Case Report

Cholestatic hepatitis in a child with typhoid fever –a case report

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Abstract

Typhoid fever is a common infectious disease in developing countries. It is caused by *Salmonella typhi*. *Salmonella* is a genus of the family *Enterobacteriaceae*. They are rod-shaped, Gram-negative, facultative anaerobic bacteria, most of which are motile by peritrichous flagella (which bear H antigen [s]). *S. Typhi* is taxonomically designated as *Salmonella enterica* subspecies *enterica* serovar Typhi. In addition to the H antigen (s), 2 polysaccharide surface antigens aid in further characterization of *S. enterica*, namely the somatic O antigen and capsular Vi (virulence) antigen. Vi antigen is associated with resistance to complement-mediated bacterial lysis and resistance to complement activation by the alternate pathway.

Salmonella enterica serovars Paratyphi A and Paratyphi B (and uncommonly Paratyphi C) cause a disease (paratyphoid fever) that is clinically indistinguishable from typhoid fever, particularly in parts of Asia. Typhoid fever and paratyphoid fever are collectively termed enteric fever.

Keywords: Typhoid fever, Enteric fever, Clinical manifestations

Introduction

Typhoid fever is an acute generalized infection, caused by a highly virulent and invasive enteric bacterium, *Salmonella enterica* serovar Typhi, generally termed *Salmonella* Typhi (*S. Typhi*). Typhoid fever is an important public health problem in many low and middle-income countries (LMICs).

With emergence multidrug-resistant Salmonella typhi (MDRST) the clinical picture of typhoid fever has changed considerably [1]. Cholestatic hepatitis secondary to typhoid fever has only been reported infrequently in children. The clinical picture of typhoid hepatitis frequently mimics acute viral hepatitis [2-4]. There is marked inter- and intra-country heterogeneity in typhoid fever incidence in both Asia and Africa. Higher incidence rates have been reported in different studies both in rural and urban settings with poor sanitation systems, demonstrating that typhoid is not restricted to urban slums. Similarly, variable patterns of seasonal trends can occur but are not always observed [5-7]. We report an adolescent child who presented with fever and jaundice found to have cholestatic hepatitis secondary to typhoid fever.

Global estimates of typhoid fever burden range between 11 and 21 million cases and approximately 128 000 to 161 000 deaths annually [8]. The majority of cases occur in South/South-East Asia and sub-Saharan Africa. Data since 2000 show a reduced global burden of typhoid fever compared with the 1990s. Children are disproportionately affected by typhoid fever, with peak incidence long known to occur in individuals aged 5 to <15 years of age [9-10]. There is marked inter- and intra-country heterogeneity in typhoid fever incidence in both Asia and Africa [11-12].

Humans are the only known reservoir of *S. Typhi*. Transmission of the infection is by the fecal-oral route and may occur in 2 main patterns: (i) short-cycle, with

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contamination of food and water in the immediate environment through inadequate hygiene and sanitation measures, either by shedding from temporary or chronic carriers, or (ii) long-cycle, with contamination of the broader environment, such as pollution of water supplies by sewage, inadequate treatment of piped water or use of raw human feces or untreated sewage as a crop fertilizer. The risk of transmission of *S. Typhi* is increased in populations lacking access to safe water and adequate sanitation, and in the context of poor hygiene among food handlers. Other, often interrelated, factors associated with an increased individual or population risk are: high population density and overcrowding; low socioeconomic status; low literacy rates; and handling of *S. Typhi* by clinical microbiology laboratory staff. However, clustering of cases can occur without an obvious association with population density.

Enteric fever is a major health problem in developing countries. The term enteric fever includes typhoid and paratyphoid which is characterized by generalized infection of the reticuloendothelial system and intestinal lymphoid tissue accompanied by sustained fever and bacteremia. Hepatic involvement was known for a long time and it was first described by Osler in 1899 who documented cases of typhoid fever with jaundice and hepatomegaly.

Typhoid fever presents with a wide range of hepatic complication; however, jaundice is a rare clinical manifestation. The exact mechanism by which salmonella typhi causes jaundice is not very clear, it may be due to interaction between salmonella endotoxin and hepatic macrophages and immunological factor.

It usually starts as an acute systemic disease without localization and is clinically indistinguishable from other infections, including malaria, bacterial, and viral infections. Multiple organs are known to be affected by the disease. Hepatic involvement could be considered important, as it may be associated with a higher relapse rate.

Case Report

A 14-year-old boy presented with high-grade fever for 11days with a vague right hypochondrium discomfort, jaundice and, vomiting for 3 days. There was no history of diarrhea and pruritis. He did not gave a history of contact with muddy water and blood transfusion or iv drug abuse, prior to hospitalization he had received empirical antibiotics without any improvement in clinical parameters, on examination he was ill-looking with icterus with mild dehydration with fever 102 F, Blood pressure 110/70 mm of hg and Pulse rate was 98/min. There were no signs of liver failure or hepatic encephalopathy. Per the abdomen, examination revealed firm hepatomegaly liver span 11cm and moderately enlarged soft splenomegaly. The rest of the systemic examination was normal. laboratory investigation showed hemoglobin 9.2gm/dl, total leukocyte count 5700cells/cubic mm platelet count 0.72lac/cubic mm, and peripheral blood smear showed normocytic normochromic anemia without any abnormal cells. The liver biochemistry showed total proteins 5.2gm/dl with an elevation of AST and ALT which were276units/l and178 units respectively. Gamma GT 219u/l the alkaline phosphatase was 546 units/l, Indirect bilirubin was 2.3 mg% and direct bilirubin was 6 mg%. The urine full report showed bile and bile pigments. prothrombin time12.5sec (control 13 sec INR.96) APTT34sec (control 34 sec INR.94), his renal function was normal. Her blood sugar was 96mg/dl. The Blood culture and urine culture were sent. Serology for HIV, Hepatitis A, B, C, and Dengue IgM, MP Elisa for malaria were negative. His Widal test was positive with a titer of O1/320and H1/320. The ultrasound scan of abdomen showed an enlarged liver 15.8cm and Gall bladder distended and show minimal hypoechoic sludge and minimal diffuse wall thickening, spleen enlarged in size 16.7 cm. on day 5th blood culture yielded salmonella, with sensitivity to cefotaxime and azithromycin, meropenem, the final diagnosis of cholestatic hepatitis was postulated. He was treated with IV ceftriaxone and azithromycin for 7 days. Patient responded with remission of fever after 04 days and Serum bilirubin decreased to half in 0n 6th day of admission and clinically complete resolution of jaundice in the next 14 days with LFT becoming normal.

Discussion

The often-non-specific presentation of typhoid fever makes clinical diagnosis difficult as it may be confused with a wide range of other common febrile illnesses in regions where typhoid fever is endemic. Reliance on clinical diagnosis leads to inaccurate surveillance data and a considerable misrepresentation of the incidence of typhoid fever and can also result in inappropriate treatment. In most settings, confirmation of the diagnosis relies on the isolation of *S. Typhi* by blood culture. The sensitivity of a single blood culture is approximately 60% and is affected by the volume of blood obtained for culture. The sensitivity of blood culture is further reduced by the common practice of starting treatment with antibiotics before confirmation of the

diagnosis. Blood culture is not performed for the majority of cases in LMICs, especially among those treated in non-hospital settings. In some countries blood culture is underutilized in infants and young children, resulting in underestimation of the burden of typhoid fever in those age groups. The currently available serological tests are compromised by a variable antibody response to the pathogen which may persist for variable periods and cross-reactivity of *S. Typhi* (and *S. Paratyphi A*) with other enteric bacteria.

Children are disproportionately affected by typhoid fever, with peak incidence long known to occur in individuals aged 5 to <15 years of age. A recent systematic review and meta-analysis of studies on typhoid fever in children in Asia and Africa found that estimates of the proportion of typhoid fever cases in those aged <5 years ranged from 14% to 29%, compared with 30% to 44% in those aged 5–9 years and 28% to 52% in those aged 10–14 years [13]. The burden of typhoid fever in children was further evaluated based on inpatient and outpatient data collected between 1998 and 2017, from sites in Africa, Asia and the Americas where typhoid fever surveillance or studies of typhoid fever epidemiology were carried out. Data representing >10 000 blood culture-confirmed cases of typhoid fever sufficiently severe to require outpatient or inpatient care showed that 27% of all cases occurred in the age group 0–4 years. In this age group, approximately 30% of cases occurred in children aged <2 years and 10% in infants aged <1 year.

Data on the maternal and fetal morbidity and mortality associated with typhoid fever are limited and mostly based on small case series. Some published reports suggest that typhoid fever in pregnancy can result in a range of maternal complications as well as miscarriage, fetal death, and neonatal infection [14].

Conversely, a comparison of pregnant women with blood culture-confirmed typhoid and pregnant women without typhoid did not find a significant difference in maternal complications or pregnancy outcomes among the 2 groups [15]. Cross-sectional sero-epidemiological surveys in some countries suggest that a substantial proportion of typhoid fever cases are undiagnosed (up to 80% in the Pacific region) [16].

Estimates of case fatality rates in typhoid fever range from 1% to 4% in patients who receive adequate therapy (~1% with prompt initiation of appropriate antimicrobial therapy), but can rise to 10–20% in untreated cases, or cases treated with inappropriate antibiotics. Case fatality rates in children aged <4 years have been reported in one study to be 10 times higher than in older children (4.0% vs 0.4%). Case fatality rates correlate with the prevalence of antimicrobial resistance and the timely administration of antibiotics to which the circulating *S. Typhi* strains are susceptible.

In approximately 2%–5% of cases, depending on the individual's age and whether there is a pre-existing disease of the gallbladder mucosa, a chronic gallbladder carrier state can develop. This can also occur following subclinical *S. Typhi* infection. Chronic biliary carriers of *S. Typhi* have an increased risk of developing hepatobiliary cancer. Chronic carriers represent a reservoir of infection and contribute to the long-term endemicity of typhoid fever in communities through ongoing shedding of *S. Typhi* into the environment and possibly contaminated water and food supplies; short-cycle transmission may occur through contaminated food if the carriers are food handlers. Typhoid cholestatic hepatitis is less frequently reported entity in children, with the emergence of multidrug-resistant salmonella typhi (MDRST) the clinical presentation of typhoid fever has changed considerably.

Cholestatic jaundice is a rare clinical manifestation presentation of typhoid fever. It is very important as it mimics acute viral hepatitis, malaria, dengue, leptospirosis, acute on chronic hepatic in developing countries. Hepatic manifestation in typhoid fever can occur with or without hepatomegaly.

Hepatitis in typhoid fever can be caused by either due to direct invasion of the liver by salmonella or endotoxins damage hepatocytes with reticuloendothelial cell hyperplasia. Jaundice usually manifests in the second or third week of typhoid fever. In viral hepatitis, nonspecific symptoms precede jaundice and fever usually subsides with the onset of jaundice.

A significant rise in serum bilirubin without a corresponding increase in liver enzymes is a finding in typhoid hepatitis which differentiates it from viral hepatitis where liver enzymes are correspondingly elevated concerning bilirubin levels. Other possible infections were ruled out by relevant clinical examination and investigations.

In tropical areas, the differential diagnosis of a child presenting with fever and jaundice should include typhoid cholestatic hepatitis. Although rare, cholestatic hepatitis should be recognized as an associated manifestation of typhoid fever.

Conclusion

Although a very rare phenomenon, cholestatic hepatitis should always be considered as an associated manifestation of enteric fever, especially in typhoid endemic regions.

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References

1. Roberts EA. Neonatal hepatitis syndrome. In Seminars in neonatology 2003;8(5):357-374. doi: https: //doi. org/10.1016/S1084-2756(03)00093-9

2. Khosla SN. Typhoid hepatitis. Postgrad Med J. 1990; 66 (781):923-925. doi: 10.1136/pgmj.66.781.923.

3.Shetty AK,Mital SR, Bahrainwala AH, Khubchandani RP, Kumta NB. Typhoid hepatitis in children. J Trop Pediatr.1999;45(5):287-290.doi:10.1093/tropej/45.5.287

4. Ratnayake EC, Chrishan S, Bandula CW. Cholestatic hepatitis in a patient with typhoid fever- a case report. Ann Clin Microbiol Antimicrob. 2011; 10:35. doi: 10. 1186/ 1476-0711-10-35

5. Arabaci F, Irmak H, Akdeniz H, Demiröz AP. Jaundice with cholestasis: a case of typhoid hepatitis. Turkish J Infect. 2003;17:99-102.

6. Karoli R, Fatima J, Chandra A, Singh G. Salmonella hepatitis: an uncommon complication of a common disease. J Fam Med Prim care. 2012;1(2):160-162. doi: 10.4103/2249-4863.104992.

7. Albayrak A, Seda Gunbey S, Aktas F. Cholestatic hepatitis due to Salmonella typhi. Clin Pract. 2011;1(1): e13.doi:10.4081/cp.2011.e13.doi:10.4081/cp.2011. e13

8. WHO. Background paper to SAGE on Typhoid Policy Recommendations. 2017. Available at http:// www.who.int/immunization/sage/meetings/2017/octobe r/1_Typhoid_SAGE_background_paper_Final_v3B.pdf ?ua=1, accessed December 2017.

9. Thompson CN, Kama M, Acharya S, Bera U, Clemens J, Crump JA, Typhoid fever in Fiji: a reversible plague? Trop Med Int Health. 2014;19(10): 1284-1292. doi: 10.1111/tmi.12367. Epub 2014 Jul 25.

10. Als 1, Radhakrishnan A, Arora P, Gaffey MF, Campisi S, Velummailum R, Global Trends in Typhoidal Salmonellosis: A Systematic Review. Am J Trop Med Hyg. 2018;99(3_Suppl):10-19. doi: 10.4269/ ajtmh. 18-0034. Epub 2018 Jul 24.

11. Marks F, von Kalckreuth V, Aaby P, Adu-Sarkodie Y, El Tayeb MA, Ali M, Incidence of invasive salmonella disease in sub-Saharan Africa: a multicentre population-based surveillance study. Lancet Glob Health. 2017;5(3):e310-e323. doi: 10.1016/S2214-109X (17) 30022-0.

12. Breiman RF, Cosmas L, Njuguna H, Audi A, Olack B, Ochieng JB, et al. Population-based incidence of typhoid fever in an urban informal settlement and a rural area in Kenya: implications for typhoid vaccine use in Africa. PLoS One. 2012;7(1):e29119. doi: 10. 1371 / journal.pone.0029119. Epub 2012 Jan 19.

13. Britto C, Pollard AJ, Voysey M, Blohmke CJ. An Appraisal of the Clinical Features of Pediatric Enteric Fever: Systematic Review and Meta-analysis of the Age-Stratified Disease Occurrence. Clin Infect Dis. 2017; 64 (11):1604-1611. doi: 10.1093/cid/cix229.

14. Carles G, Montoya Y, Seve B, Rakotofananina T, Largeaud M,MignotV.[Typhoid fever and pregnancy]. J Gynecol Obstet Biol Reprod (Paris). 2002;31(5):495-499.doi:JGYN-09-2002-31-5-0368-2315-101019-ART8

15. Sulaiman K, Sarwari AR. Culture-confirmed typhoid fever and pregnancy. Int J Infect Dis. 2007; 11 (4): 337-341. doi: 10.1016/j.ijid.2006.09.007.

16. Watson CH, Baker S, Lau CL, Rawalai K, Taufa M, Coriakula J, et al. A cross-sectional seroepidemiological survey of typhoid fever in Fiji. PLoS Negl Trop Dis. 2017; 11(7): e0005786. doi: 10.1371/ journal. pntd. 0005786. eCollection 2017 Jul.

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