Hepatobiliary Complications of Enteric Fever

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In spite of the progress made in control of communicable diseases, enteric fever continues to carry a high morbidity and mortality in developing countries. In fact, it has shown a recent upsurge with emergence of multidrug resistant strains of *Salmonella typhi* (MDRST) which is felt to be more virulent and associated with higher frequency of multisystem complications. The purpose of this review is to emphasize the frequency and significance of hepatobiliary complications of typhoid fever with particular reference to children and recent outbreaks all over India.

Hepatomegaly and Hepatitis

Although hepatic enlargement in enteric fever was reported as early as 1898(1,2), very few studies, especially dealing with liver involvement, have been reported(3-9). Even in these studies most of the patients were adults.

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Khosla *et al.*(5) have classified the hepatic involvement into three types, depending on hepatomegaly and biochemical abnormalities on liver function tests (LFTs). Isolated elevation of SGOT/SGPT, with or without elevation of 5-nucleotidase and abnormal prothrombin index was graded as type I involvement, while hepatomegaly with altered LFTs was graded a type II, and the both in presence of jaundice as type III. The classification is useful for grading severity of hepatic involvement in clinical practice. Nonetheless, hepatitis may be present sometimes without hepatomegaly at least in adults(4,5), while isolated hepatomegaly may be present as a nonspecific sign.

In the recent outbreaks of typhoid fever in children, hepatomegaly was found in 39-90%(10-15). The frequency is apparently much higher as compared to adults, in whom the reported figures ranged between 25-33%(3,5). It is usually observed after first week of the fever, often persist through period of high fever and subsides with defervescence(3). Isolated liver enlargement is considered as a nonspecific response to toxemia and is therefore more likely to be present with severe illness(5) and with typhoid fever than paratyphoid fever(3). The enlargement is caused by hypertrophy and hyperplasia of Kupffer's cells(4).

Hepatitis of typhoid fever is often of mild to moderate nature with abnormal LFTs: severe type with icterus has been considered relatively rare. Patients with pre-existing anemia, malnutrition and poor health are more likely to get severe hepatitis(5), as also the patients with the relapse of disease(4). In the recent outbreaks of

typhoid fever from various parts of India the reported frequency of jaundice or severe hepatitis has varied widely between 1-10%(10-16) while elevated SGOT and SGPT has been described in 51% children(13%). The elevation of the enzymes is perhaps due to endotoxic effects of the infection on hepatic parenchyma causing edema and stasis(5).

No specific clinical features can be attributed to typhoid hepatitis. It can easily mimic viral hepatitis, malaria and amebic liver disease; differentiation may be difficult as all these diseases tend to occur in similar populations(7). Presence of continuous fever, and jaundice at peak of fever favours typhoid hepatitis; in viral hepatitis fever usually comes down after the appearance of jaundice. A blood culture may clinch the diagnosis. Liver biopsy may be necessary in difficult cases.

Pathological changes in liver probably occur due to toxemia as well as direct invasion. These consist of nonspecific changes to marked cloudly swelling, parenchymal degeneration, peripheral infiltration by mononuclear cells and central area of necrosis (Mallory's bodies), and enlarged and hypertrophied Kupffer's cells(4,5,8).

Specific antibacterial therapy for enteric fever in addition to the supportive measures required for any hepatitis are generaly enough for typhoid hepatitis. Complications such as upper gastro intestinal bleed may require attention. Usually hepatitis resolves with defervescence of fever.

Hepatic Abscess

Typhoid liver-abscess is a fatal disease if untreated(17,18). Because of the nonspecificity of symptomatology and its insidious onset and clinical course, diagnosis can be difficult(19). A review of English literature reveals a few documented cases of liver abscess caused by *S. typhi* and other *Salmonella* infection. All of these were among adults, except one case of a 14-year-old child.

Three groups of cases of liver abscess have been described in typhoid fever : solitary abscess, suppurative pylephlebitis, and suppurative cholangitis. Solitary abscess may be a direct consequence of ulceration of the bowel or secondary to complications of typhoid fever(20). Cholangitis due to biliary obstruction from various causes, and septicemia has also been implicated. Interestingly, there is a marked predilection for the right lobe of the liver(21,22).

The diagnosis can be difficult because of nonspecificity of the clinical features and the insidious onset. Jaundice is rare. While a fixed and elevated right hemidiaphragm on plain *X*-ray suggests a liver abscess, hepatic scintiscan and ultrasonography are more sensitive diagnostic tools. A definitive diagnosis can be made only after culture of *Salmonella typhi* from the pus obtained from the abscess. In the management of these patients percutaneous aspiration of the pus, specific antibiotic and supportive therapy had been successful.

Biliary Complications

Circulating typhoid bacilli are filtered by the liver and excreted in the bile. The biliary tract, however, is infected only rarely. The routes by which gall bladder may become infected include the blood stream, by way of the biliary system from the contiguous infected organs and perhaps by lymphatics from gastrointestinal tract(23). Sherlock described two type of typhoid cholecystitis, acute and chroni (24).

Acute Cholecystitis

It has been considered a rare disease(23). Indeed several recent reports on typhoid fever did not include any symptomatic case of acute cholecystitis with MDRST enteric fever(10-12,14-16). Verma *et al.* could collect only nine cases of acute typhoid cholecystitis over a period of 15 years(25). However, a recent study from Bangalore, in which ultrasound criteria were used for the diagnosis, found a very high incidence of 24% in 143 children with MDRST enteric fever hospitalized during the year 1991(13).

In symptomatic patients signs of acute cholecystitis mostly appear at the end of the second week of the illness or sometimes during convalescence. The severity of the illness may vary from mild catarrhal type to dangerous perforation of the gall bladder(26). Typically the patient has high fever, right upper quadrant abdominal pain without associated vomiting, hepatomegaly and localized tenderness and guarding; gall bladder may not be palpable(23,25). Often the SGOT, SGPT, LDH and occasionally alkaline phosphatase levels are elevated(23).

Abdominal ultrasound examination is helpful in making the diagnosis. Rao *et al.* made the diagnosis if 2 of the following 6 criteria were present: thickness of gall bladder wall >4 cm, pericolic collection, biliary sludge, mucosal irregularity with or without intramural collection, and ultrasound Murphy's sign(27). Verma *et al.* found a distended gall bladder with cellular debris in all the several patients on whom ultrasonography was performed(25). Resolution of the ultrasound signs coincided with clinical recovery.

Conservative management with effective antibiotics and supportive measures alone is good enough(23,25,27). The choice of effective antibiotic should take into account the expected peak concentration of the drug in gall bladder and bile ducts. Generally 3 weeks' therapy is sufficient. Infrequently, an acalculous cholecystitis associated with suppuration, ischemia or septic complication may require cholecystectomy(23).

Chronic Cholecystitis and the Carrier State

The typhoid carrier passes organisms in the feces derived from a focus of infection in the gall bladder or biliary tract. Chronic typhoid cholecystitis is symptomless. The carrier state is not cured by antibiotic therapy. Cholecystectomy is successful if there is no associated infection of the biliary ducts. Chronic typhoid cholecystitis is not an important cause of gall stones. Biliary carriers of other *Salmonellae* have been reported and treated with ampicillin and cholecystectomy(24).

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