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# A study of aetiology of portal hypertension in adults (including the elderly) at a tertiary centre in southern India

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***Background & objectives*: There are only a few studies on aetiology of portal hypertension among adults presenting to tertiary care centres in India; hence we conducted this study to assess the aetiological reasons for portal hypertension in adult patients attending a tertiary care centre in southern India.**

***Methods*: Causes of portal hypertension were studied in consecutive new adult patients with portal hypertension attending department of Hepatatology at a tertiary care centre in south India during July 2009 to July 2010.**

***Results*: A total of 583 adult patients (>18 yr old) were enrolled in the study. After non-invasive testing, commonest causes of portal hypertension were cryptogenic chronic liver disease (35%), chronic liver disease due to alcohol (29%), hepatitis B (17%) or hepatitis C (9%). Of the 203 patients with cryptogenic chronic liver disease, 39 had liver biopsy - amongst the latter, idiopathic non cirrhotic intrahepatic portal hypertension (NCIPH) was seen in 16 patients (41%), while five patients had cirrhosis due to non alcoholic fatty liver disease. Fifty six (10%) adult patients with portal hypertension had vascular liver disorders. Predominant causes of portal hypertension in elderly (>60 yrs; n=83) were cryptogenic chronic liver disease (54%) and alcohol related chronic liver disease (16%).**

***Interpretation & conclusions*: Cryptogenic chronic liver disease was the commonest cause of portal hypertension in adults, followed by alcohol or hepatitis B related chronic liver disease. Of patients with cryptogenic chronic liver disease who had liver biopsy, NCIPH was the commonest cause identified. Vascular liver disorders caused portal hypertension in 10 per cent of adult patients. Cryptogenic chronic liver disease was also the commonest cause in elderly patients.**

**Key words** cryptogenic chronic liver disease - non cirrhotic intrahepatic portal hypertensionn - vascular liver disorders

Portal hypertension can present as oesophageal variceal bleeding, ascites or hypersplenism. It is important to understand the cause of portal hypertension to put in place strategies to prevent/ameliorate the same. The causes of portal hypertension in a country can vary over time. With increasing affluence, better standards of living as well as change to more sedentary lifestyle in India, metabolic syndrome leading to non-alcohol related fatty liver disease (NAFLD) as well as alcohol related cirrhosis are expected to increase in the coming years while hepatitis B or C virus related cirrhosis may be expected to decline. In addition, for as yet unclear reasons, some vascular disorders causing non-cirrhotic portal hypertension-like idiopathic non cirrhotic intrahepatic portal hypertension (NCIPH) and portal vein thrombosis [also known as extra-hepatic portal vein obstruction (EHPVO)] in children are known to be more common in India[1].

The different causes of portal hypertension are likely to vary in frequency among patients of different age groups and different socio-economic classes. While portal vein thrombosis is the predominant cause of paediatric portal hypertension in India[2,3], hepatic Wilson's disease is another important cause in this age group[2]. There are a few studies focussed on the cause of portal hypertension in adults in India[4,5]. A study from eastern India reported hepatitis B as the most important cause of portal hypertension in adults.[4] Studies from other parts of the world have reported hepatitis C and alcohol as the predominant aetiology of chronic liver disease[6-8].

This study was conducted to document the aetiology of portal hypertension in adult patients attending a tertiary care centre in southern India.

## Material & Methods

Consecutive patients with portal hypertension (defined as presence of gastro-oesophageal varices and/or ascites with serum to ascites albumin gradient >1.1 g/dl) seen in the department of Hepatology, Christian Medical College & Hospital, Vellore, Tamil Nadu, India, from July 2009 to July 2010 were prospectively enrolled in this study, after obtaining their consent. Only adult patients with age >18 yr were included in the study. The study protocol was approved by the Institution Review Board and Ethics Committee.

All patients had the following evaluation to ascertain the aetiology of portal hypertension - history (especially regarding alcohol intake), physical examination, laboratory tests [liver function tests, hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, serum ceruloplasmin and serum ferritin] and ultrasound abdomen. Further aetiological evaluation such as serology for autoimmune liver disease, Doppler scan of portal vein and hepatic venous outflow tract was done as and when indicated. Liver biopsy was done when deemed necessary.

In the study subjects (all of whom had portal hypertension), chronic liver disease was defined as presence of any of the following changes noted in the liver on imaging (ultrasound, CT or MRI scan): volume reduction/re-distribution, irregular margins, coarse texture or nodular liver. Cirrhosis was reported only when histological confirmation of the same was obtained.

In patients with chronic liver disease or cirrhosis, the following criteria were used to define different aetiologies of liver disease - alcohol related : history of significant alcohol consumption (>30 g/day for >10 yr)[9]; hepatitis B virus related: HBsAg positive; HCV related: HCV antibody positive; Wilson's disease: low serum ceruloplasmin, elevated 24 h urinary copper and presence of Kayser Fleischer ring on slit lamp examination of eye (≥2 criteria satisfied)[10]; autoimmune liver disease: based on the simplified criteria for autoimmune hepatitis (≥7 points)[11]; haemochromatosis: transferrin saturation >45 per cent, compatible liver histology; primary biliary cirrhosis: positive for anti-mitochondrial antibody with characteristic liver histology[13]; primary sclerosing cholangitis[14]: typical cholangiogram with no obvious cause for secondary sclerosing cholangitis; biliary cirrhosis: long standing biliary obstruction; NAFLD: characteristic liver histologic features and negative workup for an alternative aetiology[15]; cryptogenic: aetiology of portal hypertension not evident after non-invasive evaluation.

The three vascular liver disorders were defined as follows: portal vein thrombosis: portal vein showing cavernoma formation (on Doppler scan), Budd Chiari syndrome: block in hepatic venous outflow tract (on Doppler scan) and NCIPH: Doppler showing patent portal vein and hepatic venous outflow tract, no obvious aetiology of chronic liver disease and liver biopsy negative for cirrhosis / advanced fibrosis[16]. Diagnosis of hepatocellular carcinoma was based on focal liver lesion with typical enhancement pattern on CT/MRI scan, elevated serum alpha foetoprotein level and liver biopsy.

Age at first presentation to our centre, sex, place of residence, and socio-economic score (as per modified Kuppuswamy's score[17]) of the patients were also documented.

We retrospectively looked for presence of risk factors for NAFLD [body mass index (BMI), dyslipidemia, diabetes mellitus] among patients with cryptogenic chronic liver disease, who did not have liver biopsy. Patients with BMI ≥27.5 kg/m$^2$ were considered obese[18]. Dyslipidemia was considered as fasting serum triglycerides >150 mg% and/or low high-density lipoproteins (<40 mg% in males, <50 mg% in females)[19]. Diabetes mellitus was defined by ongoing management of diabetes mellitus (*i.e.* diet restriction, oral hypoglycaemic agents or Insulin) or presence of high fasting sugar (≥126 mg%)[19].

*Statistical analysis*: Different aetiologies of portal hypertension were analysed in all adults (19-59 yr age) and in elderly (>60 yr old) age groups. Male : female ratios was also analysed in different aetiological groups. SPSS version 16 Inc. USA was used for analysis. Continuous variables were expressed in mean and standard deviation or median and range. Fisher's exact test (discrete variable) was used for comparison in two unrelated samples and a 2-tailed *P* value of <0.05 was considered as significant.

## Results

During the study period, a total of 610 new patients with portal hypertension were seen, 27 patients aged <18 yr were excluded from this study. Thus, 583 adult patients (>18 yr old), including 83 elderly patients (>60 yr), constituted the study population.

*Aetiology of portal hypertension in all adult patients (including the elderly)*: Baseline demographic details of the 583 adult patients are shown in Table I. After the initial work-up (*i.e.* prior to liver biopsy) commonest aetiology for portal hypertension was cryptogenic (n=203, 35%) chronic liver disease, followed by alcohol (n=168, 29%), hepatitis B (n=100, 17%) and HCV (n=55, 9%) related chronic liver disease. Other aetiologies were portal vein thrombosis, with or without associated cryptogenic chronic liver disease (n=19, 3%), Budd Chiari syndrome (n=21, 4%), autoimmune liver disease (n=2, 0.3%), biliary aetiology (n=6, 1%), Wilson's disease (n=2, 0.3%), cardiac cirrhosis (n=2) and 1 patient each with splenic vein thrombosis, lymphoma, constrictive pericarditis, myxedema and methotrexate related hepatic fibrosis. Twenty four patients had >1 aetiology for chronic liver disease and portal hypertension: hepatitis B and alcohol (17 patients); hepatitis C and alcohol (7 patients); 25 patients had hepatocellular carcinoma.

**Table I.** Demographics of 583 consecutive, new adult patients (including elderly patients) with portal hypertension

| Demographic parameters | | | |
|---|---|---|---|
| Age (yr) median (range) | | | 46 (19-79) |
| Sex (% males) | | | 480 (82) |
| Regional distribution | Southern India | | 160 (27) |
| | Eastern India | | 342 (59) |
| | Northern India | | 23 (4) |
| | Western/Central India | | 5 (1) |
| | Neighbouring countries | | 53 (9) |
| Socio-economic class* | Upper | | 53 (11) |
| | Middle | Upper middle | 236 (50) |
| | | Lower middle | 93 (20) |
| | Lower | Upper lower | 84 (18) |
| | | Lower | 2 (0.4) |

*Socio-economic scoring was done as per modified Kuppuswamy's score[17] in 468 adults

*Cryptogenic chronic liver disease*: Of the 203 patients with cryptogenic chronic liver disease after non-invasive evaluation, 39 (19%) had liver biopsy. After liver biopsy, aetiologies of portal hypertension identified were NCIPH (n=16), NAFLD (n=5), cryptogenic cirrhosis (n=5), hepatic amyloidosis (n=1) and Wilson's disease (n=1). After liver biopsy, eight patients fulfilled the criteria for autoimmune liver disease. The liver biopsy sample was inadequate for evaluation in three patients.

Of the 164 patients with cryptogenic chronic liver disease who did not have liver biopsy, 126 (77%) had a risk factor for NAFLD [diabetes mellitus-62/164 patients, dyslipidemia- 99/125 patients tested, and/or obesity (BMI >27.5 kg/m$^2$)- 21/83] and five patients satisfied the criteria for probable autoimmune hepatitis.

*Vascular liver disorders*: Of the 583 patients, 56 (10%) had vascular liver diseases. These comprised portal vein thrombosis with or without associated cryptogenic chronic liver disease (n=19), Budd Chiari syndrome (n=21) and NCIPH (n=16). Age at presentation of patients with portal vein thrombosis, with or without associated cryptogenic chronic liver disease (34, 21-50 yr; median, range) was similar to patients with NCIPH (31, 20-59 yr) and Budd Chiari syndrome (34, 19-58 yr).

**Table II.** Age group-wise break-up of aetiology of portal hypertension, after complete aetiological evaluation (including liver biopsy), in 583 consecutive, new adult patients

| Age group (yr) | N | Aetiology of portal hypertension | | | | |
|---|---|---|---|---|---|---|
| | | Cryptogenic[@] | Alcohol | Viral[#] | Vascular[*] | Others |
| 19-59 | 500 | 128 | 155 | 133 | 56 | 28 |
| Elderly (≥ 60) | 83 | 44 | 13 | 22 | – | 4 |
| Total | 583 | 172 | 168 | 155 | 56 | |

[@]Of the 203 patients with cryptogenic chronic liver disease after non-invasive testing, only 39 underwent liver biopsy. The 172 patients with cryptogenic chronic liver disease includes 164 who did not have liver biopsy and those in whom the cause for liver disease remained unclear (*i.e.* had 'cryptogenic cirrhosis'- 5 or had inadequate liver tissue obtained-3) after liver biopsy
[#]Adults (19-59 yr): Hepatitis B: 88 patients, Hepatitis C: 45 patients; Elderly: Hepatitis B: 12 patients, Hepatitis C: 10 patients
[*]portal vein thrombosis: 19 patients; Idiopathic non cirrhotic intrahepatic portal hypertension : 16 patients; Budd Chiari syndrome: 21 patients

In the 16 NCIPH patients, the liver biopsies (12 were transjugular and 4 were percutaneous) showed no significant fibrosis (5 patients), mild portal/periportal fibrosis (10), moderate periportal fibrosis (1 patient), mild peri-sinusoidal fibrosis (1), abnormal portal venous ectasia (6), mild diffuse sinusoidal dilatation (9); no patient had cirrhosis or severe fibrosis.

In patients with Budd Chiari syndrome (n=21), 11 had isolated hepatic vein block, four had isolated inferior vena cava block and six had combined block of hepatic vein and inferior vena cava. Of the 44 patients with vascular liver disorders who had their socio-economic status assessed two belonged to upper class (NCIPH:1; BCS:1), 30 belonged to middle class (portal vein thrombosis:7; NCIPH:13; BCS:10) and 12 belonged to lower class (portal vein thrombosis:6; NCIPH:1; BCS:5).

*Socio-economic class distribution*: Socio-economic class scoring was done in 468 adult patients - the majority belonged either to middle class (n=329; 70%) or lower class (n=86; 18%) (Table I).

*Regional distribution*: Most of the study patients were from eastern and southern parts of India. After the initial evaluation, cryptogenic chronic liver disease was significantly more common in patients from eastern compared to southern India (137/342 vs 39/160; $P<0.001$).

*Analysis of male: female ratios in different aetiologies of portal hypertension*: Marked male preponderance was noted in patients with chronic liver disease due to alcohol [male:female (male:female ratio) : 166:2 (83.0)] or hepatitis B [93:7 (13.3)]. In contrast, male preponderance was lesser in patients with cryptogenic chronic liver disease [129:43 (3)]; HCV related chronic liver disease [38:17 (2.3)] and vascular liver disorders: NCIPH [10:6 (1.7)], portal vein thrombosis [12:7 (1.7)] and Budd Chiari syndrome [11:10 (1.1)].

*Aetiology of portal hypertension in elderly patients*: In 83 elderly patients (71 males; age: 64, 60-79 yr; median, range) causes of portal hypertension were chronic liver disease which was cryptogenic (n=45) or related to alcohol (n=13), hepatitis B (n=12), hepatitis C (n=10); biliary cirrhosis (n=2) and myxedema (n=1). Liver biopsy, done in three patients with cryptogenic chronic liver disease, showed amyloidosis (n=1), cryptogenic cirrhosis (n=1) and inadequate liver sample (n=1). Of the 42 patients with cryptogenic chronic liver disease, a risk factor for NAFLD was noted in 32 patients (diabetes mellitus: 16/42, dyslipidemia: 21/29 tested and/or obesity: 2/19). Four patients had hepatocellular carcinoma.

Table II depicts broad aetiologies of portal hypertension in different age groups after a complete work-up (this includes the aetiologies identified after liver biopsy in patients with cryptogenic chronic liver disease). On comparison with adults aged 19-59 yr, elderly patients (>60 yr) had significantly higher proportion of cryptogenic chronic liver disease ($P<0.001$) and lesser proportion of alcohol related liver disease ($P<0.005$) and vascular liver disease ($P<0.001$). The proportion of patients with hepatitis virus induced liver disease was the same in both age groups.

## Discussion

In this study, majority of patients were from middle socio-economic class, and cryptogenic chronic liver disease was found to be the predominant cause of portal hypertension, followed by chronic liver disease related to alcohol and hepatitis B. This is at variance to reports

from other countries, where alcohol and hepatitis C were the main causes of portal hypertension[6-8]. In our study, among patients with cryptogenic chronic liver disease who underwent liver biopsy, commonest cause of portal hypertension identified after the biopsy was NCIPH; majority of cryptogenic chronic liver disease patients who did not have liver biopsy, had >1 risk factor for NAFLD, this could suggest NAFLD as a cause of portal hypertension in these patients.

In India, portal hypertension due to cryptogenic chronic liver disease could be caused by cirrhosis due to occult or prior hepatitis B infection, NAFLD or autoimmune disease or by NCIPH. Though a previous report from our centre noted serum HBV DNA positivity in only 3.3 per cent patients with cryptogenic chronic liver disease[20], other studies from India have reported occult hepatitis B in up to 9 per cent patients with chronic liver disease[21]. All patients with cryptogenic chronic liver disease in the current study were HBsAg negative, however serum anti hepatitis B core antibody and serum HBV DNA were not done in all. Thus, the current study findings do not indicate the contribution of occult hepatitis B infection as the cause of chronic liver disease in the patients studied.

Of the 39 patients with cryptogenic chronic liver disease who had liver biopsy, cirrhosis due to NAFLD was found in five patients. In majority of patients (n=164) with cryptogenic chronic liver disease who did not have liver biopsy, a risk factor for NAFLD was found in 77 per cent of patients suggesting that NAFLD cirrhosis could be the cause for liver disease in these patients. However, liver biopsy was not done and risk factors for NAFLD were not assessed in all patients, this is a limitation of this study. Further, 21 per cent patients with cryptogenic chronic liver disease who underwent liver biopsy had autoimmune liver disease. Gupta *et al*[22] found a prevalence of 3.4 per cent of autoimmune liver diseases in patients with chronic liver disease.

In an adult with idiopathic portal vein thrombosis, it is difficult to differentiate Extrahepaticportal vein obstruction (EHPVO) from portal vein thrombosis secondary to an intrahepatic pathology like NCIPH or cryptogenic cirrhosis. This is recognised as a difficult area to define[1,23]. In the present study, patients with portal vein thrombosis secondary to a known cause of liver disease (*e.g.* alcohol related chronic liver disease and portal vein thrombosis) were included in respective aetiology groups.

Similar to our prior study[24], predominant diagnosis in patients with 'cryptogenic' intrahepatic portal hypertension after liver biopsy was NCIPH. Thus, NCIPH mimics cryptogenic cirrhosis, clinically and on investigations, and can only be differentiated by liver biopsy[23]. However, as all patients with cryptogenic chronic liver disease did not have liver biopsy, the aetiological break up in all patients with cryptogenic chronic liver disease is not known. NCIPH occurs secondary to microvascular occlusion of intra-hepatic small portal vein radicles. Multiple hypotheses regarding the pathogenesis have been proposed. One such hypothesis entails linking of gut disorders and subsequent hyper-coagulability in portal circulation[25]. Role of deficiency of ADAMTS 13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), a von Willebrand factor-cleaving protease, is also being actively explored[26]. The reason for clustering of NCIPH in India and in middle/lower socio-economic strata needs to be further explored[27,28]. In our study, of the 17 NCIPH patients, 14 were from middle and lower socio-economic strata.

Elderly patients comprised 14 per cent of our patients. Cryptogenic, alcohol, hepatitis B and hepatitis C related chronic liver disease were the commonest causes of portal hypertension among them.

Alcohol intake in India is steadily increasing, with decrease in the initiation age[29]. This alarming trend is noticed in many areas of the country[29,30]. In our study, alcohol intake was a contributory factor in 29 per cent of patients with portal hypertension, which is significantly more than a prior study from eastern India[4]. This may be a reflection of referral bias, socio-economic situation or can be a reflection of a changing trend.

Further studies on aetiology of portal hypertension in adults and in elderly are needed from different parts of India, especially to analyse variations in different socio-economic categories. Further studies are also needed to know the cause of cryptogenic chronic liver disease, the commonest cause of portal hypertension, noted in this study. This information will help guide steps to prevent portal hypertension in India.

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