Review Article

Indian J Med Res 149, April 2019, pp 468-478
DOI: 10.4103/ijmr.IJMR_1405_17

Quick Response Code:

What makes non-cirrhotic portal hypertension a common disease in India? Analysis for environmental factors

Ashish Goel[1], Banumathi Ramakrishna[2], Uday Zachariah[1], K.G. Sajith[1], Deepak K. Burad[2], Thomas A. Kodiatte[2], Shyamkumar N. Keshava[3], K.A. Balasubramanian[4], Elwyn Elias[1,5] & C.E. Eapen[1]

Departments of [1]Hepatology, [2]Pathology & [3]Radio-diagnosis and [4]Wellcome Research Laboratory, Division of GI Sciences, Christian Medical College, Vellore, India & [5]Liver Unit, University Hospitals, Birmingham, UK

Received August 27, 2017

In India, an unexplained enteropathy is present in a majority of non-cirrhotic intrahepatic portal hypertension (NCIPH) patients. Small intestinal bacterial contamination and tropical enteropathy could trigger inflammatory stimuli and activate the endothelium in the portal venous system. Groundwater contaminated with arsenic is an environmental factor of epidemic proportions in large areas of India which has similar consequences. Von Willebrand factor (a sticky protein) expressed by activated endothelium may promote formation of platelet microthrombi and occlusion of intrahepatic portal vein branches leading to NCIPH. Environmental factors linked to suboptimal hygiene and sanitation, which enter through the gastrointestinal (GI) tract, predispose to platelet plugging onto activated endothelium in portal microcirculation. Thus, NCIPH, an example of poverty linked thrombophilia, is a disease mainly affecting the lower socio-economic strata of Indian population. Public health measures to improve sanitation, provide clean drinking water and eliminate arsenic contamination of drinking water are urgently needed. Till such time as these environmental factors are addressed, NCIPH is likely to remain 'an Indian disease'.

Key words Endothelial dysfunction - non-cirrhotic portal fibrosis - obliterative portal venopathy - poverty linked thrombophilia

Introduction

A two-part series published in 1967 described a new syndrome of non-cirrhotic portal fibrosis (NCPF) with portal hypertension[1,2]. The nomenclature of unexplained portal hypertension without cirrhosis of liver including NCPF, hepatoportal sclerosis, nodular regenerative hyperplasia, idiopathic portal hypertension, incomplete septal cirrhosis and partial nodular transformation of the liver (mostly histology based nomenclature)[3,4] is now regarded as representing aspects of a single clinical entity of non-cirrhotic intrahepatic portal hypertension (NCIPH)[5,6]. NCIPH is a vascular disorder of the liver, a consequence of chronic microangiopathy of portal vein branches, leading to intrahepatic portal vein occlusion. In addition to the original description of this disease from India, publication of other seminal research work from India[7-15] led to the question as to why this disease was so common in India[16].

Multifactorial diseases maybe caused by an interplay of multiple acquired and/ or genetic factors.

The incidence of NCIPH has been linked to poor sanitation and hygiene, a reflection of living standards in the strata of society affected. As Indian economic development translates into better living standards for its citizens, one can predict that the incidence of NCIPH in India will come down.

An imbalance of low ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13) and high von Willebrand factor (vWF) levels has been documented as example of a mechanistic pathway that would permit poverty-linked environmental triggers to promote obliteration of portal vein radicles in the liver in NCIPH patients[17,18]. ADAMTS13 is an enzyme which cleaves vWF multimers. Uncleaved ultralarge vWF multimers are extremely adhesive and favour platelets to stick onto the activated endothelium. It has been postulated that endothelial activation (vWF is an endothelial protein) leads to platelet plugs in the microcirculation in the liver in NCIPH[17,18].

This review describes some environmental factors which may explain the predilection of NCIPH for India, and how NCIPH is diagnosed and how NCIPH masquerades (and is often mislabelled) as cryptogenic cirrhosis in India.

Diagnosis of non-cirrhotic intrahepatic portal hypertension (NCIPH)

As the disease process is limited to small intrahepatic portal vein radicles not visualized by currently available imaging techniques, the diagnosis of NCIPH is based on the presence of colour Doppler documenting patent inflow into (portal vein) and outflow out of (hepatic venous outflow tract) the liver, negative aetiological workup for any aetiology of liver disease (*e.g.* hepatitis B or C virus, iron or copper overload, autoimmune liver disease), liver biopsy documenting absence of bridging fibrosis/cirrhosis and excluding other causes that can closely mimic NCIPH on histology (*e.g.* schistosomiasis, primary biliary cirrhosis and sarcoidosis)[5]. History of significant alcohol intake (>20 g/day), risk factors for non-alcoholic fatty liver disease (metabolic syndrome), portal vein thrombosis and hepatic malignancy are exclusion criteria for making a diagnosis of NCIPH.

Role of liver biopsy

Cryptogenic cirrhosis tends to mimic NCIPH and adequate liver biopsy (*i.e.* containing at least 10 portal tracts with multiple cores) is central to this differentiation. The telltale signs of microangiopathy (portal venule sclerosis/ectasia, sinusoidal dilation, nodular regenerative hyperplasia *etc*.) are present in a proportion of these patients. For diagnosis of NCIPH, absence of significant fibrosis, *i.e*. bridging fibrosis/ cirrhosis, is mandatory. Liver biopsy also excludes alternative aetiology (*e.g*. steatosis, steatohepatitis and significant inflammation) and mimickers of NCIPH (*e.g*. schistosomiasis and congenital hepatic fibrosis).

Hepatic venous pressure studies

Hepatic venous pressure measurements (balloon or catheter wedge technique[19]) can help differentiate cirrhosis from NCIPH. As the disease process (and the gradient) in NCIPH is presinusoidal, hepatic venous pressure gradient (HVPG) is expected to be normal in these patients. However, this is true only in one-third of the patients with NCIPH, and the rest tend to have higher than normal HVPG[5].

Is NCIPH still present in India?

Initial detailed reports from India described and established NCPF as a disease entity[1,2]. Multiple reports corroborate the fact that NCIPH remains prevalent in India[20-23]. Table I presents some of the recent studies from India reporting the prevalence of NCIPH[15,20,24-28]. The prevalence greatly varies depending on the group of patients studied and modalities used for diagnosis.

Several new patients with NCIPH have been diagnosed and reported[29] from a tertiary centre, catering predominantly to middle/ lower socio-economic class patients from southern and eastern parts of India every year (Figure).

Are we underdiagnosing NCIPH?

NCIPH mimics cryptogenic cirrhosis in every aspect, and as mentioned previously, diagnosis of NCIPH requires extensive evaluation. Diagnosis of NCIPH is confirmed only with liver biopsy[30], and often, the diagnosis is made with explant biopsy after transplant for presumed cryptogenic cirrhosis[5,31]. Sampling the liver for biopsy is often difficult to achieve in a patient with, often severe, thrombocytopenia. In a prospective study spanning one year from our tertiary centre, although cryptogenic chronic liver disease was the most common aetiologic label noted in 203 of 583 (35%) portal hypertensive patients, only 39 (19%) patients were subjected to liver biopsy evaluation[20].

Table I. Prevalence of non-cirrhotic intrahepatic portal hypertension (NCIPH) among patients with portal hypertension in India

Year	Study	Nature of study	Patient population (n)	Prevalence of NCIPH (%)	Basis of diagnosis of NCIPH
1991	Bhargava *et al*[24]	Prospective	Portal hypertensive bleed (404)	20.5	Liver biopsy
2001	Dhiman *et al*[15]	Retrospective	Portal hypertension (>2000)	15	Liver biopsy only in a proportion
2008	Poddar *et al*[25]	Retrospective	Paediatric portal hypertension (517)	2	Liver biopsy
2009	Simon *et al*[26]	Retrospective	Paediatric portal hypertension (171)	3.5	Liver biopsy
2009	Madhu *et al*[27]	Retrospective	Adult cryptogenic portal hypertension (62)	48	Liver biopsy
2012	Nayak *et al*[28]	Retrospective	Adult liver transplant (372)	2.4	Liver biopsy
2013	Goel *et al*[20]	Prospective	Adult portal hypertension (583)	2.7	Liver biopsy

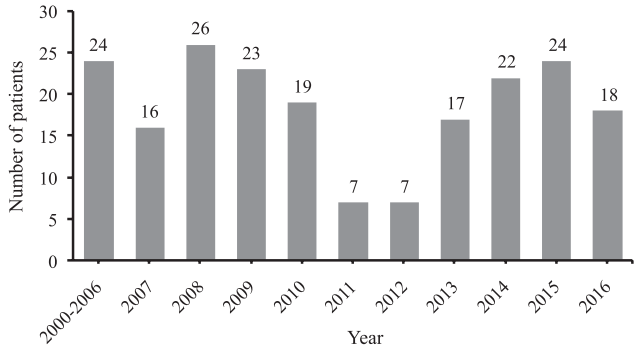

Figure. Number of new non-cirrhotic intrahepatic portal hypertension (NCIPH) patients (liver biopsy proven) diagnosed in a single tertiary centre in southern India from 2000 to 2016 (unpublished data).

Most centres in India have limited access to transjugular liver biopsy and hepatic venous pressure measurement. In addition, pathogenesis of NCIPH remains poorly understood and consequently has limited treatment options available. As oesophageal and gastric variceal bleeds are now almost exclusively managed by endotherapy, shunt surgeries are rarely performed for portal hypertension. As a consequence, peroperative liver biopsy (common method of liver sampling for histology previously for NCIPH) is hardly ever done now in India[12,20,27].

Madhu *et al*[27], in a retrospective analysis of liver biopsy in patients with previously labelled as cryptogenic cirrhosis, noted that 48 per cent had NCIPH. Another prospective study[20] noted 41 per cent prevalence of NCIPH in patients undergoing liver biopsy for cryptogenic cirrhosis. Although there may be a selection bias, yet it is more than likely that NCIPH forms a significant subset of Indian portal hypertensive patients who are currently labelled as cryptogenic cirrhosis. It has been estimated that in India, 10-30 per cent patients with portal hypertensive bleeds may have underlying NCIPH[32].

Role of potential environmental factors in NCIPH patients

Poverty

'Poverty-linked thrombophilia' is probably secondary to environmental factors, especially related to gut inflammation[5]. In a prospective study it was noted that most patients with NCIPH belonged to low and middle socio-economic status[20]. Limited access to clean drinking water, inadequate sewage facilities and continued close existence with animals contribute to a state of mild gut inflammation (environmental enteropathy) in India[33]. This chronic low-grade gut inflammation creates a pro-thrombotic milieu in portal circulation and can drive NCIPH[5].

Enteropathy

Microangiopathy restricted to intrahepatic small portal vein radicles suggests the active involvement of gut in the pathogenesis of NCIPH. An animal model of NCIPH has been created by repeatedly injecting *Escherichia coli* into portal circulation[34]. Often silent gut disorders (celiac disease and ulcerative colitis) accompany NCIPH[35]. The presence of these disorders was also associated with worse outcome. Higher plasma titres of IgA anti-cardiolipin antibodies[36] and deposition of IgA2-complement complexes in the kidneys of NCIPH patients who developed nephrotic syndrome after splenorenal shunt[37] also suggest the dominant role of gut in pathogenesis of NCIPH.

Tropical sprue was initially reported in residents of India, as well as visitors to India as a cause of malabsorption[38]. The epidemiology of tropical sprue in India has changed over the past several decades. Epidemics of tropical sprue are no longer reported in India. Sporadic cases of tropical sprue still constitute the main cause of malabsorption

in many centres in India[39-42]. Tropical enteropathy (subclinical malabsorption) is common in India. Xylose malabsorption was documented in 50 per cent of the apparently healthy population in southern India[43]. Despite elaborate investigations and researching putative causes[44], the definitive cause of tropical sprue has never been identified. It has been postulated that tropical enteropathy may be an adaptive response to recurrent intestinal infections[45].

It is possible that with improving sanitation, the causative environmental factor(s) may have got attenuated. However, the sporadic cases of tropical sprue suggests that the environmental causative factors are still present in India. Small intestinal bacterial overgrowth occurs in patients with tropical sprue[46]. Low-grade small intestinal bacterial growth is common in patients with non-alcoholic fatty liver disease in India[47]. Celiac disease is now increasingly recognized in India. Its prevalence varies with the wheat-consuming habits of the population[48]. The association of (asymptomatic) celiac disease and NCIPH has been reported[35,49,50].

Systematic studies looking for enteropathy in NCIPH patients unearthed an unexplained enteropathy, significantly higher in NCIPH patients compared to patients with hepatitis B or C causing portal hypertension (disease controls) as well as in healthy controls[50]. Further research is needed to explore this as yet unexplained enteropathy in NCIPH patients. Of the different types of gut disorders discussed above, it is likely that some disorders - tropical sprue, tropical enteropathy, small bowel bacterial overgrowth – affect individuals in lower socio-economic strata of society who are more exposed to the consequences of suboptimal sanitation[51].

Arsenicosis

The link between therapeutic arsenic use (Fowler's solution - arsenic trioxide - used to treat psoriasis) and non-cirrhotic portal hypertension was initially reported from Europe[52]. Chronic arsenicosis is a multisystem disorder and skin is most commonly involved (melanosis and keratosis); other organs involved include peripheral nerves, liver, lungs, *etc*. NCIPH is the typical hepatic manifestation[53,54]. In long-standing cases, cancer (of skin, lungs, liver, kidney and urinary bladder) can develop[55,56]. In affected locations, children in addition to adults are affected[23,57].

In 1970s, Datta *et al*[10] reported the link between chronic arsenicosis and NCIPH in India. These patients had consumed arsenic from three sources: consumption of groundwater contaminated with arsenic; use of arsenic mixed with opium (illegal recreational drug) and *Ayurvedic* medicines (*bhasams* prepared by repeated oxidation of ores) containing arsenic.

Ground water contamination by arsenic

The entire Ganga River basin covering large areas of land in India, Bangladesh, Nepal and Tibet, has high levels of arsenic in groundwater, water used for irrigation and in food materials. The arsenic levels here are in excess of World Health Organization standards for drinking water and United Nations Food and Agricultural Organization's standard for irrigation water (100 µg/l)[58]. Arsenic contamination of groundwater and water used for drinking continues to be documented on a significant scale in Bihar[59], Uttar Pradesh[60] and West Bengal[61]. In Kolkata Municipal Corporation, the southern parts of the Corporation face a higher degree of groundwater arsenic contamination[62].

The population affected by arsenic in India in 2018 was estimated to be 1.48 crores[62]. The States maximally affected are West Bengal (1.04 crore affected persons), Bihar (16.88 lakh affected) and Assam (14.48 lakh affected). In West Bengal, the ground water contamination by arsenic is recognized in 83 blocks in eight districts (Bardhaman, Malda, Hooghly, Howrah, Murshidabad, Nadia, North 24 Parganas and South 24 Parganas)[62]. Subclinical arsenicosis (higher level of arsenic in hair, nail or urine samples, with no overt clinical manifestations) was seen in >90 per cent of adults and children studied, residing in the affected localities[55]. Typical skin lesions of arsenicosis (hyperpigmentation and keratosis) were seen in 10 per cent of adults and six per cent of children from these localities (Uttar Pradesh, Bihar and West Bengal) who were examined[59-61]. Individuals residing in these localities and consuming arsenic-laden drinking water continue to be diagnosed with NCIPH[63].

Prevention of arsenic poisoning in India

The technology needed to remove arsenic from groundwater is expensive. Attempts to treat NCIPH with arsenic chelating agents have shown limited success[64]. The urgent need is to educate the public about the arsenic contamination of groundwater. Adequate infrastructure is needed to treat and provide arsenic free drinking water. The water supply needs to be continuously monitored for arsenic contamination. Rainwater harvesting (thus avoiding use of contaminated groundwater) is another suggested option. Cost-effective arsenic mitigation programmes

which can be sustained with public participation for implementation are urgently needed[58,65].

Use of arsenic mixed in recreational drugs and Ayurvedic/alternative medicines

A survey from Chandigarh showed highly prevalent use of substances including that of opioids[66]. Dependence rates on opioids, cannabinoids and sedative hypnotics were 1.5 per cent. The association between use of arsenic containing *Ayurvedic* medicines, arsenicosis and NCIPH has been reported in India[67]. In patients who develop drug-induced liver injury due to these drugs, the presence of arsenic or mercury is found to be associated with a higher risk of death[68].

Animal models of liver damage in arsenicosis

Chronic ingestion of arsenic (over 15 months duration of arsenic exposure) leads to hepatic fibrosis in mice. Oxidative stress in the liver has been demonstrated in murine model of arsenicosis causing hepatic fibrosis[69]. The lack of progression to portal hypertension in mice exposed to arsenic for prolonged periods suggests that arsenic exposure alone is not sufficient to produce NCIPH in mice[70].

Hypovitaminosis B12

Vitamin B12 deficiency is common in general population of India[71]. Low serum vitamin B12 may be due to subclinical malabsorption (like tropical enteropathy), genetic variations or low intake (vegetarianism)[40,71-73]. Low serum vitamin B12 level in patients with unexplained portal hypertension is a marker of NCIPH[74]. Low serum vitamin B12 predicts lack of advanced hepatic fibrosis in patients with intrahepatic portal hypertension[75]. Whether vitamin B12 deficiency (and consequent hyperhomocysteinemia) has a pathogenic role in causing portal venous obliteration in NCIPH is unclear at present. In a study from West Bengal, the degree of arsenic contamination of drinking water correlated with low serum vitamin B12 levels in the population consuming this water[76]. Whether B12 deficiency predisposes to NCIPH in areas with endemic arsenicosis in India needs further study.

Table II summarizes the findings of various case-control and observational studies regarding the prevalence of potential environmental factors in patients with NCIPH in India.

Mechanistic pathway

Platelet sequestration occurs in spleen and liver in healthy individuals as well as in syndromes of splenomegaly[77,78]. Platelet sequestration onto endothelium is one mechanism of thrombocytopenia in patients with portal hypertension. Marked, at times symptomatic, thrombocytopenia is a characteristic

Table II. Analysis of potential environmental factors causing non-cirrhotic intrahepatic portal hypertension (NCIPH) in case-control (where the control was cirrhosis)/observation studies from India

Environmental factor	Study and year	Type of the study	Patients studied	Parameter studied	Findings (%)	*P*
Arsenicosis	Mazumder *et al*, 1998[54*]	Observational	156 (with arsenicosis)	Spectrum of liver disease	41 (26) had NCIPH	-
	Datta *et al*, 1979[10#]	Case-control	Cases: 9 Controls: 7	Liver arsenic content	Cases: 0.9±0.40 ppm Controls: 0.18±0.17 ppm	<0.01
	Goel *et al*, 2016[63]	Case-control	Cases: 27 Controls: 25	Arsenicosis (dermatological)	Cases: 3 (11) Controls: 0	0.2
Enteropathy	Maiwall *et al*, 2014 (Unexplained enteropathy)[50]	Case-control	Cases: 12 Controls: 59	Celiac serology and duodenal biopsy	Cases: 11 (92) Controls: 6 (10)	<0.001
	Maiwall *et al*, 2014 (Celiac disease)[50]	Case-control	Cases: 14 Controls: 59	Celiac serology and duodenal biopsy	Cases: 2 (14) Controls: 0	0.04
Hypo-vitaminosis B12	Goel *et al*, 2013[74]	Case-control	Cases: 42 Controls: 38	Low vitamin B12 levels (<250 pg/ml)	Cases: 14 (33) Controls: 1 (3)	<0.001

*Of the 156 patients with skin arsenicosis, 33 per cent had portal hypertension and 41 patients had liver biopsy findings suggesting NCIPH[54]; #Nine liver biopsy specimens of patients with NCIPH had higher liver arsenic content as compared to seven cirrhosis controls, nine still born infants and 18 normal liver controls

feature of NCIPH. Platelet sequestration onto the activated endothelium in portal vein branches in the liver is postulated as a pathogenic mechanism of NCIPH[5].

Plasma vWF levels are raised (reflecting endothelial activation) in NCIPH patients. Release of pro-inflammatory cytokines in response to the chronic inflammatory stimulus from the intestine can activate the endothelium to release vWF into portal circulation[79,80]. It is likely that chronic low-grade inflammatory stimuli released from the gut trigger vWF expression on portal venous endothelium, with potential to promote platelet sequestration and occlusion of portal vein radicles causing NCIPH. ADAMTS13 is a vWF-cleaving protease synthesized almost exclusively by hepatic stellate cells. In advancing cirrhosis, as liver synthetic functions decrease, the plasma levels of ADAMTS13 also decrease. In a study of 142 hepatitis C-infected patients, mean plasma ADAMTS13 levels were 87, 79, 63 and 31 per cent in chronic hepatitis, cirrhosis in Child's A, B and C classes, respectively. Severe ADAMTS13 deficiency was seen in five patients in Child's C cirrhosis[81]. In contrast, two studies of NCIPH patients from Birmingham, UK[17] and at Vellore, India[18] have documented severe ADAMTS13 deficiency in 10 to 28 per cent despite most patients having well-preserved liver functions. This suggests that ADAMTS13 deficiency may be a primary event and involved in pathogenesis of NCIPH; in contrast to being a secondary phenomenon due to reduced liver synthetic function in advanced cirrhosis because of hepatitis C. The association of ADAMTS13 deficiency in NCIPH patients is being increasingly recognized[82].

Genetic predisposition to NCIPH

Prevalence of familial NCIPH

There have been isolated reports of NCIPH occurring in childhood and families suggesting a possible role of genetic predisposition[83-89]. In a retrospective analysis of prospectively collected database of 174 NCIPH patients (age at presentation: 32±12 yr) at our centre, only three patients had another 1st degree family member having a chronic liver disease[29]. In a large Western study on natural history of NCIPH, none of the 69 patients reportedly had a family history of liver disease[90]. Thus, familial NCIPH appears to be uncommon.

Genetic alterations in NCIPH

Multiple studies have attempted to explore the role of genetic influence in pathogenesis of NCIPH. Whole exome sequencing in familial NCIPH revealed potential pathogenic mutations needing further studies[91,92]. Studies have attempted to analyze possible genetic influences such as immunogenetic (major histocompatibility complex), thrombophilic and metabolic (especially drug susceptibility) in pathogenesis of NCIPH[93-98]. Except for in isolated families affected by NCIPH, there are not enough data at present to suggest a monogenic cause in majority of these patients.

Genetic predisposition to microangiopathy

NCIPH may be considered as a localized form of thrombotic microangiopathy affecting the small portal vein radicles as there is evidence of low ADAMTS13[5,17,18], and alternative complement system activation[99,100], being involved in its pathogenesis. In addition, low ADAMTS13 is associated with enhanced complement activation, especially in alternative pathway[101]. Both mutations in ADAMTS13 and the complement regulators are known to predispose to thrombotic microangiopathy[102-105].

A rare non-synonymous variant in ADAMTS13 gene (CUB domain, rs2301612) was detected in a single patient with NCIPH (absent in 20 healthy controls) in a study at our centre, which was associated with ADAMTS13 protein trapping inside the hepatic stellate cells and also decrease in functional activity[106]. East Asians have been shown to harbour polymorphisms that lead to decrease in ADAMTS13 activity, which can make the population vulnerable to develop thrombotic microangiopathy in the presence of a second insult[107].

There is evidence to suggest complement activation (primary or secondary), especially alternative complement pathway may play a role in pathogenesis of NCIPH[100]. Thrombotic microangiopathy is known to be associated with mutations in alternative complement pathway[108]. These mutations render the alternative complement system hyperactive with loss of natural suppression. In a recent case-control study on 21 patients with NCIPH (compared with healthy controls), we found no significant association with a single nucleotide polymorphism at rs6677604 (polymorphism associated with decrease in complement factor H and known to predispose to thrombotic microangiopathy)[109].

Is the epidemiology of NCIPH changing in India?

Decline in incidence of NCIPH has been reported from some centres in India[110,111]. However, multiple

reports in the past decade corroborate the fact that NCIPH remains prevalent in India[20,23,25,27,28,112]. NCIPH mimics cryptogenic cirrhosis[113]. As discussed earlier, NCIPH is currently underdiagnosed in India.

Causes of NCIPH in different parts of the world

The factors triggering NCIPH are diverse[114]. In the West, haematological and malignant thrombophilic disorders are often associated with NCIPH[90,115]. Association of NCIPH with certain drugs (most commonly azathioprine and some anti-retroviral drugs) have often been reported[96,116-118]. Such association have not been reported from India, but widespread use of herbal products needs to be considered[118]. In India, gut derived environmental factors are probably the predominant triggers of NCIPH at present.

Future directions

The available evidence showed that deleterious environmental factors, entering the portal venous system through the gut, could promote endothelial-platelet interaction leading to occlusion of intrahepatic portal vein radicles in NCIPH. While it is likely that all socio-economic categories in India are exposed to these environmental factors, the impact may be more prominent in the lower socio-economic categories. Urgent public health measures to improve hygiene and sanitation are needed to reduce incidence of NCIPH. Governmental initiatives such as *Swatch Bharat* Mission or Clean India Mission[119], National Mission for Clean Ganga[120], Task Force to reduce Arsenicosis[121] as well as community-led initiatives[122] in this regard are likely to contribute to reduction of NCIPH in India, in the days to come.

***Financial support & sponsorship*:** Authors acknowledge funds received from the Science and Engineering Research Board, Government of India (EMR/2015/000570) and Fluid research funds, Christian Medical College, Vellore, India, towards conduct of these studies into non-cirrhotic portal hypertension.

***Conflicts of Interest*:** None.

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For correspondence: Dr C.E. Eapen, Department of Hepatology, Christian Medical College, Vellore 632 004, Tamil Nadu, India
e-mail: eapen@cmcvellore.ac.in