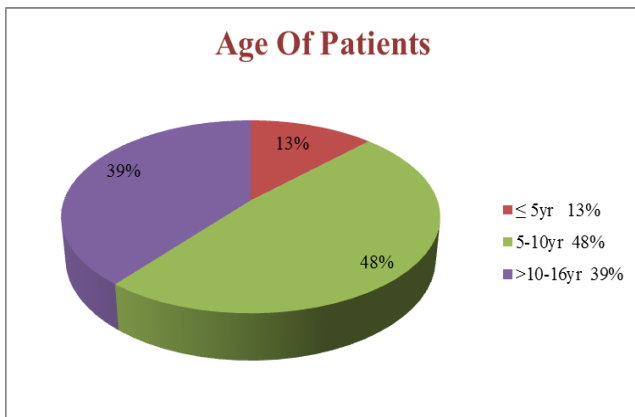


Figure 1-Age groups of patients

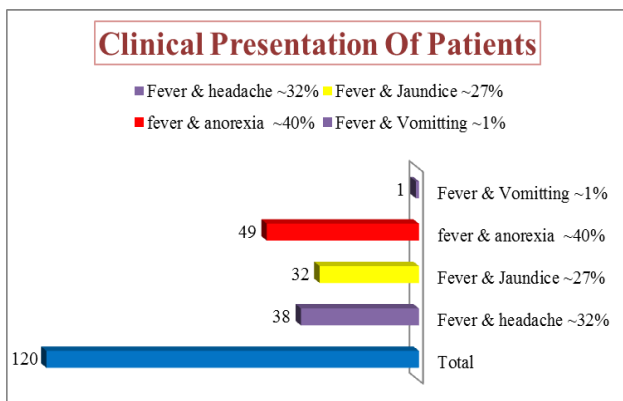


Figure2-Clinical presentation of patients

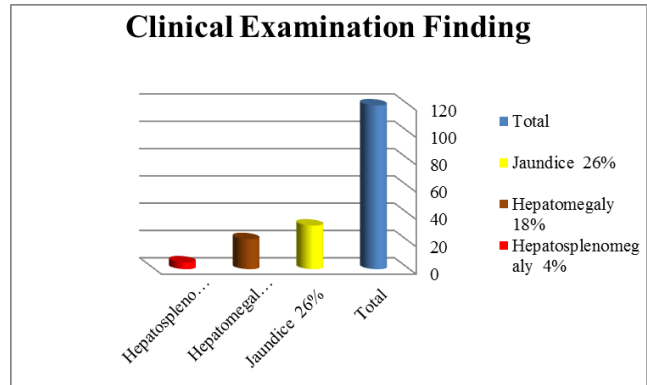


Figure3- Clinical Examination Finding

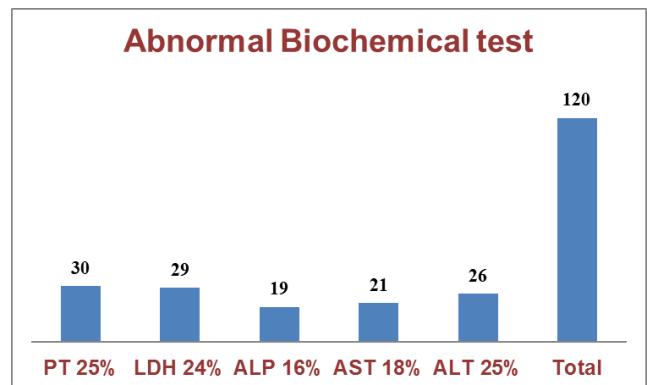


Figure4- Abnormal Biochemical test

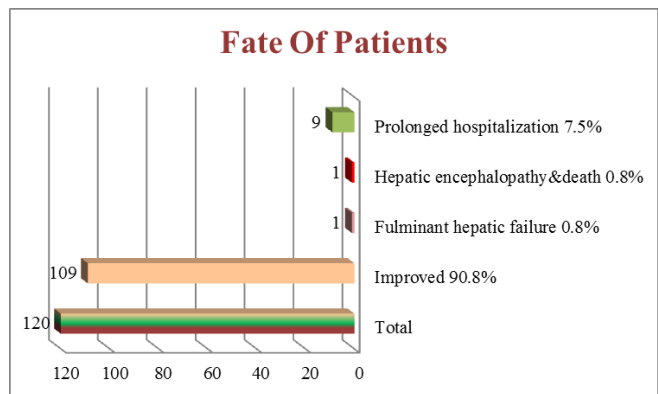


Figure5- Fate of Patients

DISCUSSION

Many reports have been published regarding typhoid fever that followed the thorough description by Osler about the hepatic involvement that was realized by hepatomegaly with pronounced clinical jaundice in 8 out of 1500 cases (9).

Early appearance of clinical jaundice is rare presentation in enteric fever. Although abnormal biochemical tests suggestive of hepatic involvement has already been suggested in 23-60 per cent of cases. The early hepatic changes have been attributed to generalized bacteremia, persistence of hepatomegaly and hepatic lesion during pyrexial stage. But the typhoid hepatitis has been ignored as a clinical entity. In this report the importance of typhoid hepatitis and its clinical significance for the diagnosis of enteric fever is highlighted, particularly at places where viral hepatitis and hepatic amebiasis are usually common and enteric fever is endemic (10).

Hepatomegaly (HM) has been reported in 25-44% cases (11,12); however, we observed it in 22 cases (18%).

In a study done in India, 55% of typhoid fever cases had hepatomegaly more than splenomegaly cases (50%).(Reference)

The cases with hepatomegaly had liver dysfunction that was characterized by the incidence of jaundice in 8% of these cases (7,8). While in our study hepatomegaly 18%, hepatosplenomegaly 4%, jaundice 27% & Biochemical involvement of liver occur in most of the patient elevated ALT 25%, AST 18%, Alkaline phosphatase ALP 16%, lactose dehydrogenase LDH 24% and abnormal PT 25%.

We observed hepatomegaly in 22 cases of jaundice (32 cases jaundice of 120 typhoid patients) while M. Rasoolinejad (2003) observed hepatomegaly in all cases of jaundice in typhoid as Osler described {all cases of jaundice had been HM} (9,13). In a study by Ayhan *et al.* (14), no jaundice was recorded in 16 cases of typhoid fever. In a study by Morgestern *et al.* (12), jaundice was shown in 9% out of 20 cases involved in that study. Gillin (year??) (11) reported 33% of 27 patients with hepatitis who had jaundice. In our study abnormal biochemical tests suggestive of hepatic involvement have been reported in 67.5% of patients during 1st week & 32.5% of patients during 2nd week of disease. Morgenstern *et al.* (11) believed that liver involvement is invariably present after the first week, M. Rasoolinejad *et al.* (2003)(13) observed liver involvement in 58 (54.2%) during the 2nd and 3rd weeks.

The alkaline phosphatase level increased in 25 patients (23.3%), in Sanyal *et al.* (2017) (15) study, alkaline phosphatase rising was more and in miller *et al.* (16) was less prevalent while we noticed that ALP was elevated in 16% of cases.

We observed that 109 cases (90.8%) clinically improved; 9 cases (7.5%) had prolonged hospitalization; one case (0.8%) end with hepatic encephalopathy & death and one case (0.8%) end with fulminant hepatic failure” he had associated immune deficiency” [the last 2 patients both not diagnosed until the 2nd week & had hepatosplenomegaly, elevated PT, ALT, AST, LDH, ALP with jaundice]. Severe hepatic involvement shows the presence of endotoxin, local inflammation with or without immune responses. More advanced symptoms appear after 2 weeks of fever such as clinical jaundice. Common features of the disease involving the liver reveal hepatomegaly and intermediate increase in the levels of transaminase. According to this involvement, symptoms of severe hepatic malfunction accompanied by liver-related encephalopathy may appear but in rare situations. Bacterial cultivation of blood or stool samples is required to definitely diagnose this bacterium as a reason for hepatitis to exclude viral hepatitis. For the histopathological pictures, hepatic involvement includes the presence of typhoid nodules with clear hyperplasia in the reticuloendothelial cells. The salmonella hepatitis has a good prognosis when treated with certain antibiotics leading to the disappearance of jaundice (17).

To differentiate between viral and *Salmonella* hepatitis, illness characterized by the occurrence of fever that is replaced by the incidence of jaundice is common. In typhoid fever, jaundice appears within 2 weeks of fever occurrence; however, the fever continues to be occurred even with presence of jaundice (18).

Hepatic dysfunction is induced either via direct invasion or endotoxin encouraging the incidence of immune-reaction-caused liver destruction (12,19). When testing for histopathological changes in the liver, some common lesions are recognized such as nodules, balloon like degeneration, cloudy swelling, mild fatty change, and patchy mononuclear cell infiltration (8,19). Moreover, intact bacterial bacilli are noticed via immunohistochemistry and recovered via cultivation from liver biopsies (20).

We believe that in our country where typhoid fever is endemic, in patients with high fever, jaundice, rise in transaminase and bilirubin *Salmonella* hepatitis is a probable diagnosis.

CONCLUSION

We believe that in our country where typhoid fever is endemic, in patients with high fever, jaundice, rise in transaminase and bilirubin *Salmonella* hepatitis is a probable diagnosis. Fever, jaundice, and normal or abnormal liver enzymes must hint for the incidence of typhoid hepatitis.

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