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Role of acute viral hepatitis as a confounding factor in antituberculosis treatment induced hepatotoxicity

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***Background & objectives*: Drug induced hepatotoxicity (DIH) is an important and commonly encountered adverse effect with antituberculosis (anti-TB) treatment. Acute viral hepatitis (AVH) is an important confounding reason which clinically, biochemically and histologically mimics DIH.**

***Methods*: The contributory role of acute viral hepatitis as a confounding factor in patients with normal baseline liver functions who developed acute hepatitis while receiving short-course anti-TB treatment was prospectively studied. The sera of all patients who developed acute hepatitis were analysed for markers for hepatitis A, B, C and E viruses.**

***Results*: Viral hepatitis was present in 15 of the 102 (14.7%) patients who developed acute hepatitis while receiving anti-TB treatment with hepatitis E virus being the most common cause Later onset of acute hepatitis [58 (5-133) vs. 26 (3-221) days; *P*=0.04], large elevations in aspartate aminotransferase (AST) [371 (30-2643) vs. 212 (63-1990 IU/l); *P*=0.03] and alanine aminotransferase (ALT) [388 (31-2997) vs. 225 (52-1670 IU/l); *P*= 0.002] and a longer time for normalization of deranged liver functions [36.7 ± 13.3 vs. 24.5 ± 19.3 days; *P*=0.02] indicated acute viral hepatitis as the cause of liver function derangement.**

***Interpretation & conclusions*: Our findings showed AVH in 14.7 per cent patients who developed hepatotoxicity while an anti-TB treatment. Therefore, in endemic areas, viral hepatitis should be sought after and excluded in all patients suspected to have DIH before attributing the hepatotoxic effect to the anti-TB drugs.**

Key words Acute - hepatotoxicity - treatment - tuberculosis - viral hepatitis

Isoniazid, rifampicin and pyrazinamide are essential first-line anituberculosis (anti-TB) drugs[1] which have hepatotoxic potential. Drug induced hepatotoxicity (DIH) is a commonly encountered adverse effect with anti-TB treatment that frequently results in interruption of treatment[2-4].

The incidence of acute hepatitis in patients receiving short-course anti-TB treatment has varied

widely and may depend on grade of trasnaminase elevation[1]. However, what is perceived as anti-TB DIH may not be drug-induced all the time. Acute viral hepatitis is an important confounding illness which clinically, biochemically and histologically mimics DIH[5]. As not much is known, we prospectively studied contributory role of acute viral hepatitis as a confounding factor in patients with anti-TB DIH.

Material & Methods

During the period January 2005 to December 2006, 2906 patients were treated for various forms of tuberculosis (TB) disease at the Medicine out-patient department, Chest Clinic, and medical wards of All India Institute of Medical Sciences (AIIMS), New Delhi and Sri Venkateswara Institute of Medical Sciences (SVIMS), Tirupati. In all of the patients baseline liver functions were within normal limits before starting anti-TB treatment. Of these, 102 (3.5%) patients [74 of 2128 (3.5%) from New Delhi; 28 of the 778 (3.6%), from Tirupati] who developed acute hepatitis while receiving short-course anti-TB treatment[3] were prospectively studied. Patients who were human immunodeficiency virus (HIV) positive, patients with chronic liver disease, chronic alcoholics (consumption of 48 *g* ethanol per day for more than a year) and those receiving other hepatotoxic drugs concomitantly, were excluded from the study. All patients gave informed written consent and Ethics Committees of both institutes approved the study.

The serum samples of all patients who developed acute hepatitis were analysed for viral hepatitis markers[3] and antibodies to HIV[6] as described previously. During treatment, liver enzymes and bilirubin were measured once in two weeks for initial two months and thereafter monthly and whenever the patients presented with clinical features of acute hepatitis. Abdominal ultrasonography was done in all patients to rule out other causes of liver disease. Biochemical testing was carried out in serum samples using Beckman Synchron Cx9 Clinical System Autoanalyser and system packs (Beckman-Coulter Inc, Fulterton, CA, USA). The same protocol and methods of estimation were followed at both the centres.

Acute hepatitis was defined as described previously[3] by the presence of at least one of the following criteria: (*i*) a rise of five times the upper limit of normal levels (50 IU/l) of serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT); (*ii*) a rise in the level of serum total bilirubin (>1.5 mg/dl); (*iii*) any increase in AST and/or ALT above pre-treatment levels together with anorexia, nausea, vomiting, and jaundice.

After detection of DIH or acute viral hepatitis, the potentially hepatotoxic drugs isoniazid, rifampicin and pyrazinamide were immediately stopped. These patients were followed up every week until the clinical and biochemical parameters of hepatic injury became normal. During this period anti-TB drugs devoid of hepatotoxic potential such as ethambutol, streptomycin, and a fluoroquinolone (ofloxacin, levofloxacin) were administered. Once the liver functions normalized, the first-line anti-TB drugs were re-introduced.

Statistical analysis: The demographic parameters, type of TB, time for development of hepatotoxicity, various laboratory parameters and time for normalization of the liver function tests between patients who developed DIH and those who had acute viral hepatitis were compared using Fisher's exact test, Student's t-test and Mann-Whitney U test. Statistical software package SPSS (version 10.0, SPSS Inc, Chicago, IL, USA) was used for analysis.

Results

The mean age of the patients who developed acute hepatitis (n=102) was 34.7±12.7 yr; there were 47 males; 24 (23.3%) had pulmonary TB, 52 (50.5%) had extrapulmonary TB and 26 (25.2%) patients had disseminated/miliary TB. Majority of the patients (n=92; 90%) presented with symptoms of acute hepatitis such as anorexia, nausea, vomiting; clinically evident jaundice was present in 30 (29.4%) patients. Only 10 (9.8%) of 102 patients had asymptomatic elevation of liver enzymes.

Fifteen (14.7%) patients had serological evidence of acute viral hepatitis. Serological evidence confirmed recently acquired acute viral hepatitis A in 1 (6.7%), hepatitis B in 2 (13.3%), hepatitis C in 3 (20%) and hepatitis E in 8 (53.3%) patients; hepatitis E was the most common cause of viral hepatitis (Table I).

In patients with acute viral hepatitis, the onset of acute hepatitis was delayed compared with those with DIH (P=0.04). The extent of elevation of AST (P=0.03) and ALT (P=0.002) was significantly higher in patients with acute viral hepatitis compared to those who had DIH (Table II). Furthermore, time taken for normalization of liver functions was significantly longer in patients with acute viral hepatitis compared to those with DIH (P=0.02). The abdominal

Table I. Positive serological markers for viral hepatitis in patients (n=15) who developed acute hepatitis while receiving anti-TB treatment

Positive viral marker	No. (%)
Anti-HAV IgM antibody	1 (6.7)
HBsAg, Anti-HBc IgM antibody	2 (13.3)
Anti-HCV IgM antibody	3 (20)
Anti-HEV IgM antibody	8 (53.3)
Anti-HCV and Anti-HEV IgM antibody	1 (6.7)

HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HBcAg, hepatitis B core antigen; HCV, hepatitis C virus; HEV, hepatitis E virus; IgM, immunoglobulin M

Table II. Comparison between patients who developed drug induced hepatotoxicity (DIH) and those who had viral hepatitis

Variables	DIH (n=87)	Viral hepatitis (n=15)	*P* value
Age (yr)	34.97 ± 12.53	32.87 ± 13.66	0.56
Sex: Male	40 (46%)	7 (47%)	
Female	47 (54%)	8 (53%)	0.96
Type of TB:			
Pulmonary	21 (24%)	3 (20%)	
Extra-pulmonary	44 (51%)	8 (53%)	
Disseminated/miliary	22 (25%)	4 (27%)	0.94
BMI (kg/m^2)*	18.8 ± 2.6	19.6 ± 2.6	0.28
MAC (cm)*	22.1 ± 3.1	23.2 ± 2.7	0.21
Total serum proteins (g/dl)*	7.45 ± 0.65	7.88 ± 0.78	0.06
Baseline serum albumin (g/dl)*	3.8 ± 0.7	4.1 ± 0.7	0.15
Baseline serum bilirubin (mg/dl)*	0.6 ± 0.1	0.7 ± 0.1	0.85
Baseline serum AST (IU/l)*	35.8 ± 9.7	36.7 ± 10.0	0.70
Baseline serum ALT (IU/l)*	36.3 ± 11.5	32.2 ± 11.3	0.21
Base line serum ALP (IU/l)	160.0 ± 60.69	125.2 ± 43.9	0.06
Latent period (days)†	26 (3-221)	58 (5-133)	0.04
Maximum serum bilirubin (mg/dl)†	1.8 (0.5-9.7)	3.1 (0.5-14.1)	0.13
Maximum serum AST(IU/l)†	212 (63-1990)	371 (30-2643)	0.03
Maximum serum ALT (IU/l)†	225 (52-1670)	388 (31-2997)	0.002
Maximum serum ALP (IU/l)†	180 (38-883)	165 (77-1631)	0.44
Time taken for normalization of the liver function tests (days)	24.5 ± 19.30	36.7 ± 13.3	0.02

*Expressed as mean ± standard deviation; †expressed as median with range; BMI, body mass index; DIH, drug induced hepatotoxicity; MAC, mid-arm circumference; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase

ultrasonography findings were similar in patients with acute viral hepatitis and DIH.

Discussion

Wide variations have been reported in the incidence of hepatotoxic reactions during anti-TB treatment[1]. The figures are much higher in studies from developing countries compared to those from developed countries despite using similar regimens[3]. Perhaps poor nutrition, increased age, widespread parasitism, chronic infections, alcoholism, indiscriminate use of drugs without prescription, ethnic factors, severity of disease or genetic predisposition may play a role individually or collectively[1-3].

Kumar *et al*[5] from India highlighted another reason for this disparity. They reported that 17 of the 40 children (42.5%) who had acute hepatitis while on anti-TB drugs, had serological evidence of acute viral hepatitis A or B. Turktas *et al*[7] reported viral hepatitis B and C in 10 of the 57 (17.5%) patients who developed acute hepatitis while receiving anti-TB therapy. Serological tests for non-A, non-B[5] and hepatitis E[7] viruses were not performed in these studies. In the present study, we found that 14.7 per cent patients with acute hepatitis had acute viral hepatitis; hepatitis E being the most common cause. Given that India is hyperendemic for hepatitis E virus[8], this observation is not surprising. Our data suggest that, in endemic areas, if appropriate serological testing is not done, patients who develop acute viral hepatitis while on anti-TB treatment may be misdiagnosed and labelled as DIH instead. Our observations also suggest that later onset of acute hepatitis, large elevations in hepatic transaminases and a longer time for normalization indicate acute viral hepatitis rather than DIH and these factors may guide the clinicians to suspect and look for viral hepatitis.

Recognising acute viral hepatitis in patients with sputum smear-positive pulmonary TB being treated for TB is important because, the longer duration for normalization (during which time a less efficient modified treatment regimen incorporating non-hepatotoxic drugs is being used), will also facilitate disease transmission and development of drug resistance especially in patients with a high bacillary load. In India[9], and other developing countries, baseline liver function testing and serological testing to exclude viral hepatitis are not routinely performed under National TB Control Programmes where majority of the patients get treated. The problem may

become more profound in patients with HIV-TB co-infection who get treated with antiretroviral drugs with hepatotoxic potential in addition to anti-TB drugs[10].

Consensus guidelines for the management of TB in patients with deranged liver functions either due to DIH or due to acute viral hepatitis are yet to be evolved[1]. Once there is evidence of acute hepatitis, it is essential to first stop all potentially hepatotoxic drugs such as isoniaizd, rifampicin, and pyrazinamide till complete clinical and biochemical resolution of hepatotoxicity occurs. In the interim period, at least three non-hepatotoxic drugs *viz.*, ethambutol, streptomycin and quinolones such as ofloxacin can be used after appropriate checks on renal function and visual acuity. After complete resolution of transaminitis, most anti-tuberculosis drugs can be safely restarted in a phased manner.

National TB Control Programmes in resource-limited nations should provide guidelines and also make provision for the treatment of TB in settings of DIH and acute viral hepatitis. These guidelines could include provision of alternative, non hepatotoxic drugs and/or treatment interruption followed by a carefully monitored, systematic re-introduction of the first-line drugs with hepatotoxic potential.

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