

ORIGINAL ARTICLE**Year** : 2007 | **Volume** : 25 | **Issue** : 4 | **Page** : 351--353

Typhoid myopathy or typhoid hepatitis: A matter of debate

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Abstract

Purpose: The aim of the present study was to evaluate the major source of increased serum enzyme level in typhoid fever and to determine the most relevant clinical entity, hepatitis or myopathy, during typhoid fever. **Methods:** A total of 118 subjects proved to have typhoid fever were evaluated for serum enzymes such as transaminases, alkaline phosphatase, lactate dehydrogenase (LDH) and creatinine kinase (CK); and their relation with each other, clinical symptoms and serum bilirubin were evaluated by regression methods. **Results:** Hepatomegaly was revealed in 14% of the cases and was correlated with elevated serum bilirubin (5.05 ± 13.03 mg/dL in hepatomegalic subjects). Alanine aminotransferase (ALT) and CK were elevated in 22 and 60% of the cases, respectively. Correlation coefficient of CK with aspartate aminotransferase (AST) and LDH was $R^2 = 0.68$ and 0.75 , respectively, which were higher than that of ALT with that two enzymes. **Conclusions:** In conclusion, elevation of serum enzymes in typhoid is mostly of muscular origin.

How to cite this article:Mirsadraee M, Shirdel A, Roknee F. Typhoid myopathy or typhoid hepatitis: A matter of debate. *Indian J Med Microbiol* 2007;25:351-353**How to cite this URL:**Mirsadraee M, Shirdel A, Roknee F. Typhoid myopathy or typhoid hepatitis: A matter of debate. *Indian J Med Microbiol* [serial online] 2007 [cited 2020 May 4];25:351-353**Available from:** <http://www.ijmm.org/text.asp?2007/25/4/351/37337>

Full Text

Typhoid fever is yet claiming many lives in developing countries. [1] Ramachandran described typhoid hepatitis and its histopathology in 1974. [2] The hepatic manifestations of typhoid fall into three categories: i) patients with no evidence of hepatic enlargement or abnormalities in hepatic function; ii) patients with evidence of hepatic involvement, either hepatomegaly or abnormal liver function tests, in whom hepatic involvement was of no great clinical importance and occurred as an incidental feature of the illness; and iii) patients with hepatic manifestations as the dominant feature of the illness and often the mode of presentation of the disease. [1] Elevated serum enzyme level related to hepatic damage was reported in 50-100% of typhoid patients. [3],[4]

Myopathy during the course of typhoid fever is reported increasingly. [5] Both clinical entities, myopathy and hepatitis, are usually diagnosed by serum enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH) and creatinine phosphokinase (CK). AST and LDH are elevated in myopathy as well as hepatitis, whereas ALT and CK are relatively specific for liver and muscle, respectively. [6] According to the original definition of typhoid hepatitis, it is possible that an overdiagnosis for typhoid hepatitis occurred and typhoid myopathy was missed.

The aim of the present study was to evaluate the major source of increased serum enzyme level in typhoid fever and to determine the most relevant clinical entity, hepatitis or myopathy, during typhoid fever.

Materials and Methods

The present study was conducted in patients with typhoid fever, who were admitted to Montaserieh University Hospital, Mashhad, Iran. The study design was cross-sectional and prospective. Diagnosis was confirmed by a positive culture of blood and/or bone marrow or fourfold rise in Widal titer. All subjects with proved typhoid fever were included in the present study regardless of their age. Patients with paratyphoid fever were not included in this study. Demographic data and clinical findings of

liver and spleen involvement were mentioned in a questionnaire. Laboratory evaluation included serum enzyme activities (AST, ALT, ALP, LDH and CK: all evaluated by Technicon RA-1000), total and direct bilirubin, haematological assessment and urinalysis. The blood sample was drained on the first day of management at the same time with blood culture sample collection. For the determination of liver involvement, the enzymes were correlated with ALT and bilirubin (total and direct) and for the evaluation of muscular enzyme release, serum enzymes were correlated with CK. Due to the ethical considerations, tissue biopsy from liver and muscle was not performed. This study was approved by the Ethical Committee of Islamic Azad University of Mashhad (Iran).

Statistical analysis

Sample size was 110 subjects according to 0.05 alpha risk and 80% potency. Descriptive statistics was performed to generate descriptive data. In addition, correlation between the levels of different serum enzymes was calculated by regression analysis and F -statistics. Comparison of variables were tested by Chi-square and Student's t -test. A two-sided or one-sided (depended on the test) P -value of 0.05 was the criterion for statistical significance. Normal distribution of results was assessed by Kolmogorov-Smirnov test. All analyses were performed by statistical softwares epi info 2000 and spss, version 12.0.

Results

One hundred eighteen patients with an age range of 2-53 years (23.1 \bar{x} 12.3) were enrolled in the study. The diagnosis was based on positive blood culture, bone marrow culture and fourfold rise in Widal titer of typhoid fever in 94, 12 and 12 cases, respectively. The men were affected more than the women (M/F = 2/1). Fever and chill were the most prevalent symptoms (100 and 98%, respectively) followed by headache and abdominal pain (77 and 63%, respectively). Hepatomegaly and splenomegaly were found in 16 (14%) and 28 (26%) cases, respectively. There was no significant association between hepatomegaly and the increased level of AST, ALT and ALP [Table 1] although serum bilirubin level in patients with hepatomegaly was significantly higher than subjects with normal liver (5.05 \bar{x} 13.03 mg/dL in hepatomegalic subjects vs. 0.73 \bar{x} 0.84 mg/dL, t = 2.28, P F -statistics 40 and 62.4, respectively) [Table 3]; [Figure 1], in favour of muscular origin of serum enzymes in typhoid fever. Correlation of AST with ALT and LDH was significant but to a lesser degree (F -statistics 34.9 and 10, respectively) [Table 3].

Discussion

Classically, typhoid fever presents with continuous fever, abdominal pain, constipation, rose spot and relative bradycardia; but some variations in clinical findings such as diarrhoea and leukocytosis have been reported. [7] Many organs other than gastrointestinal tract may be involved in typhoid fever. Hepatic involvement is one of the earliest reported complications of typhoid fever, [2] which can cause hepatomegaly, jaundice and coma, but its course with administration of treatment is favourable. [8] As abnormal AST and ALT in combination are indicative of a hepatocyte disorder, [9] many investigators used these enzymes for evaluation of hepatic involvement during typhoid fever. The frequency of elevated serum enzyme in two previous reports was 52 and 100%, respectively. [4],[5] But in our series, hepatomegaly was observed in 14% and ALT as the hallmark of liver damage was elevated in 22% of the cases.

As a different point of view, Scheig [6] reported that the prothrombin time and serum albumin level are excellent measures of hepatic protein synthesis ability, whereas the bilirubin level is probably the best marker of overall liver function. Khan et al. , [10] reported jaundice as a main predictor of severe liver injury in 36% of typhoid fever. Jaundice was only present in 5% of our patients but it was significantly associated with hepatomegaly [Table 1].

The invasion of intestinal lymphatic tissue is suggested to result in a host reaction with hyperplasia of the liver reticuloendothelial system and infiltration of portal spaces as well as the reduction of the microcirculation causing necrosis. [11] Hepatic damage by Salmonella typhi appears to be mediated by bacterial endotoxin. [12] The presence of intact bacilli has been demonstrated in the hepatic tissue that may be related to presence of Salmonella bacteria in reticuloendothelial system and hyperplasia of Kupffer cells (typhoid nodule), [12] without significant liver injury.

Myopathy is another reported complication of typhoid fever, which can cause severe myoglobinuria and elevated CK. [5],[13] In the present study, the pattern of serum enzymes is more comparable to what is found in myopathy (60%) rather than liver disease (22%), as the association of AST and CK is stronger than AST and liver enzymes [Table 3].

In conclusion, liver is involved in 14% of typhoid patients manifesting with hepatomegaly and elevated bilirubin. Elevation of serum enzymes in typhoid fever is presumably of a muscular origin, while elevation of liver enzyme is relatively less common.

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Monday, May 4, 2020

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